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(54) Title: SUBSTITUTED OXOAZAHETEROCYCLYL COMPOUNDS

(57) Abstract: This invention is directed to oxoazaheterocyclyl compounds which inhibit Factor Xa, to oxoazaheterocyclyl compounds which inhibit both Factor Xa and Factor IIa, to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds, to a method of directly inhibiting Factor Xa and to a method of simultaneously directly inhibiting Factor Xa and Factor IIa.

Description

SUBSTITUTED OXOAZAHETEROCYCLYL COMPOUNDS

FIELD OF THE INVENTION

This invention is directed to oxoazaheterocyclyl compounds which inhibit Factor

This invention is directed to oxoazaheterocyclyl compounds which inhibit Factor Xa, to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds and to a method of inhibiting Factor Xa. This invention is also directed to oxoazaheterocyclyl compounds which directly inhibit both Factor Xa and Factor IIa (thrombin), to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds and to a method of simultaneously directly inhibiting both Factor Xa and Factor IIa (thrombin).

BACKGROUND OF THE INVENTION

Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) activate prothrombin (Factor II) to generate thrombin (Factor IIa). Factor Xa is strategically located at the intersection of extrinsic and intrinsic pathways of the blood coagulation system. Thus, an inhibitor of Factor Xa inhibits the formation of thrombin and, therefore, is useful for preventing or treating disorders related to blood coagulation in mammals.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting (CABG) of the coronary or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and

cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems.

In addition to their use in anticoagulant therapy, Factor Xa inhibitors are useful in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF and DNA syntheses. Inhibition of Factor Xa will effectively block thrombin generation and therefore neutralize any physiologic effects of thrombin on various cell types.

The representative indications discussed above include some, but not all, of the possible clinical situations amenable to treatment with a Factor Xa inhibitor.

Oxoazaheterocyclyl Factor Xa inhibitors are disclosed in International Patent Application Numbers PCT/US98/07158, published Oct. 22, 1998; PCT/US98/07159, published Oct. 22, 1998; PCT/US98/07160, published Oct. 22, 1998; PCT/US98/07161, published Oct. 22, 1998; and PCT/US96/09290, published Dec. 19, 1996. Oxoazaheterocyclyl fibrinogen antagonists are disclosed in International Patent Application Number PCT/US92/09467, published May 13, 1993.

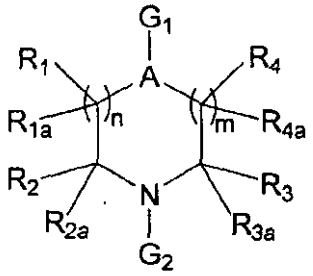
Vascular injury, caused by biochemical or physical perturbations, results in the activation of the coagulation system, culminating in the generation of thrombin. Thrombin promotes thrombus formation by catalyzing the transformation of fibrinogen to fibrin, by activating Coagulation Factor XIII, which stabilizes the thrombus, and by activating platelets. Thrombin promotes further thrombus growth by positive feedback to the coagulation cascade (activation of Coagulation Factors V and VIII), resulting in the explosive production of thrombin. Thrombin is present, and active, in the thrombi of patients with thrombotic vascular disease. Thrombin inhibition prevents the action of thrombin after thrombin has been activated from prothrombin. An inhibitor of thrombin inhibits cleavage of fibrinogen to fibrin, activation of Factor XIIIa, activation of platelets, and feedback of thrombin to the coagulation cascade to generate more thrombin. Consequently, inhibition of thrombin activity with a direct thrombin inhibitor would be useful for preventing or treating disorders related to blood coagulation in mammals.

The combined inhibitors of Factor Xa and Factor IIa described herein inhibit thrombin *activity* (via IIa inhibition) *and* thrombin *production* (via Factor Xa inhibition). Therefore, these

agents inhibit any thrombin that may be present and also inhibit the further production of thrombin. Other agents which have this dual activity include heparin and low molecular weight heparins (LMWHs), which have demonstrated efficacy in thrombotic diseases. However, heparin and LMWHs act indirectly through a cofactor, antithrombin-III (ATIII), to inhibit Xa and IIa. The heparin/ATIII complex is too large, however, to inhibit thrombus-bound Xa and IIa, thus limiting its efficacy. Direct inhibitors of Factor Xa and Factor IIa, as described herein, are capable of inhibiting soluble and thrombus-bound Xa and IIa, thus providing an important therapeutic advantage over currently available Xa/IIa inhibitors.

SUMMARY OF THE INVENTION

This invention is directed to a compound of formula I



I

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof

wherein

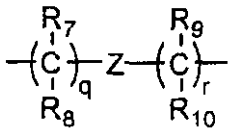
G_1 and G_2 are L_1-Cy_1 or L_2- Cy_2, provided that when R_1 and R_{1a} or R_4 and R_{4a} taken together form O or S, then G_1 is L_2- Cy_2 and G_2 is L_1- Cy_1, or when R_2 and R_{2a} or R_3 and R_{3a} taken together form O or S, then G_1 is L_1- Cy_1 and G_2 is L_2- Cy_2;

Cy_1 and Cy_2 are independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

L_1 is absent, O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, -C(O)Y-C(X)Y-, -C(X)YC(O)-,

-C(O)NR_5-S(O)p-, or -C(O)C(O)NR_5S(O)p-;

L_2 is absent or a group of formula



L_3 and L_5 are independently absent, optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene;

L_4 is optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene;

Q and Q' are independently absent, O, S, NR_5, -S(O)p-, -S(O)pNR_5- or -C(X)Y-;

A is CH or N;

R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a}, R_3 and R_{3a}, or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_3 and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

m and n are independently 0, 1 or 2, provided that m and n are not both 0 and further provided that when R_1 and R_{1a} taken together form O or S, n is 1, and when R_4 and R_{4a} taken together form O or S, m is 1;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH_2)v$-, $R_6O_2C(CH_2)x$-, $Y_1Y_2NC(O)(CH_2)x$-, or $Y_1Y_2N(CH_2)v$-;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y_1 and Y_2 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted aryl, optionally substituted aralkyl or

optionally substituted heteroaralkyl, or Y_1 and Y_2 taken together with the N through which Y_1 and Y_2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when any of R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α-substituted to an N, O or S in Z;

X is O or S;

Y is absent or is selected from O, S and NR_5;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, -C(O)-, S(O)p, NR_5, $-NR_5C(O)-$ and $-C(O)NR_5-$;

x is 1, 2, 3 or 4;

v is 2, 3 or 4;

p is 1 or 2; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0,

and provided that when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen;

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then R_4 and R_{4a} taken together form O or S;

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then Cy_1 is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol and Cy_2 is amino-quinazolin or pyrrolo-pyridin;

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ then R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together

with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_3 and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;.

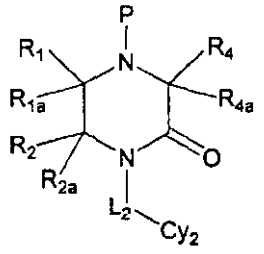
or when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, then R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently $Y_1Y_2NC(O)$- and Y_1 and Y_2 are independently hydrogen, optionally substituted alkoxy or optionally substituted aryloxy, but Y_1 and Y_2 are not simultaneously hydrogen,

or when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, then Z is –C(O).

In another aspect, this invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I or formula II and a pharmaceutically acceptable carrier.

In another aspect, this invention is directed to a method of treating a physiological disorder capable of being modulated by inhibiting Factor Xa comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I or formula II.

In another aspect, this invention is directed to a compound of formula III



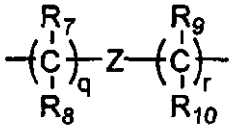
III

wherein P is H or a nitrogen protecting group;

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a} or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_1 and R_{1a} taken together with the carbon atom through wrich they are linked form a 3 to 7

membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through wrich they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

L_2 is absent or a group of formula



Cy_2 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH_2)v$-, $R_6O_2C(CH_2)x$-, $Y_1Y_2NC(O)(CH_2)x$-, or $Y_1Y_2N(CH_2)v$-;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y_1 and Y_2 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y_1 and Y_2 taken together with the N through which Y_1 and Y_2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α-substituted to a N, O or S in Z;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, S(O)p, -C(O)-, NR_5, -$NR_5C(O)$- and -$C(O)NR_5$-;

x is 1, 2, 3 or 4;

v is 2, 3 or 4; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0,

which is an intermediate useful in the preparation of the compound of formula I or formula II

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

"Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group, which may be straight or branched chain, having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl may be substituted with one or more "alkyl group substituents" which may be the same or different, and include halo, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, hydroxy, oxime, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, isourea, guanidino, acylhydrazino, alkoxy, amino, carbamoyl, acylamino, aroylamino, carboxy, alkoxycarbonyl, aralkyloxycarbonyl and heteroaralkyloxycarbonyl. Representative alkyl groups include methyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, 3-pentyl, methoxyethyl, carboxymethyl, methoxycarbonylethyl, benzyloxycarbonylmethyl, and pyridylmethyloxycarbonylmethyl.

"Alkenyl" means a straight or branched aliphatic hydrocarbon group containing a carbon-carbon double bond and having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more alkyl group substituents as defined herein. Representative alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, decenyl, and the like.

"Alkylene" means a straight or branched bivalent hydrocarbon chain having from 1 to about 20 carbon atoms. The preferred alkylene groups are the lower alkylene groups having from 1 to about 6 carbon atoms. Alkylene may be substituted with 1 or more alkyl group

substituents as defined herein. Representative alkylene groups include methylene, ethylene, and the like.

"Alkenylene" means a bivalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon triple bond. The preferred alkenylene groups are the lower alkenylene groups having from 1 to about 6 carbon atoms. Alkenylene group may be substituted by one or more alkyl group substituents as defined herein. Representative alkenylene groups include -CH=CH-, $-CH_2CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CHCH_2-$, and the like.

"Alkynylene" means a bivalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. Preferred alkynylene groups are the lower alkynylene groups having from 1 to about 6 carbon atoms. Alkynylene may be substituted by one or more alkyl group substituents as defined herein. Representative akynylene include —CH≡CH—, —CH≡CH·CH$_2$—, —CH≡CH·CH(CH$_3$)—, and the like.

"Aralkylamino" means a (arylalkyl)(Y_2)N- group wherein the arylalkyl portion and Y_2 are as herein defined.

"Heteroaralkylamino" means a (heteroaralkyl)(Y_2)N- group wherein the heteroaralkyl portion and Y_2 are as defined herein.

"Heterocyclylalkyl" means a heterocyclyl-alkylene- group wherein the heterocyclyl portion and alkylene portion are as defined herein.

"Heterocyclylalkylamino" means a (heterocyclylalkyl)(Y_2)N- group wherein the heterocyclylalkyl portion and Y_2 are as defined herein.

"Heterocyclenylalkyl" means a heterocyclenyl-alkylene- group wherein the heterocyclenyl portion and alkylene portion are as defined herein.

"Heterocyclenylalkylamino" means a (heterocyclenylalkyl)(Y_2)N- group wherein the heterocyclenylalkyl portion and Y_2 are as defined herein.

"Alkoxyalkyl" means an alkoxy-alkylene- group wherein the alkoxy portion and alkylene portion are as defined herein.

"Alkylthioalkyl" means an alkylthio-alkylene- group wherein the alkylthio portion and alkylene portion are as defined herein.

"Alkylsulfinylalkyl" means an alkylsulfinyl-alkylene- group wherein the alkylsulfinyl portion and alkylene portion are as defined herein.

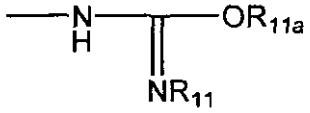
"Alkylsulfonylalkyl" means an alkylsulfinyl-alkylene- group wherein the alkylsulfinyl portion and alkylene portion are as defined herein.

"Acylalkyl" means an acyl-alkylene- group wherein the acyl portion and alkylene portion are as defined herein.

"Acylaminoalkyl" means an acyl-NH-alkylene- group wherein the acyl portion and alkylene portion are as defined herein.

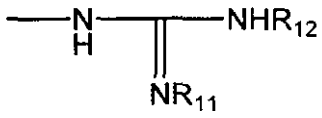
"Carbamoylalkyl" means an carbamoyl-alkylene- group wherein the carbamoyl portion and alkylene portion are as defined herein.

"Heterocyclylalkyloxycarbonyl" means a heterocyclylalkyl-O-C(O)- group wherein the heterocyclylalkyl portion is as defined herein.

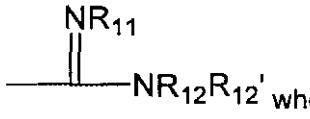


"Isourea" means a group of formula wherein R_{11} is as defined herein and R_{11a} is hydrogen, optionally substituted lower alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

"Acylhydrazino" means a group of formula Y_1Y_2N-NHC(O)-, wherein Y_1 and Y_2 are as defined herein.



"Guanidino" or "guanidine" means a group of formula wherein R_{11} and R_{12} are as defined herein.



"Amidino" or "amidine" means a group of formula wherein R_{11} is selected from hydrogen, R_6O_2C-, R_6O-, $R_6C(O)$-, cyano, optionally substituted lower alkyl, nitro or Y_1Y_2N- and R_{12} and $R_{12'}$ are independtly selected from hydrogen, optionally substituted lower alkyl, optionally substituted aralkyl and optionally substituted heteroaralkyl. Preferred amidino groups are those in which R_{11} is hydrogen, R_6O, or optionally substituted lower alkyl and R_{12} is as defined above. Most preferred amidino groups are those in which R_{11} and R_{12} are hydrogen.

"Carbamate" means a group of formula $Y_1Y_2C(O)NH$- wherein Y_1 is as defined herein; Y_2 is selected from optionally substituted alkoxy or optionally substituted aryloxy. "Alkylcarbamate" means a group of formula $Y_1Y_2C(O)NH$- wherein Y_1 and Y_2 are indepenedetly alkyl. More prefered alkylcarbamate groups are methylcarbamate, ethylcarbamate, t-butylcarbamate, benzylcarbamate and phenylcarbamate.

"Aminoalkylamino" means a Y_1Y_2N-alkylene-$(Y_2)N$- group wherein Y_1, Y_2 and alkylene are as defined herein.

"Aryloxycarbonylalkyl" means a aryl-O-C(O)-alkylene group wherein the aryl portion and alkylene portion are as defined herein.

"Heteroaryloxycarbonylalkyl" means a hetroaryl-O-C(O)-alkylene group wherein the heteroaryl portion and alkylene portion are as defined herein.

"Heterocycloxycarbonylalkyl" means a heterocyclyl-O-C(O)-alkylene group wherein the heterocyclyl portion and alkylene portion are as defined herein.

"Heterocyclenyloxycarbonylalkyl" means a heterocyclenyl-O-C(O)-alkylene group wherein the heterocyclenyl portion and alkylene portion are as defined herein.

"Basic nitrogen atom" means an sp^2 or sp^3 hybridized nitrogen atom having a non-bonded pair of electrons which is capable of being protonated. Examples of basic nitrogen atoms, which may be optionally substituted where possible, include those in heteroaryl, heterocyclyl, heterocyclenyl, fused arylheterocyclyl, fused arylheterocyclenyl, fused heteroarylcycloalkyl, fused heteroarylcycloalkenyl, fused heteroarylheterocyclyl, fused heterocyclylheterocyclenyl, imino, amino, isourea, acylhydrazino, guanidino and amidino groups.

"Cycloalkyl" means a non-aromatic mono- or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Representative multicyclic cycloalkyl rings include decalinyl, norbornyl, adamantyl, and the like. The cycloalkyl group is optionally substituted with one or more "cycloalkyl group substituents" which may be the same or different, where "cycloalkyl group substituent" includes oxo (O=), thioxo (S=), methylene (H_2C=), oxime (HO-N=), alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, amidino, amino, carbamoyl, or sulfamoyl. Preferred cycloalkyl group substituents are amino and amidino.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system containing a carbon-carbon double bond and having about 3 to about 10 carbon atoms. The cycloalkenyl group is optionally substituted by one or more cycloalkyl group substituents as defined herein. Representative monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl, and the like. A representative multicyclic cycloalkenyl ring is norbornylenyl. Preferred cycloalkenyl group substituents are amino and amidino.

"Carboxy" means a group of formula HO(O)C- (carboxylic acid group).

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 ring atoms wherein the ring system contains one or more element(s) other

than carbon. Preferred heterocyclyl comprise about 5 to about 7 ring atoms, more preferred 5 to 6 ring atoms, wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen or sulfur respectively. "Aza", "oxa" or "thia", when used as a prefix before heterocyclyl means that the ring system contains at lease one nitrogen, oxygen and sulfur atom. For example, "azaheterocyclyl" means a heterocyclyl group wherein one or more of the atoms in the ring system is/are nitrogen. The heterocyclyl group is optionally substituted with one or more heterocyclyl group substituents which may be the same or different, where " heterocyclyl group substituent" " includes oxo (O=), thioxo (S=), methylene (H_2C=), oxime (HO-N=), alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, amino, carbamoyl, and sulfamoyl. Preferred heterocyclyl group substituents include amino, amidino, halogen, hydroxy, alkoxycarbonylalkyl and carboxyalkyl. Representative heterocyclyl groups include piperidyl, pyrrolidinyl, piperazinyl, pyrazolidinyl, imidazolinyl, hexamethyleneimine, homopiperazine, tetrahydrofuryl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, 1,4-dithianyl, 1,3,5-triathianyl, tetrahydrothienyl, tetrahydrothiopyranyl, quinuclidinyl, and the like. The thio or nitrogen moiety of the heterocyclyl may also be optionally oxidized to the corresponding S-oxide, S,S-dioxide or N-oxide.

"Heterocyclenyl" means a heterocyclyl group as defined herein which contains at least one carbon-carbon or carbon-nitrogen double bond. "Aza", "oxa" or "thia", when used as a prefix before heterocyclenyl group means that the ring system contains at lease one nitrogen, oxygen or sulfur atom respectively. The heterocyclenyl group is optionally substituted with one or more heterocyclyl group substituents as defined herein. Representative heterocyclenyl groups include 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, 2H-pyranyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,4- tetrahydropyridyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. Preferred heterocyclenyl group substituents include amino, amidino, halogen, hydroxy, oxo, thioxo, methylene, oxime, alkoxycarbonylalkyl and carboxyalkyl. The thio or nitrogen moiety of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Aryl" means a 6 to 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system. The aryl group is optionally substituted with one or more "aryl group substituents" which may be the same or different, where "aryl group substituent" includes alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl,

heteroaralkyl, aryldiazo, heteroaryldiazo, hydroxy, alkylcarbamate, acylhydrazino, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, arylazo, heteroarylazo, amino, amidino, alkylamino, carbamoyl, and sulfamoyl. Preferred aryl groups are optionally substituted phenyl or optionally substituted naphthyl. Preferred aryl group substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, carboxy, sulfamoyl, alkylcarbamate, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino.

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic ring system wherein one or more of the atoms in the ring system is/are element(s) other than carbon. Preferred heteroaryl groups contain one to about 4 heteroatoms selected from oxygen, nitrogen and sulfur. "Aza", "oxa" or "thia", when used as a prefix before heteroaryl means that the ring system contains at lease one nitrogen, oxygen or sulfur atom. The heteroaryl group is optionally substituted with one or more aryl group substituents as defined herein. Representative heteroaryl groups include pyrrolyl, pyrazinyl, furyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thienopyridyl, thienopyrolyl, thieno[3,2-d]pyrimidyl, pyrrolopyridyl, furanopyridyl, furazanyl, quinoxalinyl, quinazolinyl, quinolizinyl, imidazo[1,2-a]pyridyl, phthalazinyl, imidazo[2,1-b]thiazolyl, benzofuranyl, indolyl, isoindolyl, indolizinyl, indazolyl, azaindolyl, benzimidazolyl, benzothienyl, benzisoxazolyl, benzothiazolyl, purinyl, benzotriazolyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, imidazolyl, isoquinolinyl, cinnolinyl, triazinyl, benzotriazinyl, and the like. Preferred heteroaryl group substituents include hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, carboxy, acylhydrazino, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. When the heteroaryl groups contains a nitrogen atom, the nitrogen atom may be oxidized to the N-oxide.

"Fused arylcycloalkyl" means a fused aryl and cycloalkyl, wherein the ayl and cycloalkyl portions are as defined herein. Preferred fused arylcycloalkyls groups are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 carbon atoms. Representative fused phenylcycloalkyl groups include 1,2,3,4-tetrahydronaphthyl, indanyl, and the like. The fused arylcycloalkyl group is optionally substituted with one or more fused arylcycloalkyl group substituents selected from, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl, heteroaralkyl, aryldiazo,

heteroaryldiazo, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, arylazo, heteroarylazo, amino, alkylamino, carbamoyl and sulfamoyl. The cycloalkyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=), or oxime (HO-N=). Preferred fused phenylcycloalkyl group substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino.

"Fused arylcycloalkenyl" means a fused aryl and cycloalkenyl, wherein the aryl and cycloalkenyl portions are as defined herein. Preferred fused arylcycloalkyenl groups are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 carbon atoms. The fused arylcycloalkenyl is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. Representative fused phenylcycloalkenyl groups include 1,2-dihydronaphthylenyl, indenyl, and the like. The cycloalkyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=), oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino.

"Fused arylheterocyclyl" means a fused aryl and heterocyclyl, wherein the aryl and heterocyclyl portions are as defined herein. Preferred fused arylheterocyclyl groups are those wherein the aryl portion thereof is phenyl and the heterocyclyl portion consists of about 5 to about 7 ring atoms, more preferred 5 to 6 ring atoms, wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen and sulfur. "Aza", "oxa" or "thia", when used as a prefix before the heterocyclyl portion of the fused arylheterocyclyl means that the heterocyclyl contains at lease one nitrogen, oxygen or sulfur atom. Representative preferred fused phenylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydrobenzofuran, 1H-2,3-dihydroisoindolyl, 2,3-dihydrobenz[f]isoindolyl, 1,2,3,4-tetrahydrobenz[g]isoquinolinyl, and the like. The fused phenylheterocyclyl group is optionally substituted with one or more fused phenylcycloalkyl group substituents as defined herein. The heterocyclyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino,

carbamoyl, thiocarbamoyl and amidino. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Fused arylheterocyclenyl" means a fused aryl and heterocyclenyl, wherein the aryl and hterocyclenyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heterocyclenyl portion of the fused arylheterocyclenyl group means that the heterocyclenyl portion contains at lease one nitrogen, oxygen or sulfur atom. Preferred fused arylheterocyclyl groups are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to 6 ring atoms wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen and sulfur. Representative preferred fused arylheterocycloalkenyl ring systems include 3H-indolinyl, 3H-quinazolin-4-one, 1,1-dioxo-benzo[d]isothiazolyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl, and the like. The fused arylheterocyclenyl group is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Fused heteroarylcycloalkyl" means a fused heteroaryl and cycloalkyl, wherein the heteroaryl and cycloalkyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl portion of the fused heteroarylcycloalkyl group means that the heteroaryl portion contains at lease one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylcycloalkyl groups are those wherein the heteroaryl portion thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the cycloalkyl consists of about 5 to about 6 ring atoms. Representative preferred fused heteroarylcycloalkyl groups include 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5-diazanaphthalen-2-onyl, 1,3-dihydroimidizole-[4,5]-pyridin-2-onyl, 5,6,7,8-tetrahydrobenzothiazolyl, 5,6-dihydro-4H-benzothiazol-7-one, and the like. The fused heteroarylcycloalkyl group is optionally substituted with one or more fused phenylcycloalkyl group substituents as defined herein. The cycloalkyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino.

The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl group is optionally oxidized to the N-oxide.

"Fused heteroarylcycloalkenyl" means a 5- or 6-membered heteroaryl fused with a cycloalkenyl ring. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl portion of the fused heteroarylcycloalkenyl means that the cycloalkenyl contains at lease one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylcycloalkenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the cycloalkenyl consists of about 5 to about 6 ring atoms. Representative preferred fused heteroarylcycloalkenyl include 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, and the like. The fused heteroarylcycloalkenyl is optionally substituted with one or more fused phenylcycloalkyl group substituents as defined herein. The cycloalkenyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl is optionally oxidized to the N-oxide.

"Fused heteroarylheterocyclyl" means a heteroaryl ring fused with a heterocyclyl ring wherein the heteroaryl and heterocyclyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl group means that the heteroaryl or heterocyclyl potion contains at lease one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylheterocyclyl groups are ring systems wherein one or two of the ring atoms of the heteroaryl are independently selected from oxygen, nitrogen and sulfur and the heterocyclyl portion consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur. Representative fused heteroarylheterocyclyl groups include 4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one, 5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one, 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2yl, 2,3,-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2 yl, 5,6,7,8-tetrahydro[1,7]napthyridinyl, 1,2,3,4-tetrhydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa-4,6-diazanaphthalenyl,

4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro-5,8-diazanaphthalenyl, and the like. The fused heteroarylheterocyclyl group is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen atom of the heteroaryl portion is optionally oxidized to the N-oxide. The nitrogen or sulphur atom of the heterocyclyl portion is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl, wherein the heteoayl and heterocyclenyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl group means that the heteroaryl or heterocyclenyl portion contains at lease one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylcycloalkenyl groups are ring systems wherein the heteroaryl portion thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the heterocyclenyl portion consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur. Representative fused heteroarylheterocyclenyl groups include 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, and the like. The fused heteroarylheterocyclenyl group is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclenyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H_2C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen atom of the heteroaryl portion is optionally oxidized to the N-oxide. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Aralkyl" means an aryl-alkyl- group in which the aryl portion and alkyl portion are as defined herein. Preferred aralkyl groups contain a lower alkyl moiety. Representative aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl portion and alkyl portion are as defined herein. Preferred heteroaralkyl groups contain a lower alkyl moiety. Representative heteroaralkyl groups may contain thienylmethyl, pyridylmethyl, imidazolylmethyl and pyrazinylmethyl.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl portion and alkenyl portion are as defined herein. Preferred aralkenyl groups contain a lower alkenyl moiety. An representative aralkenyl group is 2-phenethenyl.

"Heteroaralkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl portion and alkenyl portion are as defined herein. Preferred heteroaralkenyls contain a lower alkenyl moiety. Representative heteroaralkenyl groups may contain thienylethenyl, pyridylethenyl, imidazolylethenyl and pyrazinylethenyl.

"Hydroxyalkyl" means a HO-alkylene- group in which the alkylene portion is as defined herein. Preferred hydroxyalkyl groups contain lower alkylene. Representative hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl portion is as defined herein. Preferred acyl groups contain a lower alkyl. Representative acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" means an aryl-CO- group in which the aryl portion is as defined herein. Representative aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aryldiazo" means an aryl-N=N- group in which the aryl portion is as defined herein. Representative aryldiazo groups include phenyldiazo and naphthyldiazo.

"Heteroaroyl" means an means a heteroaryl-CO- group in which the heteroaryl portion is as defined herein. Representative heteroaryl groups include thiophenoyl and pyridinoyl.

"Heteroaryldiazo" means a heteroaryl-N=N- group in which the heteroaryl group is as defined herein. Representative heteroaryldiazo groups include pyridyldiazo and thienyldiazo.

"Alkoxy" means an alkyl-O- group in which the alkyl portion is as defined herein. Representative alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

"Aryloxy" means an aryl-O- group in which the aryl portion is as defined herein. Representative aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in aralkyl portion is as defined herein. Representative aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Alkylthio" means an alkyl-S- group in which alkyl portion is as defined herein. Representative alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio.

"Arylthio" means an aryl-S- group in which the aryl portion is as defined herein. Representative arylthio groups include phenylthio and naphthylthio.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl portion is as defined herein. A representative aralkylthio group is benzylthio.

"Amino" means a group of formula Y_1Y_2N- wherein Y_1 and Y_2 are defined herein. Preferred amino groups include amino (H_2N-), methylamino, dimethylamino, diethylamino, benzylamino, phenethylamino, 5-aminoindolyl, 2-amino-2-thiazolinyl, N-(2-aminoethyl)morpholine, 2(aminomethyl)pyridine, or 4(aminomethyl)pyridine.

"Aminoalkyl" means a Y_1Y_2N-alkylene- group wherein Y_1, Y_2 and the alkylene portion are defined herein.

"Alkoxycarbonyl" and "alkyloxycarbonyl" means an alkyl-O-CO- group wherein the alkyl portion is as defined herein. Representative alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, or t-butyloxycarbonyl.

"Heterocyclylalkyloxycarbonyl" means an heterocyclyl-alkyloxycarbonyl group wherein the heterocyclyl portion and alkyloxycarbonyl portion are as defined herein. A representaivie example of a heterocyclylalkyloxycarbonyl group is pyrrolidinylethoxycarbonyl.

"Heterocyclenylalkyloxycarbonyl" means an heterocyclenyl-alkyloxycarbonyl group wherein the heterocyclenyl portion and alkyloxycarbonyl portion are as defined herein. A representaivie example of a heterocyclenylalkyloxycarbonyl group is pyrrolinylethoxycarbonyl.

"Heteroaralkyloxycarbonyl" means an heteroaryl-alkyloxycarbonyl group wherein the heteroaryl portion and alkyloxycarbonyl portion are as defined herein. A representaivie example of a heteroaralkyloxycarbonyl group is pyridylethoxycarbonyl.

"Arylalkyloxycarbonyl" means an aryl-alkyloxycarbonyl group wherein the aryl portion and alkyloxycarbonyl portion are as defined herein. A representaivie example of a aralkyloxycarbonyl group is phenylethoxycarbonyl.

"Cycloalkylalkyloxycarbonyl" means a cycloalkyl-alkyloxycarbonyl group wherein the cycloalkyl portion and alkyloxycarbonyl portion are as defined herein. A representaivie example of a ar cycloalkylalkyloxycarbonyl group is cyclohexylethoxycarbonyl.

"Cycloalkenylalkyloxycarbonyl" means a cycloalkenyl-alkyloxycarbonyl group wherein the cycloalkenyl portion and alkyloxycarbonyl portion are as defined herein. A representaivie example of a ar cycloalkenylalkyloxycarbonyl group is cyclohexenylethoxycarbonyl.

"Alkoxycarbonylalkyl" means an alkyl-O-CO-alkylene- group wherein alkyl portion and alkylene portion are defined herein.

"Aryloxycarbonyl" means an aryl-O-CO- group wherein aryl portion is as defined herein. Representative aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-CO- group wherein aralkyl portion is as defined herein. A representative aralkoxycarbonyl group is benzyloxycarbonyl.

"Carbamoyl" means a group of formula Y_1Y_2NCO- wherein Y_1 and Y_2 are defined herein. Representative carbamoyl groups are carbamoyl (H_2NCO-) and dimethylaminocarbamoyl (Me_2NCO-).

"Heterocyclylalkylcarbamoyl" means a heterocyclyl-alkylene-carbamoyl wherein the heterocyclyl, alkylene and carbamoyl portions are as defined herein. A representative example of a heterocyclylalkylenecarbamoyl group is pyrrolidinylethylcarbamoyl. "Heterocyclenylalkylcarbamoyl" means a heterocyclenyl-alkylene-carbamoyl wherein the heterocyclenyl, alkylene and carbamoyl portions are as defined herein. A representative example of a heterocyclyenlalkylenecarbamoyl group is pyrrolinylethylcarbamoyl.

"Heteroaralkylcarbamoyl" means a heteroaryl-alkylene-carbamoyl wherein the heteroaryl, alkylene and carbamoyl portions are as defined herein. A representative example of a heteroaralkylenecarbamoyl group is pyridinylethylcarbamoyl.

"Arylalkylcarbamoyl" means an aryl-alkylene-carbamoyl wherein the aryl, alkylene and carbamoyl portions are as defined herein. A representative example of an aralkylenecarbamoyl group is phenylethylcarbamoyl.

"Cycloalkylalkylcarbamoyl" means an cycloalkyl-alkylene-carbamoyl wherein the cycloalkyl, alkylene and carbamoyl portions are as defined herein. A representative example of an cycloalkylalkylcarbamoyl group is cyclohexylethylcarbamoyl.

"Cycloalkenylcarbamoyl" means an cycloalkenyl-alkylene-carbamoyl wherein the cycloalkenyl, alkylene and carbamoyl portions are as defined herein. A representative example of an cycloalkylalkenylcarbamoyl group is cyclohexenylethylcarbamoyl.

"Sulfamoyl" means a group of formula $Y_1Y_2NSO_2$- wherein Y_1 and Y_2 are defined herein. Representative sulfamoyl groups are aminosulfamoyl (H_2NSO_2-) and dimethylaminosulfamoyl (Me_2NSO_2-).

"Acylamino" means an acyl-NH- group wherein the acyl portion is as defined herein.

"Aroylamino" means an aroyl-NH- group wherein the aroyl portion is as defined herein.

"Alkylsulfonyl" means an alkyl-SO_2- group wherein the alkyl portion is as defined herein. Preferred alkylsulfonyl groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl-SO- group wherein the alkyl portion is as defined herein. Preferred alkylsulfinyl groups are those in which the alkyl portion is lower alkyl.

"Arylsulfonyl" means an aryl-SO_2- group wherein the aryl portion is as defined herein.

"Arylsulfinyl" means an aryl-SO- group wherein the aryl portion is as defined herein.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Nitrogen protecting group" means an easily removable group which is known in the art to protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of N-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, CF, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Preferred N-protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethxoycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl (BOC), 1,1-dimethylpropynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-nitrophenylsulfinyl, p-nitrobenzyloxycarbony, 2,4-dichlorobenzyloxycarbonyl, allyloxycarbonyl (Alloc), and the like.

"Compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula I or formula II as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. It is understood that the activity of individual compounds of formula I or formula II will vary depending on the individual compound and assay employed. Compounds of the invention as used herein includes all compounds of formula I or formula II having an in-vitro activity of greater than 10% at 3.9 □M in the Factor Xa in vitro enzyme assay described herein. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

"Prodrug" means a form of the compound of formula I or formula II which may or may not itself be biologically active but which may be converted, for example by metabolic, solvolytic, or other physiological means, to a biologically active chemical entity, and is suitable for administration to a patient without undue toxicity, irritation, allergic response, and the like, and effective for their intended use, including ketal, ester and zwitterionic forms. A prodrug is transformed in vivo to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series, and in Edward B. Roche,

ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule(s) is/are H_2O.

In a specific embodiment, the term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range

Where the compound of this invention is substituted with a basic moiety, acid addition salts may be formed. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate,

methylene-bis-β-hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

Acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by

dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The compounds of this invention can be regenerated from the acid addition salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial effects inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, trimethylammonia, triethylammonia, ethylenediamine, n-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, n-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The compounds of this invention can be regenerated from the base addition salts by the application or adaptation of known methods. For example, parent compounds of the invention

can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

It will be appreciated that compounds useful according to the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds useful according to the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula I or formula II hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallisation techniques, or they are separately prepared from the appropriate isomers of their intermediates.

Compounds of this invention may also exhibit geometrical isomerism. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl or alkenylenyl moieties. The present invention comprises the individual geometrical isomers and stereoisomers and mixtures thereof.

For the propose herein it is understood that tautermeric forms are included in the recitation of a given group, e.g., thio/mercapto or oxo/hydroxyl.

Preferred Embodiments

Another preferred aspect of the invention is a compound of formula I, wherein q is 0 and Z is absent.

Another preferred aspect of the invention is a compound of formula I, wherein q is 0, r is 1 and Z is absent.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylcycloalkyl, fused arylheteroclyl, optionally substituted fused arylheterocyclenyl, or optionally substituted aryl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is optionally substituted azaheteroaryl, optionally substituted azaheterocyclyl, optionally substituted azaheterocyclenyl, optionally substituted fused arylazaheteroclylyl, optionally substituted fused arylazaheterocyclenyl, optionally substituted fused heteroarylazaheteroclylyl, optionally substituted fused heteroarylazaheterocyclenyl, optionally substituted fused azaheteroarylcycloalkyl, optionally substituted fused azaheteroarylcycloalkenyl, optionally substituted azaheterocyclyl, or optionally substituted heterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is optionally substituted with one or more groups selected from amino, carbamoyl, acylamino, heteroaryl, heterocyclenyl, heterocyclyl, alkyl, alkyloxycarbonyl, amidino, hydroxy, alkoxy, aryl, isourea, guanidino, acylhydrazino, acyl, cyano, carboxy, sulfamoyl, or halo.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is optionally substituted with one of more groups selected from aralkylamino, heteroaralkylamino, heterocyclylalkylamino, heterocyclenylalkylamino, alkylcarbamate, aminoalkylamino, aryloxycarbonylalkyl, heteroaryloxycarbonylalkyl, heterocycloxycarbonylalkyl, heterocyclenyloxycarbonylalkyl, and alkoxycarbonylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 optionally contains at least substituent selected from oxime and oxo when Cy_2 is cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused arylcycloalkenyl, fused arylheterocyclyl, fused arylheterocyclenyl, fused heteroarylcycloalkyl, fused heteroarylcycloalkenyl, fused heteroarylheterocyclyl or fused heteroarylheterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_2, R_{2a}, R_4, or R_{4a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_4, and R_{4a} taken together form O or S.

Another preferred aspect of the invention is a compound of formula I, wherein R_4, and R_{4a} taken together form O.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_2 and R_{2a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_4 and R_{4a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_4 and R_{4a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_4 is optionally substituted lower alkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_4 is alkoxyalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxycarbonylalkyl, hydroxyalkyl, acylalkyl, acylaminoalkyl or carbamoylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_2 is optionally substituted lower alkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_2 and R_{2a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_2 alkoxyalkyl, alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or heterocyclylalkyloxycarbonyl, and R_{2a} is hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 and R_{1a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 is lower alkyl, carboxy, alkoxycarbonyl or carbamoyl, and R_{1a} is hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 is alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl or carbamoylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cyclohexyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cyclohexenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein L_1 is absent, optionally substituted alkylene, optionally substituted alkenylene, -C(O)NR_5-, -S(O)p-, -C(O)-, -C(O)Y-C(X)Y-, -C(O)O-, C(O)NR_5-S(O)p-, -C(O)-C(O)NR_5S(O)p-, -S(O)pNR_5-, -C(O)-alkylene-O-, -C(O)-alkenylene-O-, -S(O)p-alkenylene-, -S(O)p-alkylene-, -C(O)-alkylene-C(O)-, -C(O)-alkylene-S(O)p-, -S(O)p-alkylene-C(O)-, -C(O)-alkylene, -C(O)-alkenylene-, - alkylene-C(O)NR_5-, or -C(O)CH(OH)-alkylene-.

Another preferred aspect of the invention is a compound of formula I, wherein L_1 is methylene, -C(O)-alkylene-O-, -C(O)-alkenylene-, -S(O)p-alkenylene-, -C(O)C(O)NR_5- or -S(O)p-.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_1 is optionally substituted aryl, heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycolalkenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_1 is optionally substituted aryl, heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl or optionally substituted cycolalkenyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_1 is optionally substituted with one of more groups selected from amino, halo, hydroxyl, aryl, heteroaryl, amidino, alkyl, acylamino, carbamoyl, cyano, alkoxy, nitro, carbamate, sulfamyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_1 is optionally substituted with one of more groups selected from -NH_2, chloro, carbamate or aminosulfamyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_1 optionally contains at least substituent selected from oxime and oxo when Cy_1 is cycloalky, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused arylcycloalkenyl, fused arylheterocyclyl, fused arylheterocyclenyl, fused heteroarylcycloalkyl fused heteroarylcycloalkenyl, fused heteroarylheterocyclyl or fused heteroarylheterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 is alkyl, hydrogen or alkoxycarbonyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 is alkoxycarbonylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 is alkyl, R_4 is alkyl, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene- or $-S(O)_2$-alkylene- and Cy_1 is optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene- or $-S(O)_2$-alkylene-, and Cy_1 is optionally substituted aryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene- or $-S(O)_2$-alkylene-, and Cy_1 is optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene- or $-S(O)_2$-alkylene-, and Cy_1 is optionally substituted azaheteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene- or $-S(O)_2$-alkylene-, and Cy_1 is optionally substituted thiaheteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene- or $-S(O)_2$-alkylene-, and Cy_1 is optionally substituted benzothiophenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene or $-S(O)_2$-alkylene, and Cy_1 is optionally substituted indolyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene or $-S(O)_2$-alkylene, and Cy_1 is optionally substituted benzimidazolyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene or $-S(O)_2$-alkylene, and Cy_1 is optionally substituted thienyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1 is alkyl, R_4 is alkyl, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene or $-S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted heteroaryl and Cy_2 is optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene or $-S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted heteroaryl, and Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heteroaryl, optionally substituted heterocyclyl or optionally substituted heterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted heteroaryl, and Cy_2 is optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is heteroaryl, and Cy_2 is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted azaheteroaryl, and Cy_2 is optionally substituted azaheteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted thiaheteroaryl, and Cy_2 is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted benzothiophenyl, and Cy_2 is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted indolyl, and Cy_2 is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted benzimidazolyl, and Cy_2 is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R_1, R_{1a}, R_{1a},R_4, and R_{4a}, are hydrogen, L_1 is -$S(O)_2$-, -$S(O)_2$-alkenylene or -$S(O)_2$-alkylene, L_2 is alkylene, Cy_1 is optionally substituted thienyl, and Cy_2 is optionally substituted azaindolyl or optionally substituted quinazolinyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is quinazolinyl substituted by an amino substituent.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is quinazolinyl substituted by -NH_2 or -N(alkyl)$_2$.

Another preferred aspect of the invention is a compound of formula I, wherein R_2 is hydrogen, carboxyalkyl, alkoxyalkyl, hydroxyalkyl, alkoxycarbonylalkyl, acylamino or carbamoyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is N-substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is N-substituted piperdinyl and the piperdinyl moiety is attached to the parent moiety at the 4-position of the piperdinyl ring.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by a group selected from aryl or heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by an azaheteroaryl group.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by a group selected from 2-pyridyl, 4-pyridyl or 4-pyrimidyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by an optionally substituted pyrimidyl group.

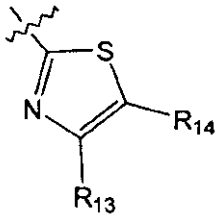
Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by a pyrimidyl group wherein said pyrimidyl group is attached to the piperdinyl moiety at the 4-position of said pyrimidyl group.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by a pyrimidyl group wherein said pyrimidyl group is substituted by an aryl group substituent, more preferably, said pyrimidyl group is substituted at its 2-position by a group selected from halogen, alkoxy, alkylthio and Y_1Y_2N-, wherein Y_1 and Y_2 are independently, hydrogen, alkyl or aralkyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is optionally subsutituted thiazolyl.

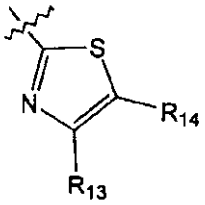
Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is thiazolyl substituted by at least one substituent selected from lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxycarbonylalkyl, carbamoylalkyl and alkoxyalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a group of formula



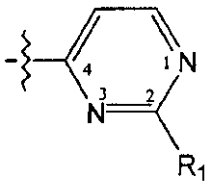
wherein R_{13} and R_{14} are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxycarbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, heterocyclenyl group, aryl group or heteroaryl group.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a group of formula



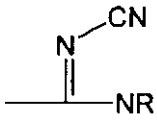
wherein R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group or heterocyclenyl group, optionally substituted with an oxo moeity.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by a pyrimidyl group of formula



R_{15} wherein R_{15} is selected from halogen, alkoxy, alkylthio and Y_1Y_2N-, wherein Y_1 and Y_2 are independently, hydrogen, alkyl and aralkyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by a group selected from alkoxycarbonyl, carbamoyl, acyl, alkyl and amidino.

Another preferred aspect of the invention is a compound of formula I, wherein Cy_2 is a piperdinyl moiety substituted on the nitrogen ring atom by  wherein R_{12} and $R_{12'}$ are independently selected from hydrogen or optionally substituted lower alkyl.

Other preferred compounds have formula I wherein m is 1; and n is 1.

Other preferred compounds have formula I wherein A is N.

Other preferred compounds have formula I wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

Other preferred compounds have formula I wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2, R_{2a} and R_4 are hydrogen; and R_{4a} is optionally substituted alkyl.

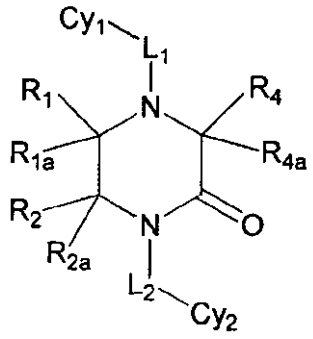
Other preferred compounds have formula I wherein R_3 and R_{3a} taken together are O; R_1, R_{1a}, R_2 and R_4 are hydrogen; and R_{2a} and R_{4a} are optionally substituted alkyl.

Other preferred compounds have formula I wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a} and R_4 are hydrogen; and R_{1a} and R_{4a} are optionally substituted alkyl.

Other preferred compounds have formula I wherein R_3 and R_{3a} taken together are O; R_1, R_2, R_{2a}, R_4 and R_{4a} are hydrogen; and R_{1a} is carboxy, alkoxycarbonyl, Y_1Y_2NCO or optionally substituted alkyl.

Other preferred compounds have formula I wherein R_3 and R_{3a} taken together are O; and R_1, R_{1a}, R_2, R_4 and R_{4a} are hydrogen; and R_{2a} is carboxy, alkoxycarbonyl, Y_1Y_2NCO or optionally substituted alkyl.

Another preferred aspect of the invention is directed to a compound of formula II



II

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof,

wherein R_1, R_{1a}, R_2, R_{2a}, R_4, R_{4a}, Cy_1, Cy_2, L_1, and L_2 are as defined in formula I.

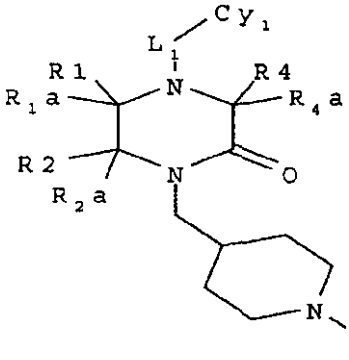
Preferred compounds have formula I or formula II wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl,

optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

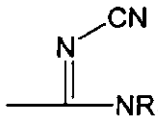
Another preferred aspect of the invention is a compound of formula I or formula II, wherein Z is absent or is selected from O, $S(O)_p$ and NR_5.

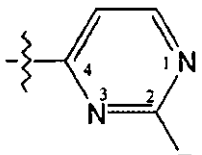
Another preferred aspect of the invention is a compound of formula I or formula II, wherein Z is $-NR_5C(O)-$ or $-C(O)NR_5-$.

Another preferred aspect of the invention is a compound of formula IIa,



IIa

wherein R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4, R_{4a}, Cy_1, and L_1, are as defined in formula I, E is alkoxycarbonyl, carbamoyl, acyl, alkyl, pyridinyl, amidino;  wherein R_{12} and $R_{12'}$ are independently selected from hydrogen or optionally substituted lower alkyl; or



wherein R_{15} is selected from halogen, alkoxy, alkylthio and Y_1Y_2N-, wherein Y_1 and Y_2 are independently, hydrogen, alkyl and aralkyl.

Another preferred aspect of the invention is a compound of formula I or formula II, wherein L_1 is $-S(O)_p-$, $-C(X)Y-$ or $-L_3-Q-L4-Q'-L5-$.

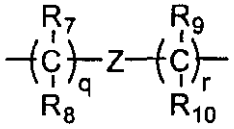
Another preferred aspect of the invention is a compound of formula I or formula II, wherein Cy_1 is optionally substituted aryl or optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I wherein R_1, R_2, R_3 and R_4 are independently alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, heterocyclyl, heterocyclenyl, heteroaryl, aryl, cycloalkyl, or cycloalkenyl or R_4 and R_{4a} taken together form O.

More preferred compounds are those having a structure of formula I or formula II, wherein L_2 is alkylene of one to three carbon atoms.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_2 is $-CH_2-$.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_2 is a group of formula



wherein Z is NR_5; q is 2; r is 0; R_5 is hydrogen or optionally substituted alkyl; and R_7 and R_8 are hydrogen.

Other more preferred compounds are those having a structure of formula I or formula II, wherein R_5 is hydrogen.

Other more preferred compounds are those having a structure of formula I or formula II, wherein Cy_2 is optionally substituted aryl or optionally substituted heteroaryl.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is $-S(O)_2-$.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is -C(X)Y-; X is O; and Y is NH.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is $-L_3$-Q-L4-Q'-L5-; Q is $-S(O)_2-$ or -C(O)-; and L_4 is optionally substituted alkenylene.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is $-L_3$-Q-L4-Q'-L5-; and L_4 is optionally substituted alkylene.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is $-L_3$-Q-L4-Q'-L5-; Q is -C(O)-; Q' is O; and L_4 is optionally substituted alkylene.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is methylene, $-L_3$-Q-L4-Q'-L5-; L_3 is optionally substituted alkylene; and L_4 is optionally substituted alkenylene.

Other more preferred compounds are those having a structure of formula I or formula II, wherein Cy_1 is optionally substituted phenyl, optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted isoquinolinyl, optionally substituted indolyl, optionally substituted thienopyridyl, optionally substituted furanyl, optionally substituted pyridyl, or optionally substituted benzimidazolyl.

Other more preferred compounds are those having a structure of formula I or formula II, wherein Cy_2 is optionally substituted phenyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted cinnolinyl, optionally substituted azaindolyl, or optionally substituted thienopyridyl.

Other more preferred compounds are those having a structure of formula I wherein A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene, sulfonyl, alkylenesulfonyl or alkylene;

Cy_1 is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroarylcycloalkyl, fused thiaheteroarylcycloalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl, thiophen-isoxazolyl, thieno-pyridineyl, benzo-thiophen, indolyl, morholinyl, aminopyridine-benzyl, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin, phenyl-triazol optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused

heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, bipyridinyl, pyridin-benzyl, thiophenyl, thiophen-benzyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl;

R_3 and R_{3a} taken together form O or S;

R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen, or carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in formula I, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

R_1 and R_{1a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in formula I, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

or R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in formula I, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl or R_4 and R_{4a} taken together with the carbon atom through which they are linked

form a 3 to 7 membered cycloalkyl or cycloalkenyl group, or R_4 and R_{4a} taken together form O or S; and m and n are each 1.

Other more preferred compounds are those having a structure of formula I wherein A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 is sulfonyl or alkylenesulfonyl;

L_2 is absent, methylene, ethylene or alkylene;

Cy_1 is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroarylcycloalkyl, fused thiaheteroarylcycloalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl, thiophen-isoxazolyl, thieno-pyridineyl, benzo-thiophen, indolyl, morholinyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl;

R_3 and R_{3a} taken together form O or S;

R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen;

R_1, R_{1a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

or the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

and m and n are each 1.

Other more preferred compounds are those having a structure of formula I wherein A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene or alkylene;

Cy_1 is thiophen-isoxazolyl, aminopyridine-benzyl, benzo-thiophen, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is bipyridinyl, amino-quinazolin, pyridin-benzyl, thiophenyl, thiophen-benzyl, pyrrolo-pyridin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

R_3 and R_{3a} taken together form O or S; and

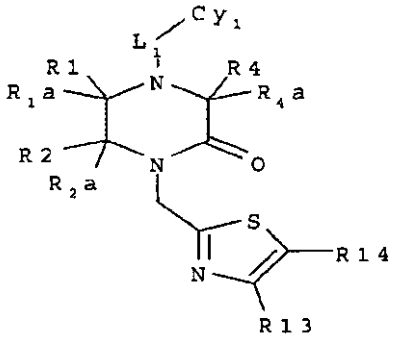
R_4 and R_{4a} taken together form O or S;

R_1, R_{1a}, R_2, R_{2a}, are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally

substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;
and m and n are each 1.

Other more preferred compounds are those having a structure of formula I wherein A is N;
G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;
L_1 and L_2 are independently absent, methylene, ethylene or alkylene;
Cy_1 is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol;
Cy_2 is amino-quinazolin or pyrrolo-pyridin;
R_3 and R_{3a} taken together form O or S;
R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1; optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; and m and n are each 1.

Another preferred aspect of the invention is a compound of formula IIb



IIb

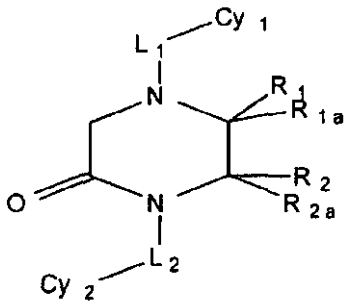
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof,

wherein L_1, Cy_1, R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are as described in compound of formula I,

R_{13} and R_{14} are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxycarbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, heterocyclenyl group, aryl group or heteroaryl group.

Another preferred aspect of the invention is a compound of formula IIb wherein R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group or heterocyclenyl group, optionally substituted with an oxo moeity.

Other preferred compounds are those which inhibit both Factor Xa and Factor IIa (thrombin) activity, having a structure of formula IIc



IIc

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein:

Cy_1 is thiaheteroaryl, benzothiopheneyl or azaheteroaryl, which are unsubstituted or substituted by halogen,

L_1 is $-S(O)_2-$, $-S(O)_2$-alkylene-, $-S(O)_2$-alkyenlene- or $-S(O)_2$-alkynylene-;

R_1, R_{1a}, R_2, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxycarbonyl, or carbamoyl; L_2 is methylene; and

Cy_2 is azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein:

Cy_1 is thiaheteroaryl or azaheteroaryl,

L_1 is $-S(O)_2-$, $-S(O)_2$-alkylene-, $-S(O)_2$-alkyenlene- or $-S(O)_2$-alkynylene-;

R_1, R_{1a}, R_2, R_{2a} are independently hydrogen, alkoxyalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, carboxyl, alkoxycarbonyl, or carbamoyl;

L_2 is methylene; and

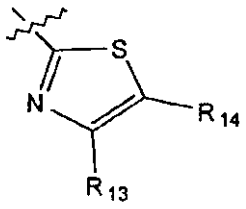
Cy_2 is azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy_2 is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdinyl.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein R_1, R_{1a}, R_2, and R_{2a} are indepedently aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

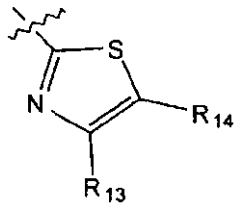
Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy_2 is an optionally substituted thiazolyl.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy_2 is is a group of formula



wherein R_{13} and R_{14} are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxycarbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, heterocyclenyl group, aryl group or heteroaryl group.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy_2 is a group of formula



wherein R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group or heterocyclenyl group, optionally substituted with an oxo or oxime substituent.

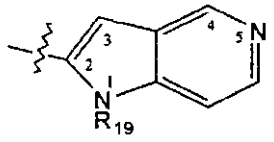
Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy_2 is optionally substituted azaindolyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy_2 is optionally substituted 5-azaindolyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein,

when Cy_2 is optionally substituted azaindolyl, the parent molecule is attached to the azaindolyl group at the 2-position.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

Cy_2 is  wherein R_{19} is hydrogen or optionally substituted alkyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

Cy_2 is optionally substituted azaindolyl;

L_1 is $-S(O)_2-$, $-S(O)_2$-alkenylene;

Cy_1 is optionally substituted thienyl or optionally substituted benzothiophenyl,

R_1 and R_2 are hydrogen;

R_{1a} and R_{2a} are independently hydrogen, alkyl, carboxyl, alkoxycarbonyl, or carbamoyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

R_1, R_{1a} and R_2 are hydrogen; and

R_{2a} is alkyl, carboxyl, alkoxycarbonyl, or carbamoyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

Cy_2 is optionally substituted azaindolyl;

L_1 is $-S(O)_2-$, or $-S(O)_2$-alkenylene;

Cy_1 is optionally substituted thienyl or optionally substituted benzothiophenyl, optionally substituted, optionally substituted bemzimidazolyl, or optionally substituted indolyl,

R_1, R_{1a} and R_2 are hydrogen; and

R_{2a} is alkyl, carboxyl, alkoxycarbonyl, or carbamoyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

R_1, R_2 and R_{2a} are hydrogen; and

R_{1a} is alkyl, carboxyl, alkoxycarbonyl, or carbamoyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

Cy_2 is optionally substituted azaindolyl;

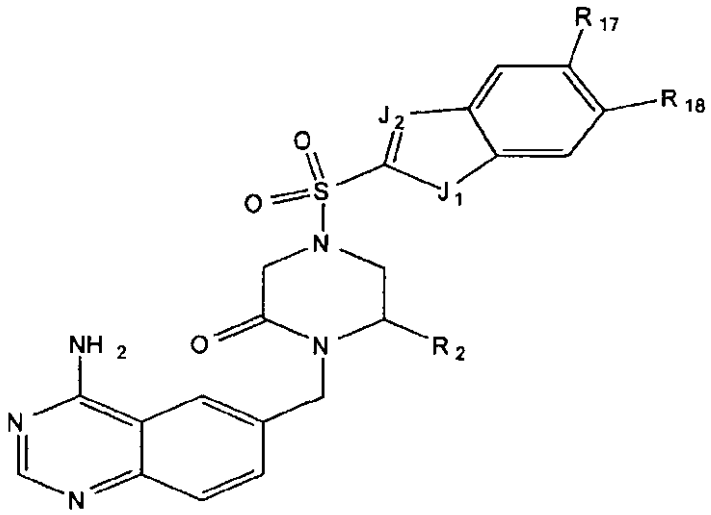
L_1 is $-S(O)_2-$, or $-S(O)_2$-alkenylene;

Cy_1 is optionally substituted thienyl or optionally substituted benzothiophenyl,

R_{1a} is alkyl, carboxyl, alkoxycarbonyl, or carbamoyl; and

R_1, R_2 and R_{2a} are hydrogen.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IId



IId

wherein R_{17} and R_{18} are independently hydrogen or halogen;

J_1 is S or NH;

J_2 is CH or N; and

R_2 is hydrogen, alkyl, carboxyl, alkoxycarbonyl, or carbamoyl.

Another preferred aspect of the invention is a compound of formula IId wherein R_2 is heterocyclylalkyloxycarbonyl, heterocyclenylalkyloxycarbonyl, heteroaralkyloxycarbonyl, arylalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, or cycloalkenylalkyloxycarbonyl.

Another preferred aspect of the invention is a compound of formula IId wherein R_2 is heterocyclylalkylcarbamoyl, heterocyclenylalkylcarbamoyl, heteroaralkylcarbamoyl, arylalkylcarbamoyl, cycloalkylcarbamoyl, or cycloalkenylcarbamoyl.

Another preferred aspect of the invention is a compound of formula IId wherein R_2 is heterocyclyl, heterocyclenyl, heteroaryl, aryl, cycloalkyl, or cycloalkenyl.

Another preferred aspect of the invention is a compound of formula IId wherein R_2 is heterocyclylalkyloxycarbonylalkyl, heterocyclenylalkyloxycarbonylalkyl, heteroaralkyloxycarbonylalkyl, arylalkyloxycarbonylalkyl, cycloalkylalkyloxycarbonylalkyl, or cycloalkenylalkyloxycarbonylalkyl.

Another preferred aspect of the invention is a compound of formula IId wherein R_2 is heterocyclylalkylcarbamoylalkyl, heterocyclenylalkylcarbamoylalkyl, heteroaralkylcarbamoylalkyl, arylalkylcarbamoylalkyl, cycloalkylcarbamoylalkyl, or cycloalkenylcarbamoylalkyl.

Another preferred aspect of the invention is a compound of formula IId wherein R_2 is alkoxyalkyl, hydroxyalkyl or aminoalkyl.

Another preferred aspect of the invention is a compound of formula IId wherein R_2 is alkyl(H)N-alkyl-.

Compounds contemplated as falling within the scope of this invention, include, but are not limited to

Preferred compounds wherein Z is $-NR_5C(O)-$ or $-C(O)NR_5-$ are selected from

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

Preferred intermediates according to this invention have formula III wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

Other preferred intermediates according to this invention have formula III wherein Z is absent.

Other preferred intermediates according to this invention have formula III wherein R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are hydrogen.

Other preferred intermediates according to this invention have formula II, wherein L_1 and L_2 independently are methylene, ethylene, propylene or butenylene; R_1, R_{1a}, R_2, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxycarbonyl, or carbamoyl; Cy_1 is heteroaryl, thiaheteroaryl, biheteroaryl, thiophenyl, isoxazolyl, isoxazolyl-thiophenyl or azaheteroaryl, which are unsubstituted or substituted by halogen; Cy_2 is azaheteroaryl, quinazolin, amino-quinazolin or 4-aminoquinazolin.

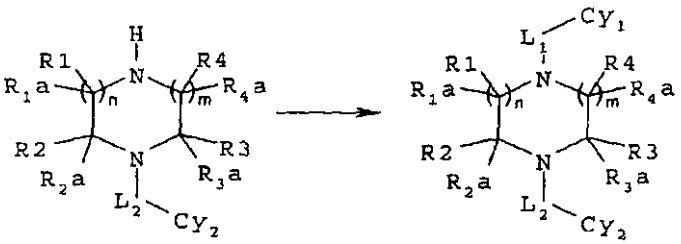
More preferred intermediates according to this invention are selected from
(2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,
(3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
(3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
(2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,
(3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,
(3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one,
4-(2-Oxopiperazin-1-ylmethyl)benzamidine,
1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one,
1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one,
2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester,
2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,
2-(2-(±)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester,

1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one,
1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one,
4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester,
1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one,
1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one,
1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one,
1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) l-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one,
(3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one,
1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one,
1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one,
1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one,
1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one trifluroacetate,
1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one,
1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one,
4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester,
4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester
4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.
4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one,
(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester and
(±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Preparation of the Compounds of the Invention

A general route to the compounds of this invention wherein A is N and R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4, R_{4a}, L_1, L_2, Cy_1, Cy_2, m and n are defined for Formula I above is outlined in Scheme 1.

Scheme 1

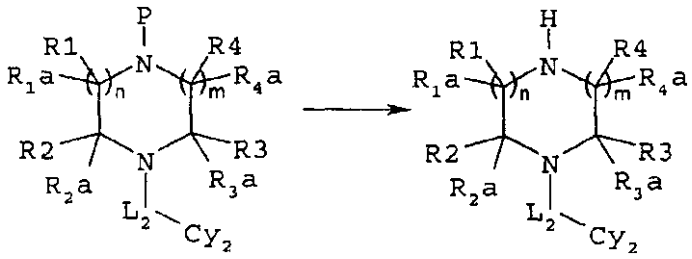


III I'

As outlined in Scheme 1, coupling of a compound of formula III with a sulfonyl chloride, an alkyl halide, an acid or an activated derivative thereof, such as an acid anhydride or acid chloride, an isocyanate, chloroformate or activated sulfamoyl ester in an appropriate solvent, generates the compound of formula I in which the L_1-Cy_1 portion is a sulfonamide, alkyl amine, amide, urea, carbamate or sulfamyl urea, respectively. Sulfonamide formation is accomplished with a base such as a trialkylamine in an inert solvent such as dichloromethane, THF or acetonitrile at about 0 °C to about 100 °C in the presence or absence of an activating agent such as dimethylaminopyridine (DMAP). Alkyl amine formation can be achieved with a suitable base such as K_2CO_3 or trialkylamine in an appropriate solvent such as DMF or acetonitrile at about 0 °C to about 100 °C. Amide, urea, carbamate and sulfamyl urea formation can be conducted with acids and coupling reagents such as EDC or TBTU or with any variant of reactive acid derivatives and the use of an appropriate base additive such as triethylamine, N-methylmorpholine or diisopropylethylamine.

The preparation of a compound of formula III wherein R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4, R_{4a}, L_2, Cy_2, m and n are as defined herein from formula 1, is outlined in Scheme 2.

Scheme 2

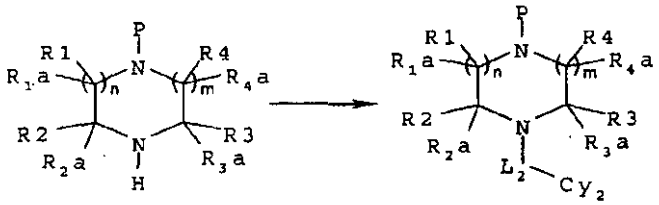


III' III

As outlined in Scheme 2, a compound of formula III is prepared by removing a nitrogen protecting group P from the compound of formula III'. In a preferred aspect, P is an alkyl, aralkyl or aryl carbamate moiety, which is removed using strong acid, strong base or catalytic hydrogenation in an appropriate solvent such as methanol or ethanol.

The preparation of a compound of formula III' wherein R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4, R_{4a}, L_1, L_2, Cy_1, Cy_2, m and n and P are defined herein is outlined in Scheme 3.

Scheme 3

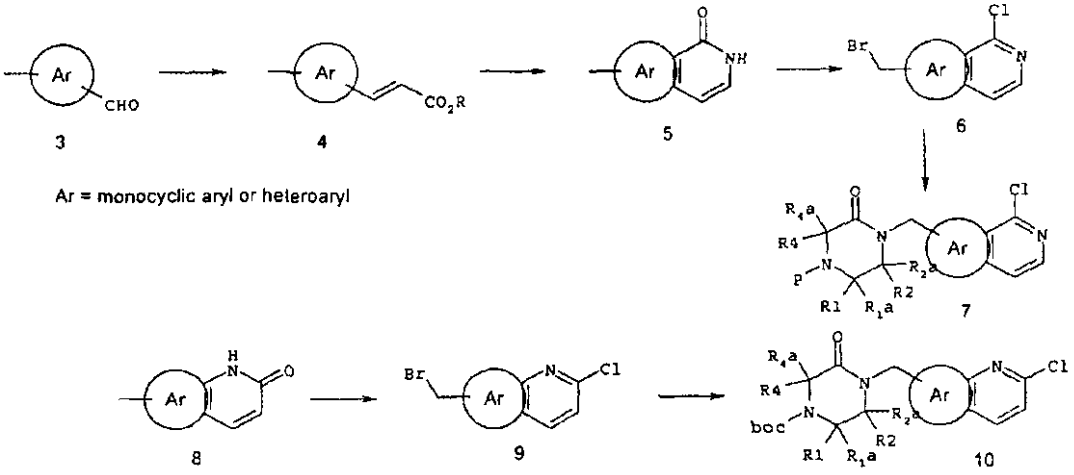


IV III'

As indicated in Scheme 3, the compound of formula III' is obtained by coupling a compound of formula IV with an appropriate Cy_2-L_2-LG compound wherein LG is a leaving group, such as chloro, bromo, iodo, or optionally substituted lower alkylsulfonyloxy or arylsulfonyloxy, in an inert organic solvent, such as THF, Et_2O or DMF, in the presence of a strong base such as NaH, lithium hexamethyldisilylazide or lithium diisopropylamine. In a preferred aspect, P is an alkyl, aralkyl or aryl carbamate group.

The preparation of intermediate compounds of formula 7 and 10 is outlined in Scheme 4.

Scheme 4



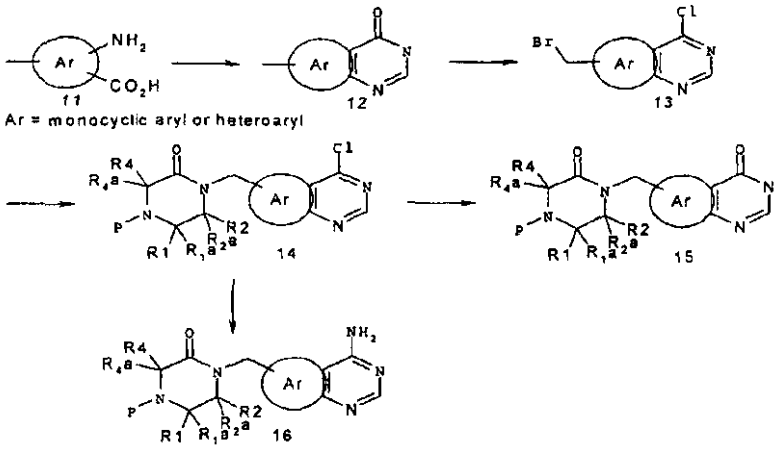
As indicated in Scheme 4, reacting a compound of formula 3 with an appropriate malonic acid in a polar , such as pyridine or ethanol, and a base, such as piperidine or pyridine, at reflux provides a compound of formula 4 wherein R is H. Alternatively, a compound of formula 3 may be reacted with a suitable Wittig or Horner-Emmons reagent in an inert solvent such as THF to give a compound of formula 4 wherein R is lower alkyl. When R is lower alkyl, the ester is hydrolyzed to the corresponding carboxylic acid (R is H) using an appropriate strong acid or alkali base. The corresponding acid is converted to the acid chloride using standard reagents such as thionyl chloride, or is converted to the mixed anhydride in a polar solvent, such as acetone or THF, to form an activated acyl compound. The activated acyl compound is then treated with a solution of NaN_3 in water at about -10 °C to about 25 °C to yield the corresponding acyl azide. The acyl azide compound is then heated slowly in an inert solvent such as benzene or toluene at about 60 °C to about 110 °C and then concentrated in vacuo and heated in a higher boiling inert solvent, such as 1,2-dichlorobenzene or phenyl ether, at about 180 °C to about 240 °C with a catalyst such as iodine or tributylamine to obtain a compound of formula 5. Alternatively the acyl azide compound can be added directly to a high boiling inert solvent, such as phenyl ether, at about 180 °C to about 240 °C with a catalyst such as iodine or tributylamine to obtain the compound of formula 5.

A compound of formula 8, prepared as described in Syn., 739 (1975), the contents of which are hereby incorporated herein by reference, or a compound of formula 5 above, may be chlorinated using standard reagents such as $POCl_3$ or $POCl_3/PCl_5$ and halogenated using standard conditions, such as N-halosuccinimide and benzoyl peroxide in an inert solvent such as carbon tetrachloride, to give the corresponding chloro-halomethyl compounds 6 and 9, respectively. Compounds of formula 6 or 9 are coupled to compounds of formula IV, in which

R3 and R3a taken together form oxo, under basic condition employing NaH, or KOtBu or some other deprotonating base, to give compounds of formula 7 or 10.

The preparation of aminoquinazoline, quinazolinone or amino-thienopyrimidine intermediates is outlined in Scheme 5.

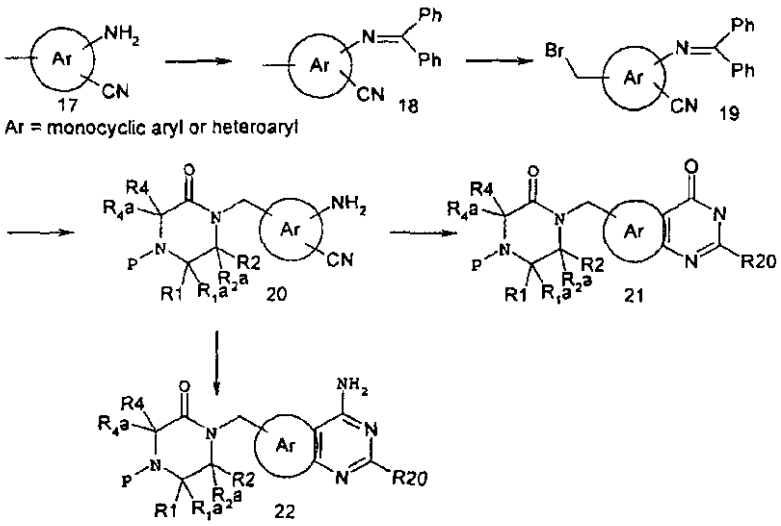
Scheme 5



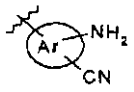
As shown in Scheme 5, an aminoheteroaryl carboxylic acid or an aminoarylcarboxylic acid of formula 11, in which the amino and carboxylic acid are ortho to each other, is treated with formamidine under heat to form the corresponding quinazolinone or thienopyrimidinone 12. The quinazolinone or thienopyrimidinone 12 is then converted to the chloroquinazoline or chlorothienopyrimidine using a chlorinating reagent such as $P(O)Cl_3$ and heat. The chloroquinazoline or chlorothienopyrimidine is brominated at the benzylic carbon using radical bromination conditions. Alternatively, a chloroquinazoline or chlorothienopyrimidine, containing a hydroxy-methylene group is converted to the corresponding bromide using CBr_4/PPh_3; or PBr_3. The bromide 13 is then reacted with the anion of the ring nitrogen of a compound of formula III, formed using NaH, $LiN(SiMe_3)_3$, $NaN(SiMe_3)_3$, LDA, lithium alkoxide, sodium alkoxide or an appropriate base, in an inert solvent such as THF, DMF, ether, or DME. This yields compounds of formula 14 which contain a chloro-quinazoline or a chloro-thienopyrimidine group. The chloro group is converted to an amino group using NH_3 in ethanol in the presence of a catalytic amount of acid, such as HOAc to give compounds of formula 16. Alternatively, the chloro group is converted to a substituted amino group using a primary or secondary amine in an inert solvent. Alternatively, the chloro group is converted to a hydroxy group using acetic acid in water with heating or using a hydroxide source to give compounds of formula 15. Alternatively, the chloro is converted to an alkoxy group using an alcoholic solvent with heated in the presence of a base.

An alternative synthesis of quinazolines and thienoquinazolines is outlined in Scheme 6.

Scheme 6.



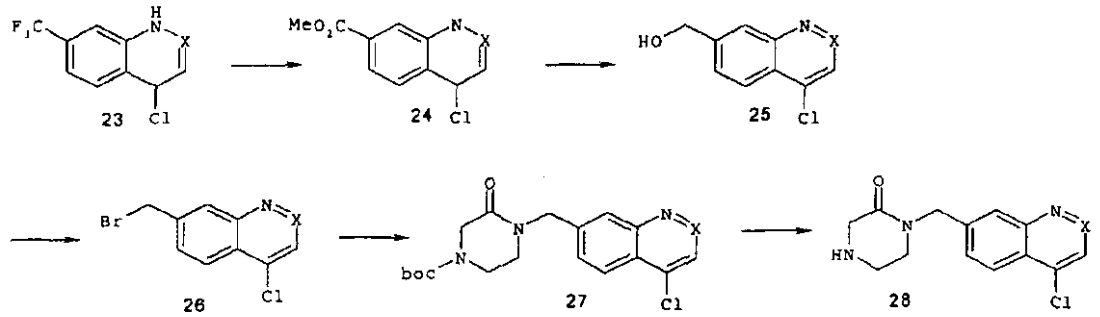
As shown in Scheme 6, an amino-aryl nitrile or an amino heteroaryl nitrile 17 is treated with an aldehyde or ketone under imine forming conditions. The corresponding aryl or heteroaryl imine is brominated using radical bromination with NBS. The bromide is then coupled with compounds of formula IV under basic conditions, such as NaH, $LiN(SiMe_3)_3$, $NaN(SiMe_3)_3$, LDA, lithium alkoxides, sodium alkoxides or an appropriate base, in an inert solvent, such as THF, DMF, ether, or DME. This yields compounds of formula 20 in which



is an imino-aryl nitrile or an imino heteroaryl nitrile. The imine is deprotected using an acid such as HCl to give the corresponding aniline. The aniline-aryl-nitrile or the aniline-heteroaryl nitrile 20, is converted to the amino-quinazoline or thienopyrimidine, formula 22 (in which R_{20}=H), using triazine or formamidine. The quinazolinone or thienopyrimidinone, formula 21, in which R_{20}=H, is formed from a compound of formula 20 using formamide. Alternatively, compounds of formula 20 can be reacted under acid conditions, such as HCl (gas) in a solvent such as ethanol in the presence of a nitrile, to give compounds of formula 22 in which R_{20} is alkyl, aryl or amino depending on the group attached to the nitrile.

The preparation of cinnoline (X = N) and quinoline (X = CH) intermediates is outlined in Scheme 7.

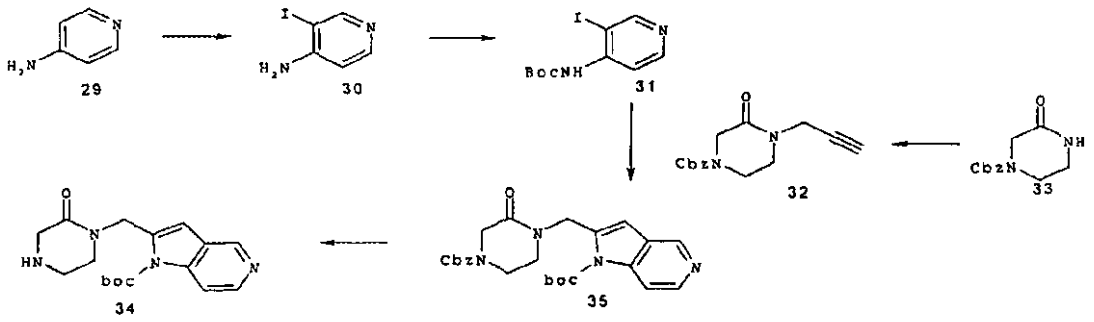
Scheme 7



As shown in Scheme 7, halogenated azaarenes 23, exemplified by 4-chloro-7-trifluoromethylquinoline or cinnoline, are treated with H_2SO_4 (70 -95 %) at 180-220 °C for about 16 to 48 hours in a sealed reaction vessel. The solution is cooled, poured into water and neutralized with base to pH ~ 3-4. The product is dissolved in aqueous base and precipitated by acidification to yield 7-carboxy-4-chloroquinoline or cinnoline. This material is converted to the alkyl ester, such as methyl (24) or ethyl, by standard methods. 7-Alkyloxycarbonyl-4-chloroquinoline or cinnoline is dissolved in an anhydrous, aprotic solvent (THF or ether). The solution is cooled (-60 to -95 °C) and treated with a reducing agent such as lithium aluminum hydride. The solution is warmed (to approximately -40 to -50 °C) for about 15 to 30 minutes and quenched with a solvent such as ethyl acetate. Standard workup gives the product 7-hydroxymethyl-4-chloroquinoline, or cinnoline (25). Material 25 is treated with 45-50 % HBr and heated to about 100-140 °C for about 45 to 90 minutes. After cooling and standard workup, 7-bromomethyl-4-chloroquinoline (or cinnoline) 26 is obtained. Alkylation as described before provides 4-chloroquinoline (or cinnoline) 27 followed by deprotection under the usual acidic conditions gives 4-chloroquinoline (or cinnoline) 28.

The preparation of pyrrolopyridine derivatives is outlined in Scheme 8.

Scheme 8

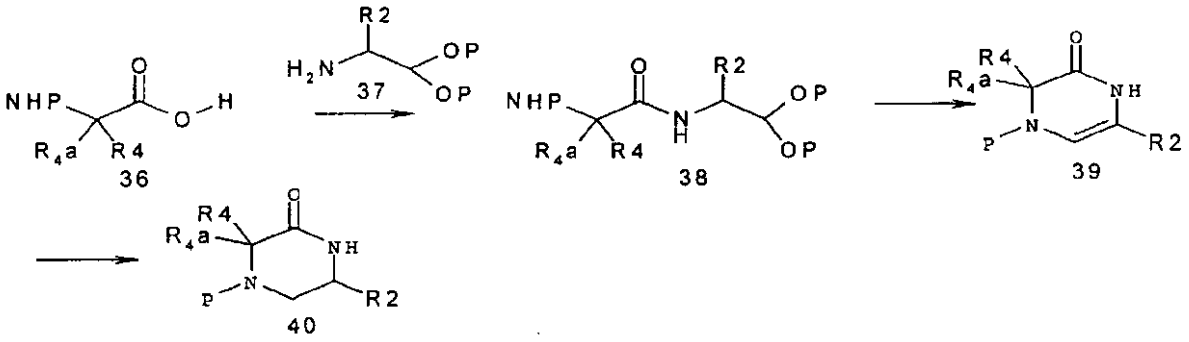


As indicated in Scheme 8, pyrrolopyridine derivatives are prepared by alkylation of a suitably protected oxopiperazine 33 with propargyl bromide in the presence of a base such as sodium hydride. The resulting alkyne 32 is heated (100-120 °C) with a halopyridine 31,

optionally substituted with hydroxy, alkoxycarbonylamino, or sulfhydryl, a catalyst, such as $Pd(PPh_3)_2Cl_2$, copper iodide and triethylamine, in a suitable solvent, such as acetonitrile, in a sealed vessel or in DMF for 2-20 hours. When the pyridine is substituted with an alkoxycarbonylamino moiety, additional treatment with DBU at about 60 °C in DMF yields pyrrolopyridine 35. Subsequent carbamate deprotection using transfer hydrogenation conditions such as Pd black in formic acid yields the desired oxopiperazine pyrroloopyridines 34. After further reaction of 34 with the L_1-Cy_1 group, an additional deprotection step such as Boc removal using, for example, TFA, HCl is required for generating the oxopiperazine pyrrolopyridines with L_1-Cy_1 in place. Halopyridine 31 is prepared from iodination of 4-aminopyridine 29 to give iodo-aminopyridine 30 followed by Boc protection.

The preparation of compounds of formula 40 is outlined in Scheme 9.

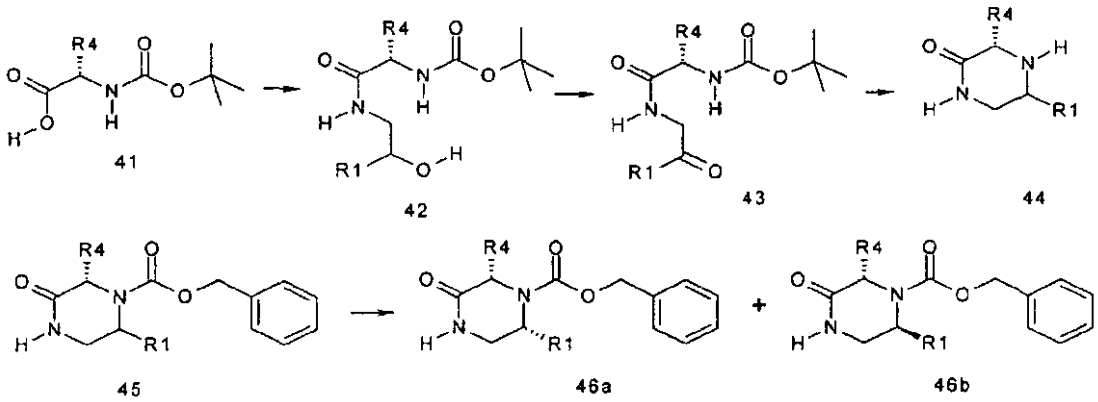
Scheme 9



As shown in Scheme 9, compounds of formula 40 are prepared from an appropriately protected mono- or di- substituted amino-acid 36. To this is added an amino-acetaldehyde, protected as an acetal derivative 37, under standard peptide coupling procedures, employing activating reagents such as EDC, TBTU, or BOP. The resulting dipeptidyl moiety 38 is subjected to conditions which remove the acetal, such as acidic conditions (TsOH). The resulting cyclic material 39 is reduced using hydrogenating conditions to yield a compound of formula 40. This reduction, alternatively, can be carried out using a reagent which acts as a hydride source, such as LAH or NaH..

The preparation of compounds of formula 46a and 46b is outlined in scheme 10.

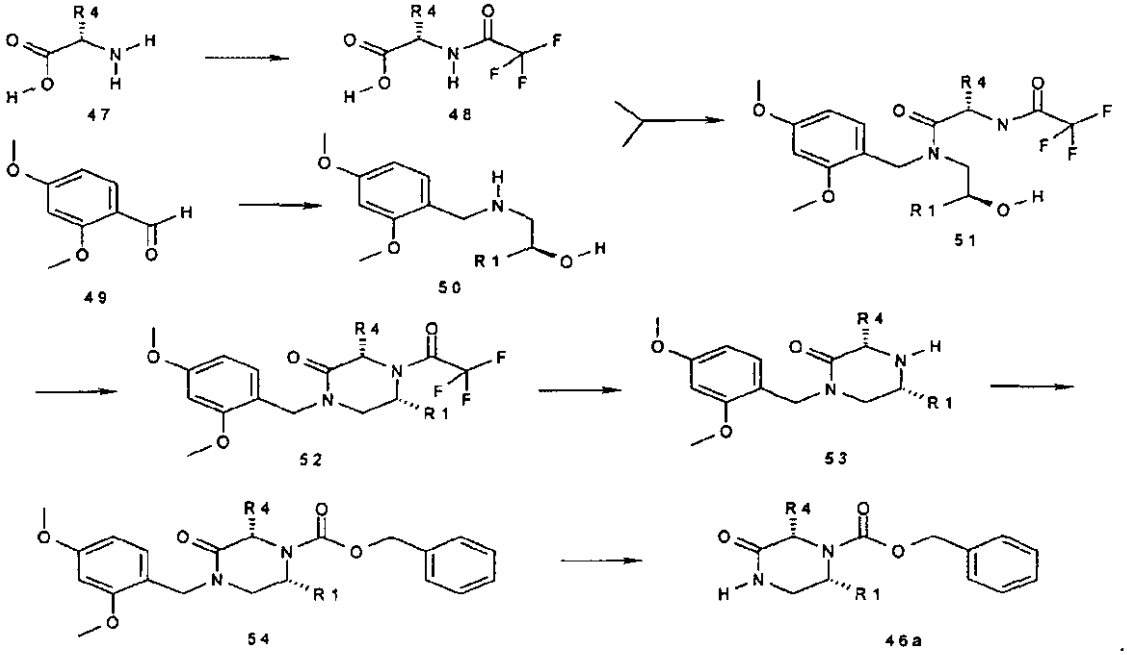
Scheme 10.



As inidcated in Scheme 10, a protected amino acid 41 is coupled to a beta-aminoalcohol using standard peptide coupling procedures (iso-propyl chloroformate and triethylamine). The alcohol 42 is then oxidized to a ketone 43 using, for example, Swern oxidation conditions. The protecting group is removed with trifluoroacetic acid and the resulting cyclized compound is reduced under hydrogenation conditions to give the 2-piperidinone 44. The piperazin-2-one ketopiperazine is reacted with N-(benzyloxycarbonyloxy)-succinimide to give a mixture of diastereomers 45 which are separated by chromatographic methods, or in some cases by recrystallization, to give compounds 46a and 46b.

A chiral synthesis of compounds of formula 46a is outlined in Scheme 11.

Scheme 11

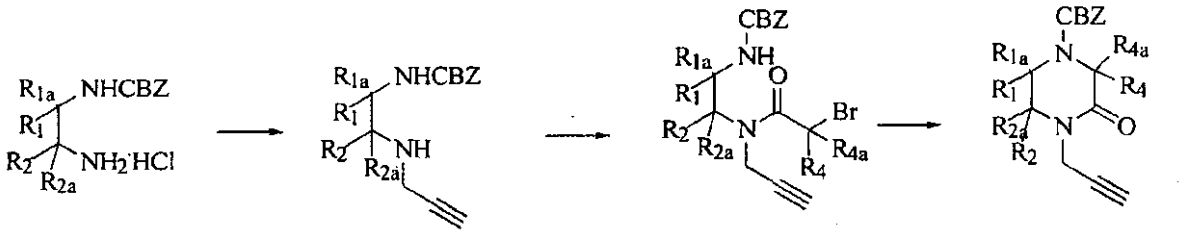


As shown in Scheme 11, amino acid 47 is protected as its trifluoroacetate derivative using trifluoroacetic anhydride and a base to yield compound 48. Amino-alcohol 50 is obtained via reductive amination conditions using a benzaldehyde derivative, such as 2,4-

dimethoxybenzaldehyde 49 and the corresponding primary amine. The resulting amino-alcohol 50 is then coupled to amino-acid 48 using standard peptide coupling procedures (iso-propyl chloroformate and triethylamine) to afford compound 51. Ring closure of compound 51 is then accomplished by utilizing Mitsinobu conditions to yield 2-piperidinone 52. The trifluoroacetate group of compound 52 is removed under basic conditions to give amine 53, which reacts with N-(benzyloxycarbonyloxy)succinimide to give carbamate 54. Deprotection of compound 54 is achieved with an aqueous solution of potassium persulfate and sodium phosphate and heat to produce compound 46a. All possible enantiomers of piperazin-2-one, shown in scheme 2c, can be made from the corresponding amino-alcohol 50 and amino acid 47.

The preparation of the compound of formula 58 wherein R_1, R_2, R_{2a} ,R_4 and R_{4a} are hydrogen and R_{1a} is carbomethoxy, methoxymethyl, or a protected hydroxymethyl group is shown in Scheme 12.

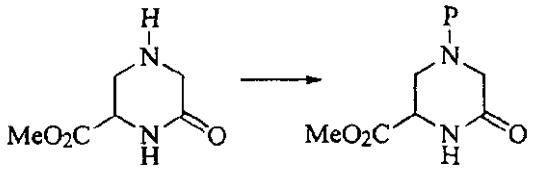
Scheme 12



As shown in Scheme 12, alkynylating a compound of formula 55 with propargyl bromide in the presence of an amine base such as triethylamine provides the compound of formula 56. Coupling with bromoacetic acid using a standard reagent such as DCC gives the compound of formula 57, which can be cyclized using a non-nucleophilic strong base, such as NaH, in a solvent, such as THF, to yield the desired compound of formula 58.

The preparation of a compound of formula 59 is outlined in Scheme 13.

Scheme 13



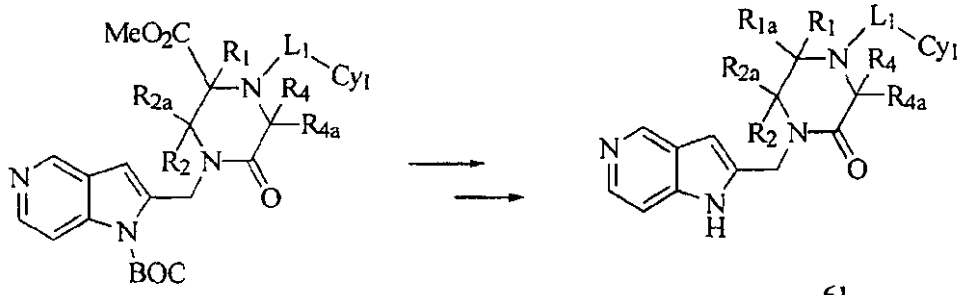
59

As indicated in Scheme 13, protection of methyl 6-oxopiperazine-2-carboxylate (Aebischer, B., Helv. Chim. Acta 1989, 72, 1043-1051) using, for example, benzyl chloroformate or allyl chloroformate under standard conditions provides compound 59.

Alkynylation of 59 with propargyl bromide using a strong base such as NaH in polar solvents as THF or DMF provides the compound of formula 58 (Scheme 12).

The preparation of a compound of formula 61 wherein R_1, R_2, R_4, R_{4a}, L_1 and Cy_1 are as defined in formula I above, and R_{1a} and R_{2a} are independently carboxy, acetamido or hydroxymethyl, is outlined in Scheme 14.

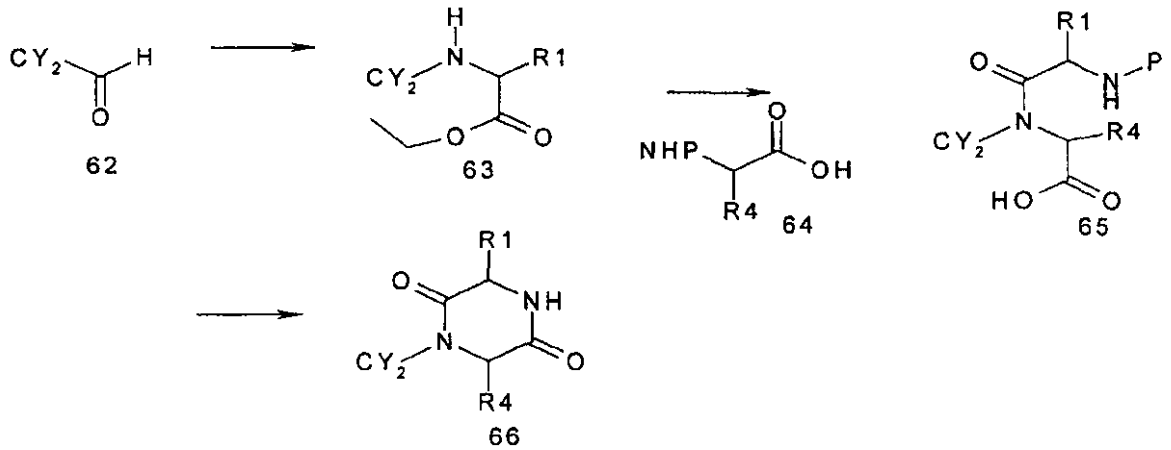
Scheme 14



As shown in Scheme 14, the compound of formula 61 is prepared by hydrolysis of the corresponding ester 60 using a base such as NaOH or LiOH to yield the acid 61. Coupling the acid with a primary or secondary amine or ammonia using standard coupling reagents such as TBTU or EDC gives the amide 61. Alternatively, reduction of the ester 60 using a reducing agent such as $NaBH_4$ yields a hydroxymethyl resin of 61.

The preparation of diketopiperazine compounds of formula 66 is outlined in Scheme 15.

Scheme 15

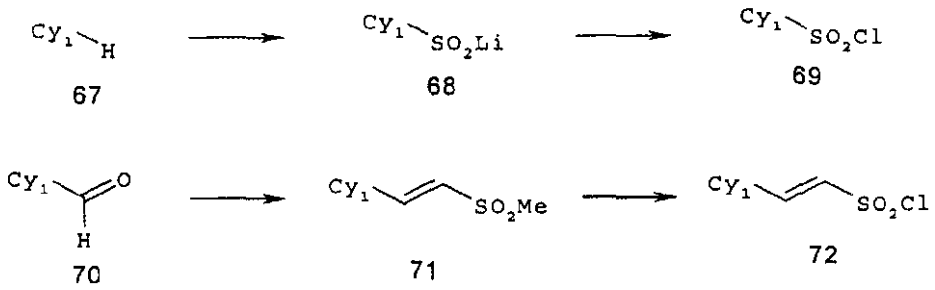


As shown in Scheme 15, an aldehyde 62 containing the Cy_2 group is condensed with an amino acid ester under reductive amination conditions. The resulting secondary amine 63 is then coupled to an N-protected amino acid 64. The resulting dipeptide 65 is deprotected which, in general, results in cyclization to the N-Cy_2 diketopiperazine 66. Alternatively, for dipeptides

65 which do not cyclize, diketopiperazine 66 formation can be achieved using a peptide coupling reagent such as EDC, TBTU, or BOP.

The preparation of sulfonyl chloride intermediates 69 and 72 is outlined in Scheme 16.

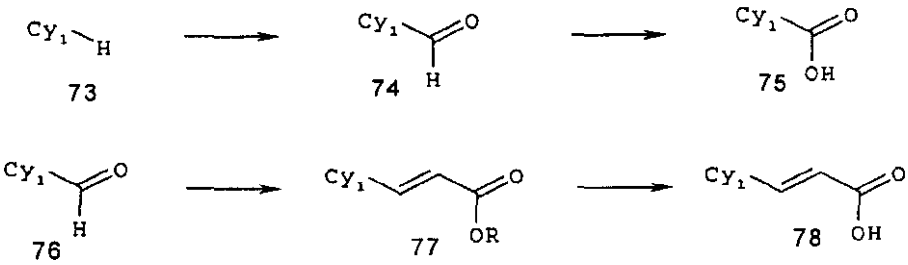
Scheme 16



As shown in Scheme 16, Cy_1 substituted sulfonyl chlorides 69 and 72 are prepared by treatment of the appropriate aryl or heteroaryl compounds 67 with a strong base such as n-BuLi at -78 °C followed by the addition of SO_2 gas and treatment of the resulting lithium aryl or heteroaryl sulfonate 68 with a chlorinating agent such as NCS or SO_2Cl_2 to yield compound 69 or, alternatively, by homologation of the appropriate aryl or heteroaryl aldehydes 70 using, for example, ethylmethanesulfonate to yield compound 71 and ethylchlorophosphonate to yield compound 72.

The preparation of intermediate compounds 75 and 78 of formula Cy_1-CO_2H is outlined in Scheme 17.

Scheme 17

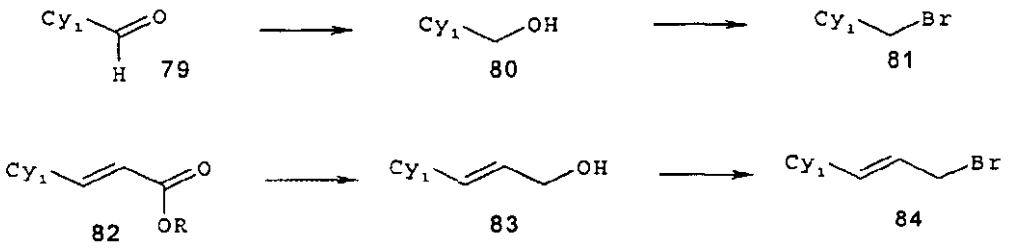


As shown in Scheme 17, the requisite Cy_1 acids 75 and 78 can be obtained by oxidation of the corresponding alcohols or the aldehydes 74 using, for example, MnO_2, PDC or $AgNO_3$ in an appropriate solvent, such as CH_2Cl_2 or H_2O/EtOH. The Cy_1 substituted aryl and heteroaryl groups 73 can be functionalized by deprotonation methods using an appropriate non-nucleophilic base such as n-BuLi in an appropriate solvent such as Et_2O or THF and quenching with an appropriate carbonyl electrophile such as DMF, CO_2 or alkyl chloroformate. Alternatively, the acids can also be generated by hydrolysis of the corresponding esters 77

using, for example, NaOH or LiOH. For example, in the acrylic esters, the Cy_1-(alkenylene)-groups as defined above are generated by homologation of the Cy_1 aldehydes 76 using the usual Wittig type or Horner-Emmons type reagents in an appropriate solvent such as CH_2Cl_2 or THF.

The preparation of Cy_1 alkyl (81) and alkenyl (84) halides is outlined in Scheme 18.

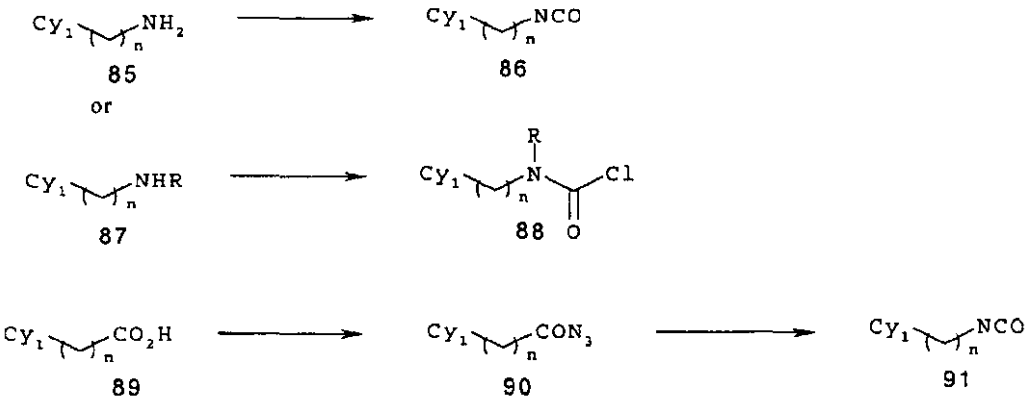
Scheme 18



As shown in Scheme 18, Cy_1 alkyl and alkenyl halides 81 and 84 can be prepared by halogenation of the corresponding alcohols 80 and 83 using either NBS, CBr_4 or PBr_3 under standard solvent conditions. The alcohols are generated by reduction of the corresponding aldehydes 79 or esters 82 using $NaBH_4$ or DIBAL in an appropriate solvent.

The preparation of Cy_1 isocyanate intermediates 86, 88 and 91 is outlined in Scheme 19.

Scheme 19

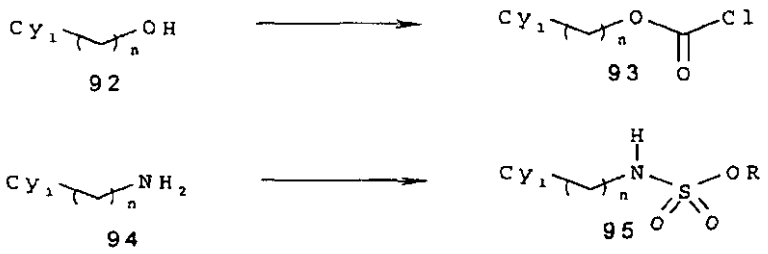


As shown in Scheme 19, Cy_1 isocyanates 86 and 88 are obtained by chlorocarbonylation methods using phosgene or triphosgene in an appropriate solvent such as CH_2Cl_2 with an appropriate base additive such as triethylamine or pyridine on the corresponding primary or secondary amines 85 and 87. Alternatively, the isocyanates 91 can also be generated by Curtius rearrangement in an appropriate solvent such as toluene, p-dioxane or DMF of the corresponding Cy_1 carbonyl azides 90. The carbonyl azides 90, in turn, are derived

from the corresponding carboxylic acids 89 using either DPPA reagent or by proceeding through the mixed anhydride via an alkyl chloroformate reagent in an appropriate solvent such as DMF or acetone and using an appropriate base additive such as treithylamine.

The preparation of Cy_1 chloroformate intermediates 93 and sulfamoyl esters 95 is outlined in Scheme 20.

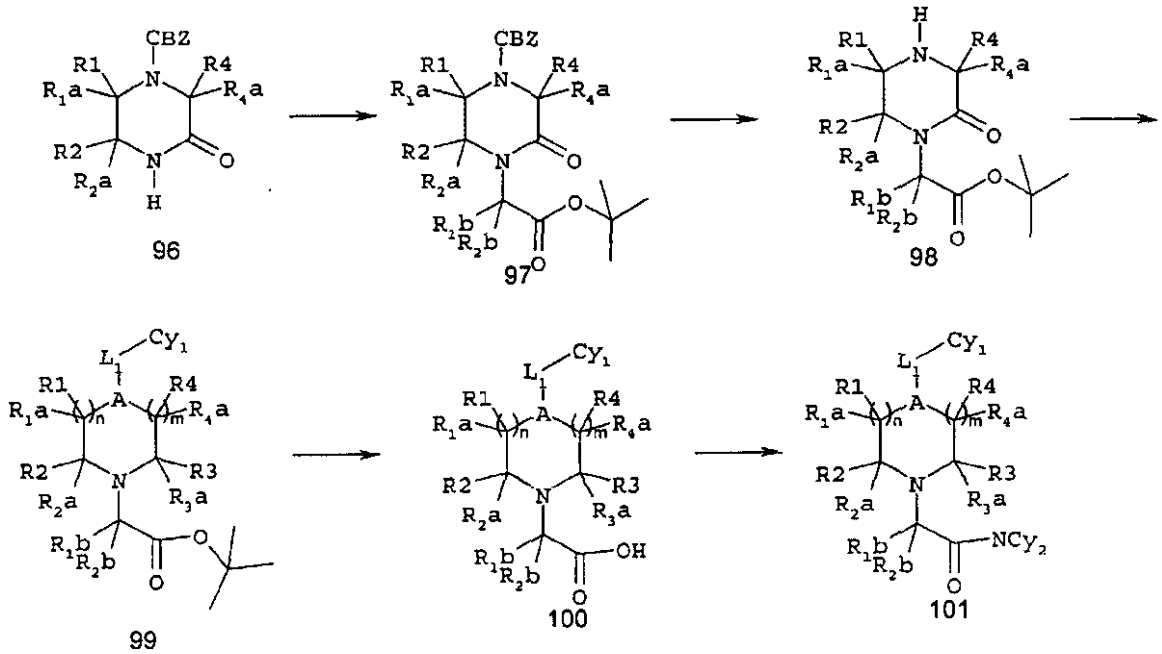
Scheme 20



As indicated in Scheme 20, Cy_1 chloroformates 93 are obtained by chlorocarbonylation of the corresponding alcohols 92 using reagents such as phosgene, triphosgene or 1,1'-carbonyldiimidazole in an appropriate solvent such as CH_2Cl_2. Activated sulfamyl esters 95 are prepared from the corresponding amines 94 using catechol sulfate in an appropriate solvent.

The preparation of acetamido compounds 101 of this invention is outlined in Scheme 21.

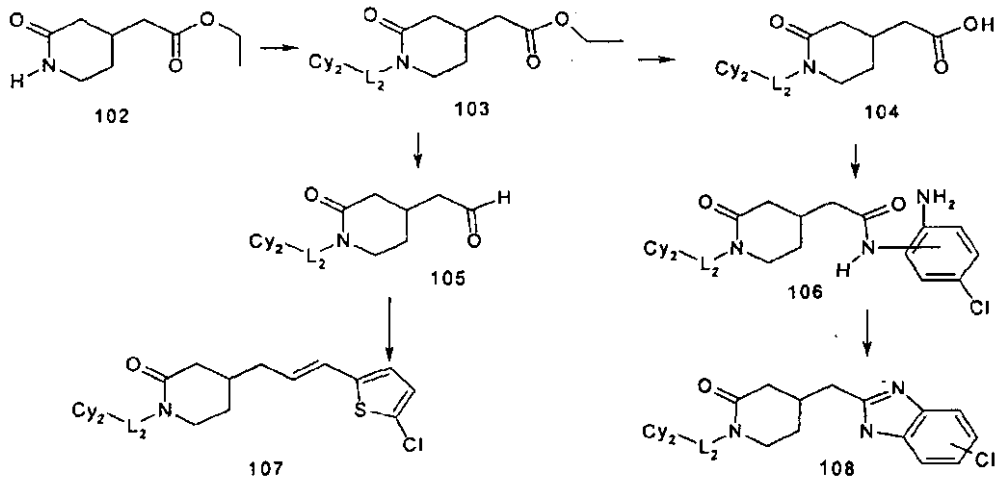
Scheme 21



As indicated in Scheme 21, alkylation of piperazin-2-one 96 is achieved with a strong base such as NaH and a t-butyl ester of haloacetic acid to give the acetate 97. Pd-catalyzed hydrogenation effects removal of the CBZ group from the acetate 97 to give amine 98, which is converted to the L_1-Cy_1 derivative 99 as described in Scheme 1 above. Hydrolysis of t-butyl ester 99 to the corresponding acid 100 is accomplished using, for example, TFA/CH_2Cl_2. The resulting acid 100 is coupled with the optionally protected amine $HNCy_2$ under typical amide bond formation conditions to give acetamide 101.

The preparation of compounds 107 and 108 of this invention wherein Cy_1 is benzimidazol-2-yl is outlined in Scheme 22.

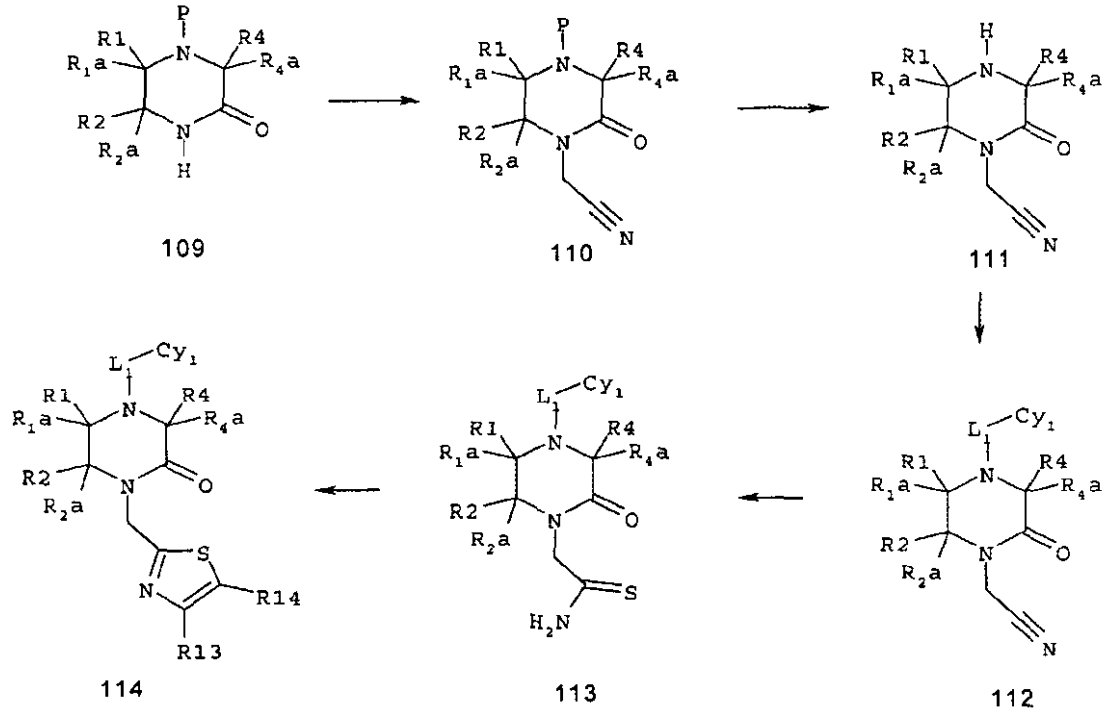
Scheme 22



Piperidin-2-one 102 is alkylated by a procedure analgous to that described in Scheme 3 to give the N-Cy_2-L_2 ester derivative 103, which is hydrolyzed to give the acid 104 or reduced to give aldehyde 105. Coupling of the acid 104 with an amine affords amide 106, which is cyclized with acetic anhydride to give the compound 108. Wittig-coupling of aldehyde 105 produces compound 107.

The preparation of the compound of formula 114 is outlined in Scheme 23, wherein R_1, R_{1a}, R_2, R_{2a}, R_4, R_{4a}, L_1, Cy_1,P, are defined in formula I and R_{13} and R_{14} are defined herein.

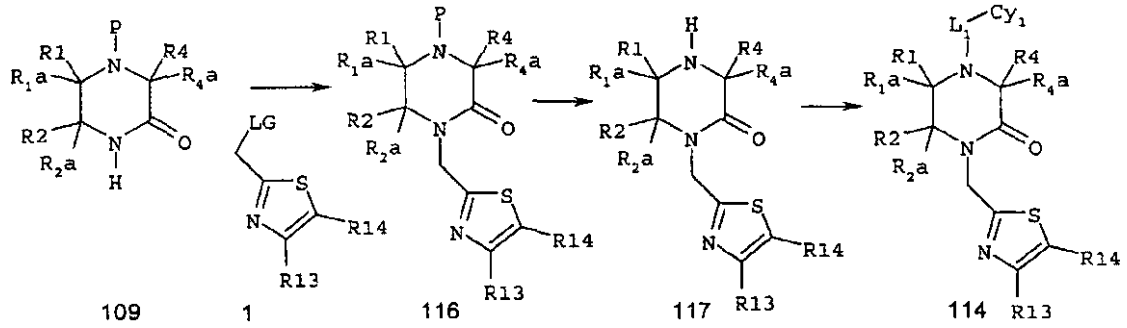
Scheme 23



As shown in Scheme 23, alkylation of a compound of formula 109 with an appropriate LG-CH2-CN group wherein LG is a leaving group such as chloro, bromo, iodo, or optionally substituted lower alkylsulfonyloxy or arylsulfonyloxy in an inert organic solvent such as THF, Et_2O or DMF in the presence of a strong base such as NaH, lithium hexamethyldisilylazide or lithium diisopropylamine provides a compound of formula 110. In a preferred aspect, P a tertiaryalkyl or aralkyl carbamate moiety. Removal of the group P can be accomplished by either strong acid such as TFA, a lewis acid or a reagent such as trimethylsilyl iodide to provide a compound of formula 111. Coupling of a compound of formula 111 with an appropriate LG-L_1-Cy_1 can be performed as previously described in Scheme 1 to give a compound of formula 112 in which the L_1-Cy_1 portion is a sulfonamide, alkyl amine, amide, urea, carbamate or sulfamyl urea. Reaction of a compound of formula 112 with hydrogen sulfide dissolved in ethanol, methanol or another suitable solvent, in the presence of diisoproplyethylamine, triethylamine or another suitable base at an elevated temperature, preferrably >80 °C, provides a compound of formula 113. A compound of formula 114 can be prepared by heating ketone groups of the formula, R_{13}-C(O)-CH(LG)-R_{14}, with a compound of formula 113 in a suitable high boiling solvent. LG is a leaving group as previously defined. If R_{13} or R_{14} contains a protecting group, this group can be removed at this point.

An alternative preparation of a compound of formula 114 (Scheme 23) is shown in Scheme 24.

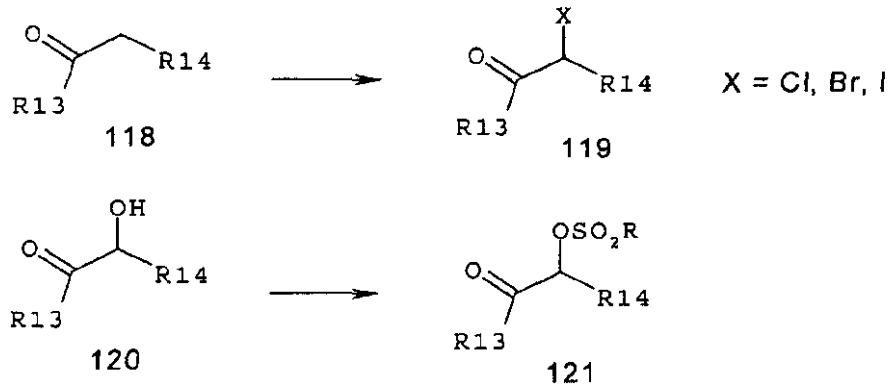
Scheme 24



A compound of formula 116 can be prepared from a compound of formula 109 using conditions previously described in Scheme 3 for the alkylation of Cy_2-Lg_2-LG, which is represented by a compound of formula 115. Removal of the group P using a strong acid, strong base or reducing conditions provides a compound of formula 117. A compound of formula 114 is prepared from compound 117 using conditions previously described in Scheme 1.

The preparations of ketone groups of the formula, R_{13}-C(O)-CH(LG)-R_{14} which are shown as compounds of formulas 119 and 121 are outlined in Scheme 25.

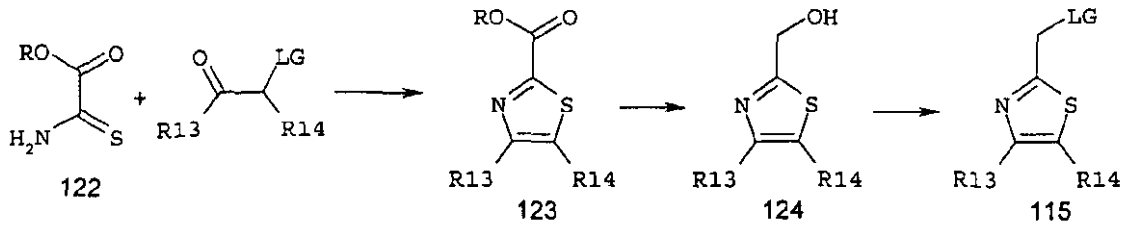
Scheme 25



Halogenation of a compound of formula 118 with an appropriate reagent such as thionyl chloride, bromine, bromine/HOAc, NBS or iodine produces the corresponding halide of formula 119. A compound of formula 120 can be reacted with a sulfonyl chloride and a suitable base such as pyridine or triethylamine to provide a compound of formula 121.

Preparation of thiazole of formula 115 is outlined in Scheme 26.

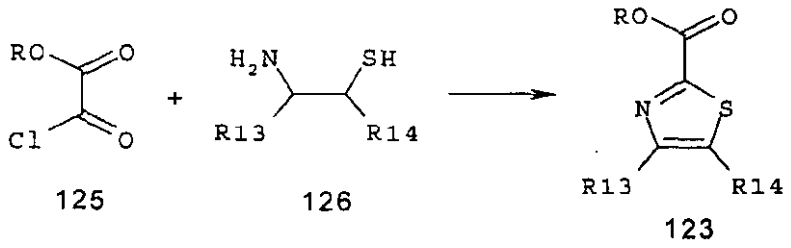
Scheme 26



Condensation of a thioamide compound of formula 122 with a ketone of the formula, R_{13}-C(O)-CH(LG)-R_{14} at elevated temperatures provides the thiazole compound of formula 123. Reduction with LAH, DIBAL or a similar reagent provides the alcohol of formula 124. Preparation of the compound of formula 115 can be acheived with PBr_3 to give the bromide (or with a sulfonyl chloride and base to provide the sulfonate ester).

An alternative preparation of a thiazole intermediate of formula 123 is outlined in Scheme 27

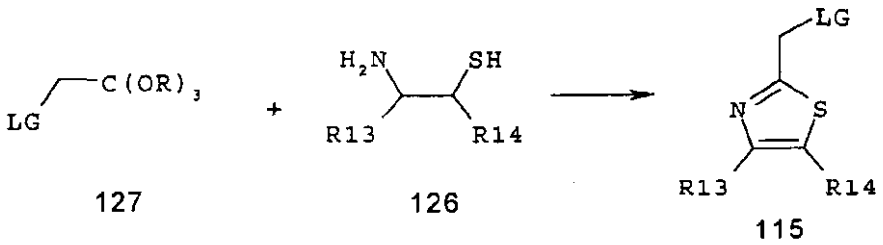
Scheme 27



Condensation of a compound of formula 125 with an aminio-thiol compound of formula 126 with a base such as pyridine provides a thiazole of formula 123. This method is especially useful in cases where R_{13} and R_{14} are combined to form an aromatic ring system.

An alternative preparation of a thiazole intermediate of formula 115 is outlined in Scheme 28.

Scheme 28

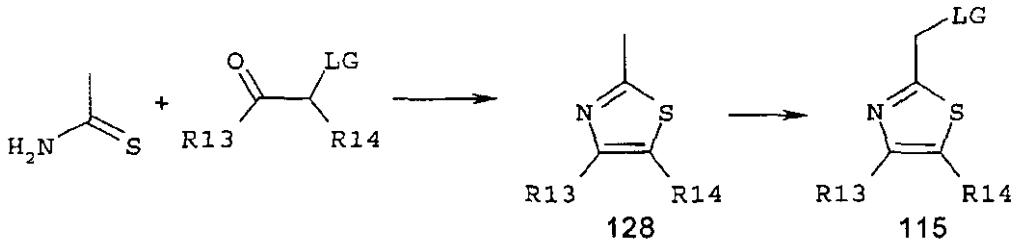


A compound of formula 127, such as 2-chloro-1,1,1-triethoxyethane, can be condensed with a compound of formula 126 at elevated temperatures to provide a compound of formula

115. This method is especially useful in cases where R_{13} and R_{14} are combined to form an aromatic ring system.

An alternative preparation of thiazole intermediate of formula 115 is outlined in Scheme 29.

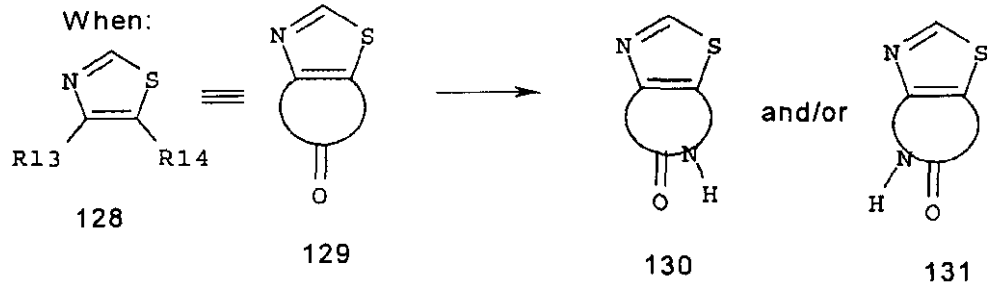
Scheme 29



Condensation of thioacetamide with a ketone of the formula, R_{13}-C(O)-CH(LG)-R_{14} at an elevated temperature provides a thiazole of formula 128. Functiononalization to provide a leaving group such as Br can be accomplished using NBS and an initiator at an elevated temperature in a solvent such as carbontetrachloride to provide a compound of formula 115. This method is especially useful in cases where R_{13} and R_{14} are combined to form an aromatic ring system.

Ring expansion of a compound of formula 128 to provide lactam products of formulas 130 and 131 is shown in Scheme 30.

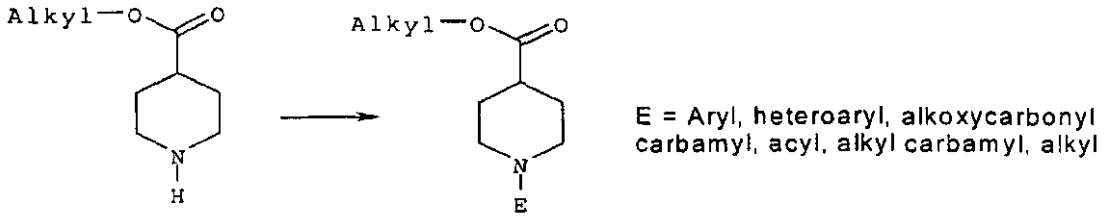
Scheme 30



When R_{13} and R_{14} are combined to form a carbocyclic ring containing a ketone as shown in formula 21, then ring expansion to form the lactone products 130 and 131 can be achieved using the Schmidt reaction. At 0 °C to room temperature a mixture of the ketone 129 is stirred with sodium azide in sulfuric acid and chloroform. The Beckman ring expansion can also be used when the ketone 129 is first treated with hydroxylamine hydrochloride to give the intermediate oxime. An aniline byproduct can also be observed when the Semmler-Wolf aromatization mechanism predominates when thiazole-cycohexanone substrates are used.

Preparation of an intermediate of formula 133 is shown in scheme 31.

Scheme 31

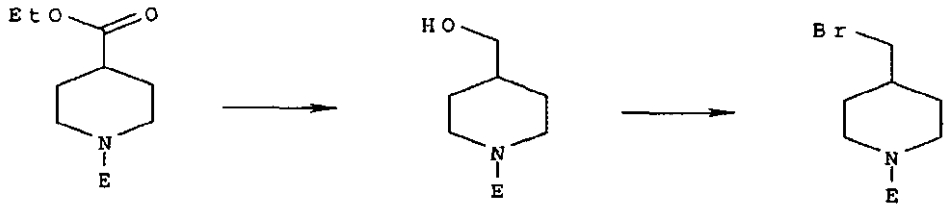


132 133

When E of formula 133 aryl or heteroaryl, a compound of formula 133 can prepared using a Pd catalyzed aromatic carbon-nitrogen bond forming reaction developed by Buchwald and Hartwig. *This reaction has been reviewed (Acc. Chem. Res. 1998 31, 805-818) and can be* generalized to include the reaction of an aromatic bromide, chloride or triflate in an inert solvent in the presence of a Pd (0) catalyst and a base such as sodium tert-butoxide, at an elevated temperature, with a primary or secondary amine. When E of formula 133 is alkoxycarbonyl, acyl, alkyl carbamyl or alkyl, the corresponding halide can be used to couple to a compound of formula 132 in the presence of a base. When E of formula 133 is carbamyl, an isocyanate can be used to produce compound 133 from 132.

The preparation of a compound of formula 135 which can be used as an intermediate is outlined in Scheme 32.

Scheme 32

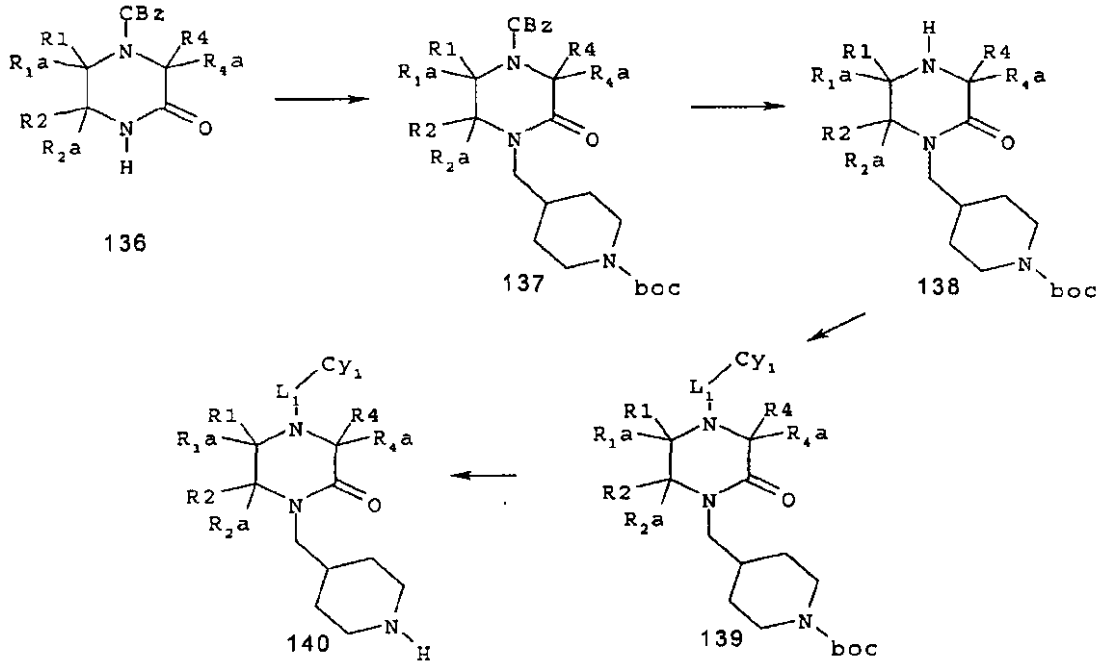


133 134 135

Reduction of a compound of formula 133 with a reducing agent such as LAH, DIBAL or another similar reagent in a nonprotic solvent can provide an alcohol of formula 134. Conversion of the alcohol 134 into a good leaving group, such as the bromide, can be acheived using CBr_4/PPh_3 or another similar reagent to provide a compound of formula 135.

The preparation of the compound of formula 140, wherein R_1, R_{1a}, R_2, R_{2a}, R_4, R_{4a}, L_1, Cy_1 are defined above is outlined in Scheme 33.

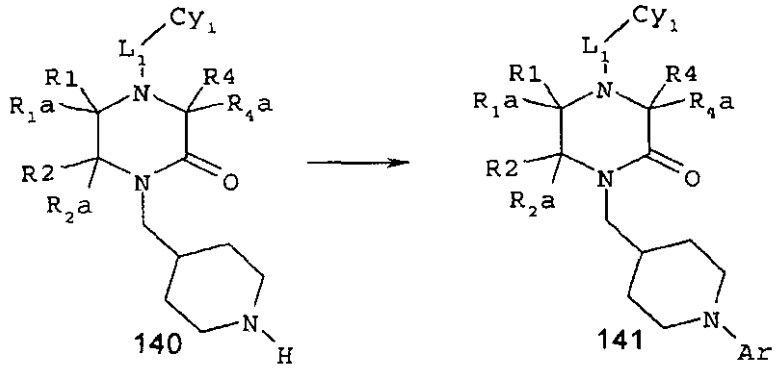
Scheme 33



Alkylation of a compound of formula 136 with a compound of formula 135, where E is tert-butoxycarbonyl, in an inert organic solvent such as DMF in the presence of a strong base such as NaH, lithium hexamethyldisilylazide or lithium diisopropylamine, provides a compound of formula 137. Removal of the CBz (benzyloxycarbonyl) group by catalytic hydrogenation in an appropriate solvent such as ethanol provides a compound of formula 138. Coupling of a compound of formula 138 with LG-L_1-Cy_1 can be performed as previously described above to give a compound of formula 139 in which the L_1-Cy_1 portion is a sulfonamide, alkyl amine, amide, urea, carbamate or sulfamyl urea. Removal of the Boc (t-butoxycarbonyl) group with a strong acid, such as TFA, provides a compound of formula 140.

Preparation of a compound of formula 141, where Ar is an aromatic ring, is shown in scheme 34.

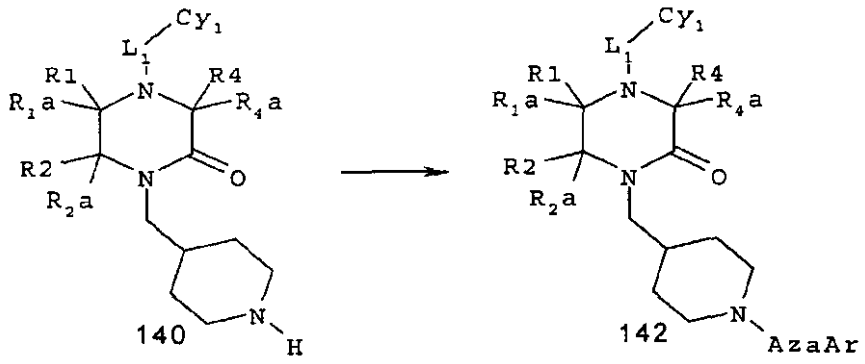
Scheme 34



A compound of formula 140 can be converted to a compound of formula 141 using a Pd catalyzed aromatic carbon-nitrogen bond forming reaction developed by Buchwald and Hartwig. This reaction has been reviewed (*Acc. Chem. Res.* 1998 *31*, 805-818) and can be generalized to include the reaction of an aromatic bromide, chloride or triflate in an inert solvent in the presence of a Pd (0) catalyst and a base such as sodium tert-butoxide at an elevated temperature with a primary or secondary amine.

Preparation of a compound of formula 142, where AzaAr is an azaaromatic ring, is shown in scheme 35.

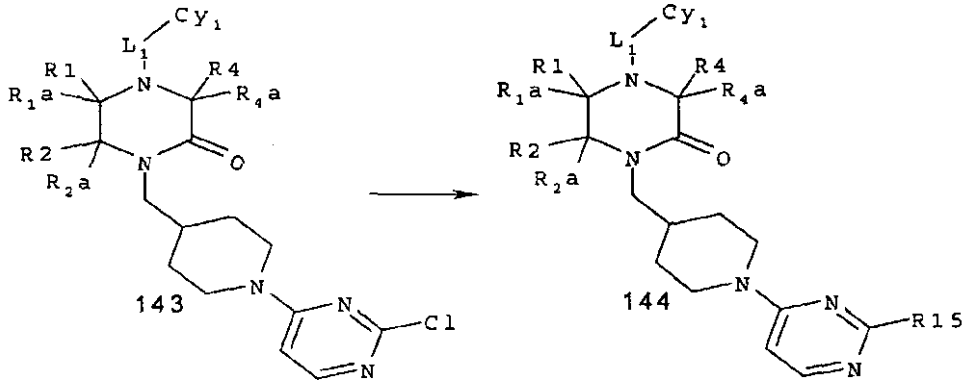
Scheme 35



A compound of formula 142 can be prepared from a halo-substituted azaheteroaromatic compound by heating the halo substituted compound with a compound of formula 140 at an elevated temperature in an inert high boiling solvent such as n-butanol, xylene or NMP. The types of azaheteroaromatic compounds which are best suited for this reaction employ a halogen leaving group in a position of the ring which is activated toward displacement. Such systems are represented by, but not limited to, 2-fluoropyridine, 2-chloroquinoline, 2-chloro-pyrimidine, 4-chloro-pyrimidine and 2,4-dichloro-pyrimidine.

Preparation of a compound of formula 144, where R15 is alkylamine, alkylether or alkylthio, is shown in scheme 36.

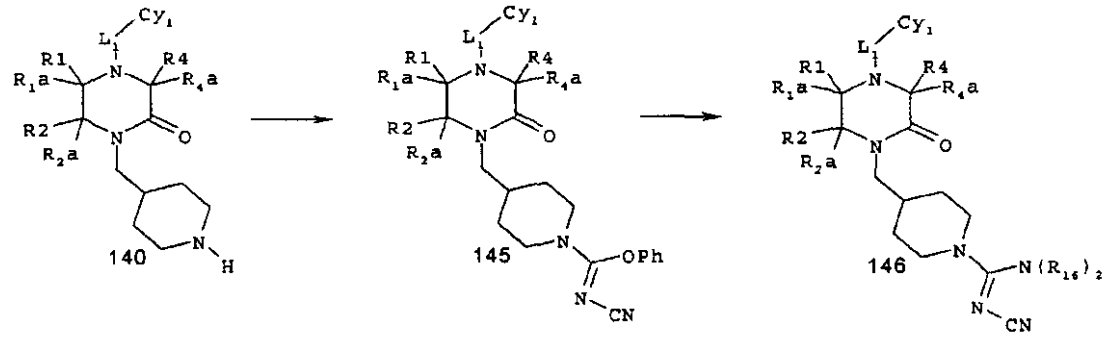
Scheme 36



A compound of formula 143 can be heated with either an amine, alcohol or thiol in an inert solvent to give the corresponding compound of formula 144.

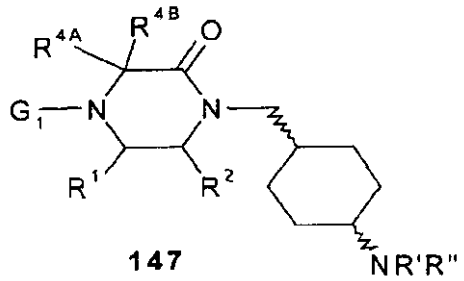
Preparation of a compound of formula 145 and conversion to a compound of formula 146, where each R_{16} is independently H or alkyl, is outlined in scheme 37.

Scheme 37



A compound of formula 145 can be prepared by combining a compound of formula 140 with a reagent such as diphenyl cyanocarbonimidate at ambient temperature or with heating. Heating compound 145 with amine $NH(R_{16})_2$, where each R_{16} is independently H or alkyl, in an inert solvent provides a compound of formula 146.

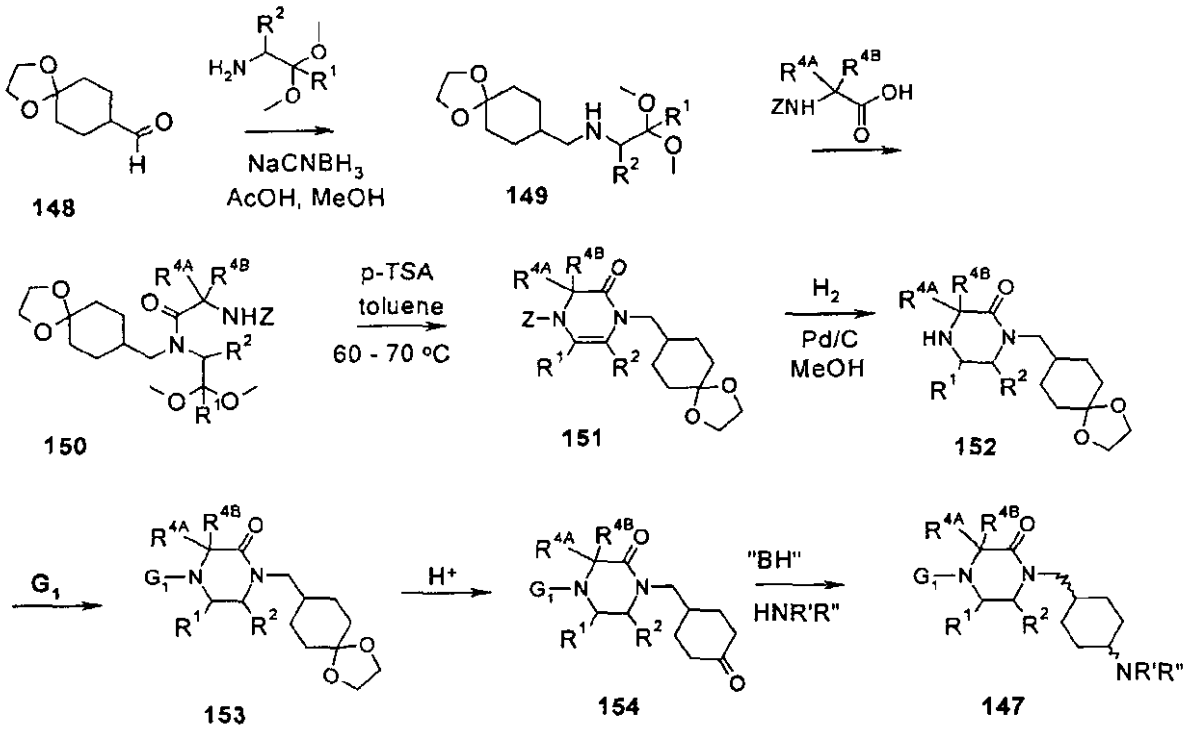
General Methods for the preparation of 1-(alkyl,arly)amino-4-methylcyclohexyl-ketopiperazines of Formula 147 are outlined in Scheme 38.



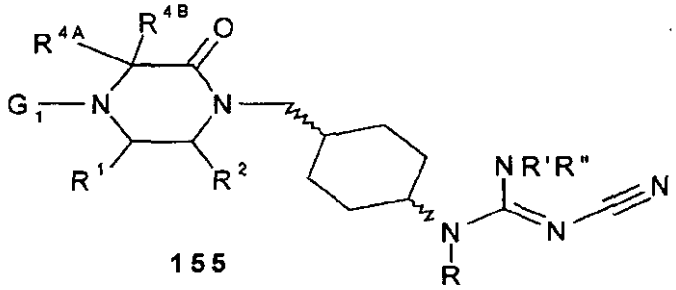
147

As indicated in the scheme 38, a preferred method of preparation of compounds of formula 147 involves construction of a ketopiperazine 152 containing the cyclic ketal of 4-methylcyclohexan-1-one as an N-1 substituent. Construction of intermediate 152 begins with reductive amination of intermediate 148 (prepared according to the method of Pearson et al.; *J. Org. Chem.* 62, 1997, 5284) with the substituted acetal of aminoacetaldehyde to provide intermediate 149. Intermediate 149 is then acylated with a suitably N-protected substituted *a*- amino acid to provide intermediate 150. Treatment of intermediate 150 with p-toluenesulphonic acid provides the unsaturated ketopiperazine 151. Deprotective hydrogenation of intermediate 151 provides intermediate 152. Attatchment of the moiety G_1 provides intermediate 153. The acetal of the 4-substituted cyclohexanone is hydrolyzed under acidic conditions to provide intermediate 154. Reductive amination with the appropriate amine afford compounds of Formula 147. Reductive amination of the cyclohexanone with the selected amines can be achieved using standard methods known to those skilled in the art using borohydrides such as sodium borohydride or lithium tri-*sec*-butylborohydride in an appropriate solvent such as methanol or acetic acid at temperatures between 0 and 100 °C. The isomeric cis/trans products of reductive amination can be separated by silica-gel chromatography or RP-HPLC.

Scheme 38



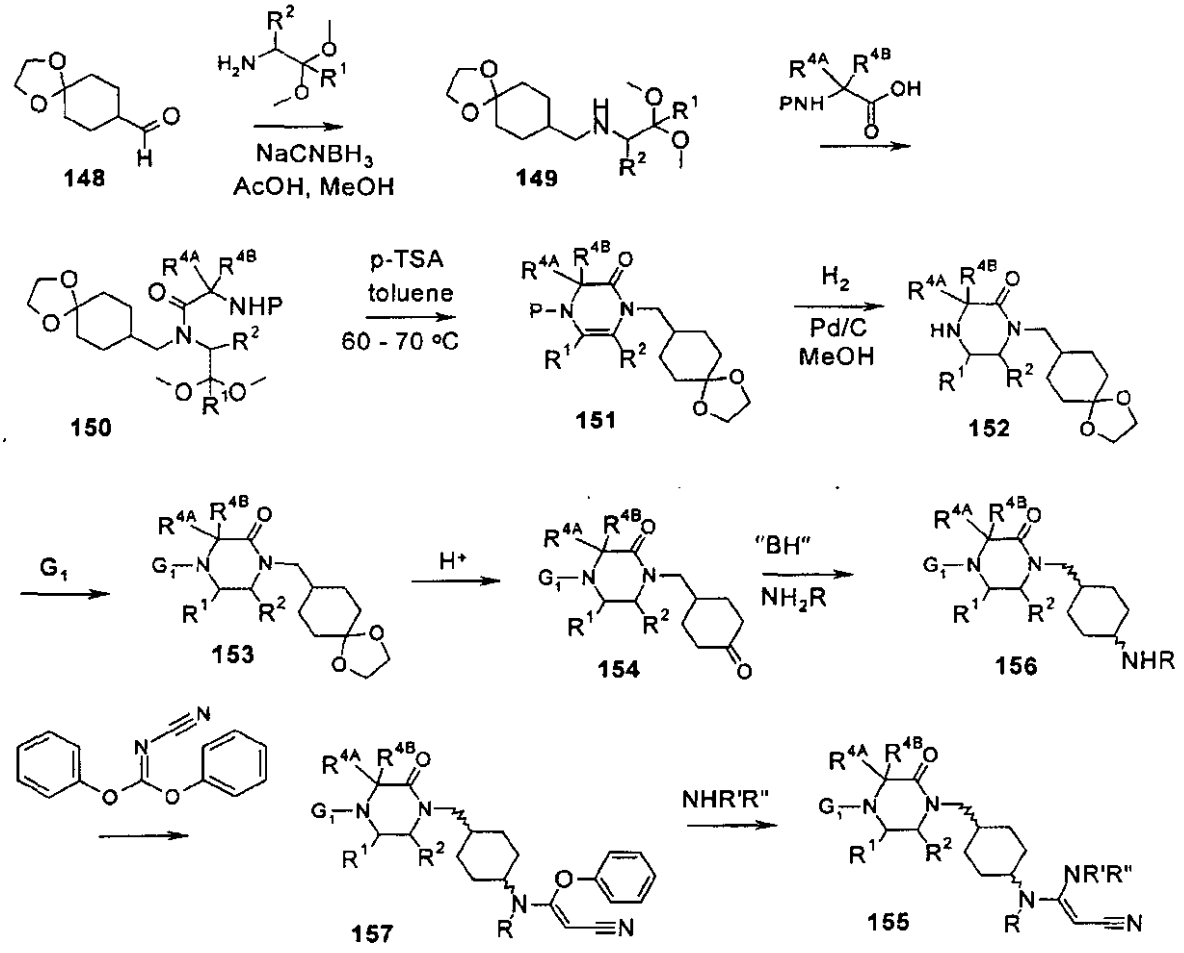
General Methods for the preparation of 1-(*N,N'*-aryl/alkyl-cyanoguanidine)-4-methylcyclohexyl-ketopiperazines of Formula 155 are outlined in scheme39.



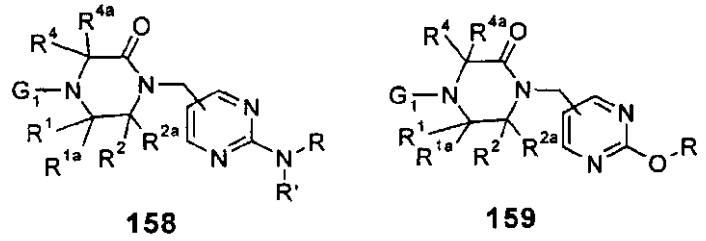
As shown in scheme 39, a preferred method of preparation of compounds of formula 155 involves construction of a ketopiperazine 152 containing the cyclic ketal of 4-methylcyclohexan-1-one as an N-1 substituent. Construction of intermediate 152 begins with reductive amination of intermediate 148 (prepared according to the method of Pearson et al.; *J. Org. Chem.* 62, 1997, 5284) with the substituted acetal of aminoacetaldehyde to provide intermediate 149. Intermediate 149 is then acylated with a suitably N-protected substituted *a*- amino acid to provide intermediate 150. Treatment of intermediate 150 with p-toluenesulphonic acid provides the unsaturated ketopiperazine 151. Deprotective hydrogenation of intermediate 151 provides intermediate 152. Attatchment of the moiety G_1 provides intermediate 153. The acetal of the 4-substituted cyclohexanone is hydrolyzed under acetic conditions to provide intermediate 154. *Reductive amination with the appropriate primary amine provides intermediate* 156. *Reductive* amination of the cyclohexanone with the selected amines can be achieved using standard

methods known to those skilled in the art using borohydrides such as sodium borohydride or lithium tri-*sec*-butylborohydride in an appropriate solvent such as methanol or acetic acid at temperatures between 0 and 100 °C. The isomeric cis/trans products of reductive amination can be separated by silica-gel chromatography or RP-HPLC. Intermediate 156 is reacted with diphenyl cyano-carbonimidate to provide intermediate 157. Intermediate 157 is reacted with appropriate primary and secondary amines to provide a compound of Formula 155.

Scheme 39

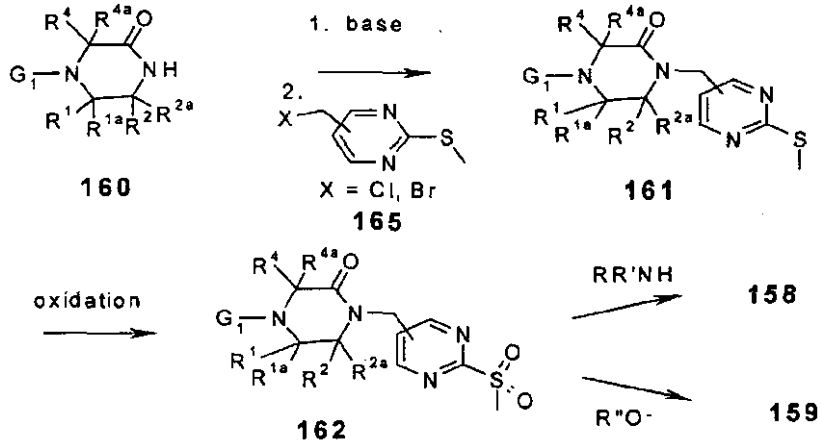


General Methods for the preparation of 2-substituted-4&5-methylpyrimidyl-ketopiperazines of Formulas 158 & 159 are outlined in Scheme 40 below.



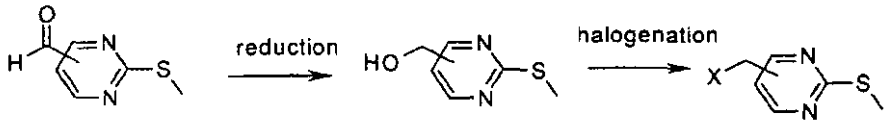
As shown in scheme 40, a preferred method of preparation of compounds of formula 158 and 159 involves alkylating a ketopiperazine intermediate 160 containing a desired N-4 substituent (designated G-1) with either 4 or 5-halomethyl 2-thiomethylpyrimidine to provide intermediate 161. Oxidation of the thiomethyl group of intermediate 161, to provide intermediate 162, followed by displacement with the appropriate amine or alkoxide affords compounds of Formula 158 or 159, respectively. Alkylation of the amide of intermediate 160 can be achieved using standard methods known to those skilled in the art such as deprotonation with NaH in DMF or *t*-butoxide in *t*-butanol at temperatures between -78 and 100°C followed by addition of the halide intermediate 165 and stirring at 0 to 100°C for 0.5 hours to 24 hours. Oxidation of the sulfide of intermediate 161 to the sufone of intermediate 162 can be accomplished in standard fashion, such as using oxone in a mixture of MeOH and H_2O or *m*-CPBA in CH_2Cl_2. Displacement of the sulfone of intermediate 162 with the appropriate amine can be acheived by simply stirring the components neat or in an unreactive solvent such as CH_2Cl_2 or DMF for 0.5 to 24 hours at 20 to 100°C. Similary, reaction of an alkoxide in an inert solvent leads to the desired displacement product.

Scheme 40



The 4&5-halomethyl-2-methylthiopyrimidines intermediates 165 can be prepared as illustrated in scheme 41 from the corresponding 4&5-carboxaldehydes intermediate 163, respectively. 2-Methylthiopyrimidine-4-carboxaldehyde can be prepared using the procedure of Bredereck et al. (*Chem. Ber.* 1964, 3407). 2-Methylthiopyrimidine-5-carboxaldehyde can be prepared by the procedure of Gupton et al. (*J. Het. Chem.* 28, 1991, 1281).

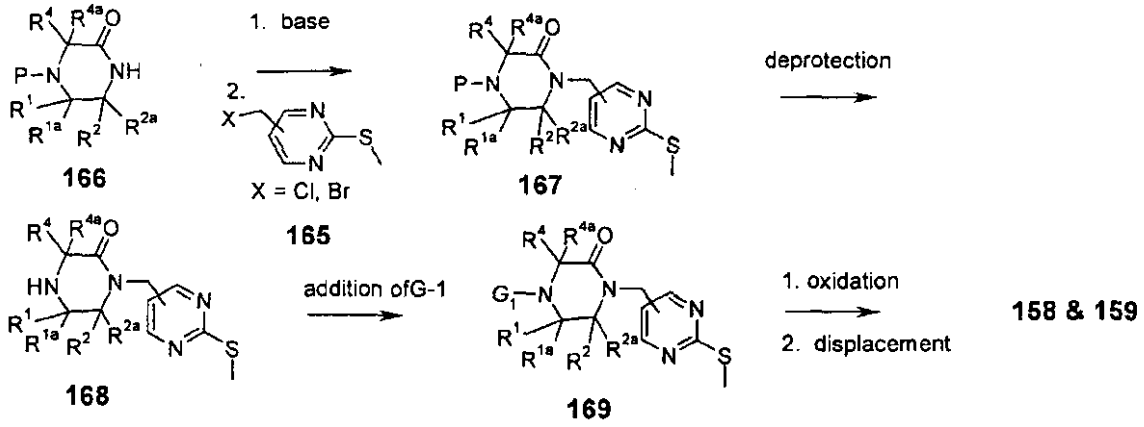
Scheme 41



163 164 165

Alternatively, as illustrated in scheme 42, compounds of formula 158 and 159 can be prepared by alkylating suitably protected [at N-4 (designated P)] ketopiperazine intermediate 166, with either the 4- or 5-halomethyl-2-methylthiopyrimidine (intermediate 165) to provide intermediate 167. The protecting group of intermediate 167 can then be removed to provide intermediate 168 and the desired G-1 substituent added to provide intermediate 169. Suitable protecting groups include Boc, Cbz, Alloc and Fmoc, which can be manipulated in the usual manner.

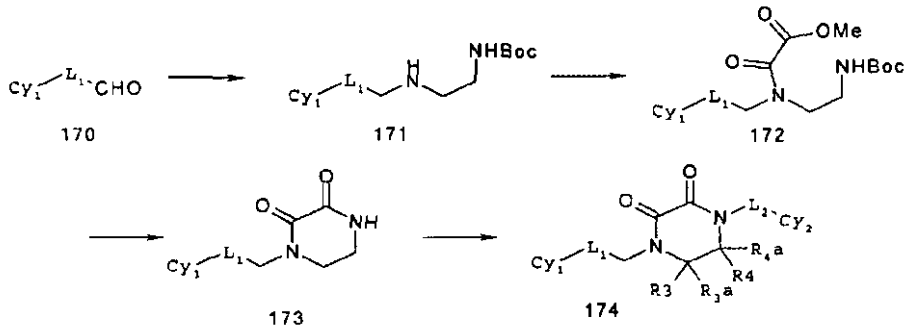
Scheme 42



166 165 167 168 169

Diketopiperazine compounds of formula I, in which A is N, both R_1 and R_{1a} taken together and R_2 and R_{2a} taken together are oxygen, are prepared in general as described in *J. Org. Chem.* 1998, *63*, 4131 and *Chem. Pharm. Bull.* 1981, *29*, 684. The synthetic route used is outlined in Scheme 43 below.

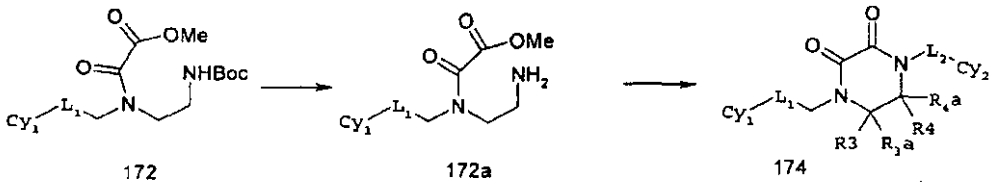
Scheme 43



170 171 172 173 174

As shown in Scheme 43 above, an aryl, heteroaryl or biaryl aldehyde or alkenyl aldehyde derivatives representative of Cy_1-L_1 groups defined herein can be aminated with a suitably protected form of ethylenediamine using a reducing agent such as sodium borohydride. The secondary amine 171 is treated with an appropriate form of oxalyl chloride, notably methyl chlorooxoacetate, in the presence of base to form oxalamic ester intermediate 172. 2,3-Diketopiperazine 203 is formed by removal of the protecting group under acidic conditions (HCl or TFA) followed by cyclization under base conditions (TEA). Appropriate Cy_2-L_2 groups can be appended to compounds of formula 173 by alkylation with a suitable aryl chloromethyl or bromomethyl ring system, such as a compound of formula 179 using NaH, $LiN(SiMe_3)_3$, $NaN(SiMe_3)_3$, LDA, or an appropriate base, in an inert solvent such as THF or DMF to provide compounds of formula 174 in which Cy_2 is a chloroquinazoline, chloroquinoline, aminoquinazoline or another group defined herein.

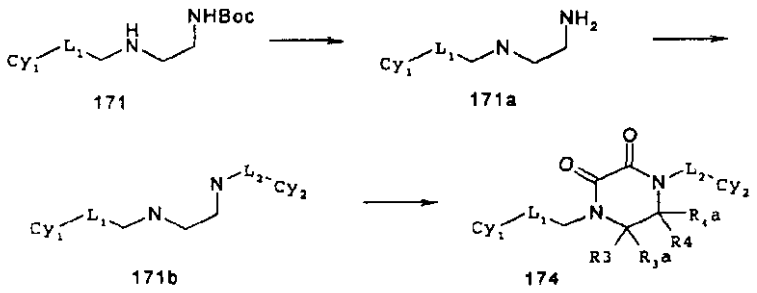
Scheme 43A



172 172a 174

As shown in Scheme 43 A above deprotection of oxalamic ester intermediate 172 under acidic conditions can also be used to isolate intermediate 172a (Scheme 43A) and followed directly by reductive amination conditions with aryl aldehydes to incorporate the respective Cy_2-L_2 groups using a reducing agent such as sodium borohydride or sodium cyanoborohydride. Ring closure occurs under these conditions to provide the 2,3-diketopiperazines 174 *in situ*.

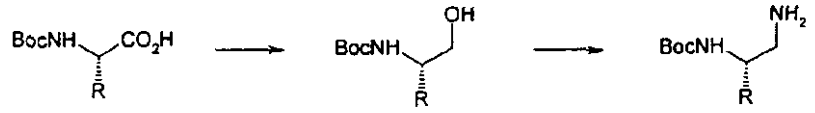
Scheme 43B



171 171a 171b 174

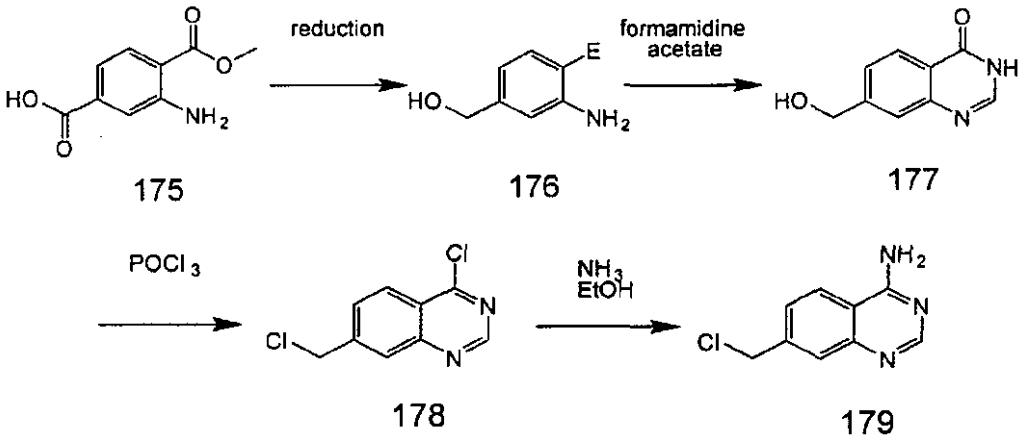
Alternatively, the route shown above in Scheme 43B can be used by deprotecting the secondary amine 171 under acidic conditions (HCl or TFA) to diamine 171a and followed directly by reductive amination with aryl aldehydes to incorporate the respective Cy_2-L_2 groups using a reducing agent such as sodium borohydride or sodium cyanoborohydride. Diamine 171b is then cyclized by reacting with dimethyl oxalate to provide 2,3-diketopiperazines 174.

Scheme 43C



As shown in Scheme 43 C above substituted unsymmetrical ethylenediamine units can be employed by preparing from corresponding amino acids (Scheme 43C). Formation of the mixed anhydride from the acid moiety (iso-butyl chloroformate) followed by reduction (sodium borohydride) gives the respective amino alcohol intermediate. The alcohol moiety can be derivatized as the mesylate (methanesulfonyl chloride), converted to the azide (sodium azide) and reduced by hydrogen to generate the appropriately protected ethylenediamines.

Scheme 44



As shown in Scheme 44, the quinazoline 179 can be prepared by reduction of the acid 175 with Super Hydride in THF to afford the alcohol 176. The alcohol 176 is then reacted in formamide at about 180°C to afford cyclised compound 177. The cyclised compound 177 is then converted to its chloro derivative 178, by reacting with $POCl_3$. The chloro derivative 178 is then converted to the amino compound 179 by using NH_3 in ethanol or $NH_4OAc/PhOH$.

This invention is further exemplified but not limited by the following examples which further illustrate the preparation of the compounds of this invention. The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods used heretofore or described in the literature, for example those described by R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

The compounds of the invention, their methods or preparation and their biological activity will appear more clearly from the examination of the following examples which are presented as an illustration only and are not to be considered as limiting the invention in its scope.

EXAMPLE 1. 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.

A. 1-Chloro-3-(2,2-dimethoxyethylsulfanyl)benzene.

To a solution of 3-chlorothiophenol (2.4 g, 16.6 mmol) in THF (200 mL) at 0°C is added bromoacetaldehyde dimethyl acetal (2.8 g, 16.6 mmol). To the solution is added sodium hydride (60% mineral oil dispersion, 0.70 g, 17.4 mmol). The reaction is stirred for 16 hours, and then is quenched by the addition of saturated NH_4Cl (aq.). The solution is diluted with EtOAc. The organic layer is washed with a saturated NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with hexanes. The title compound (3.7 g, 15.9 mmol) is obtained as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 1H), 7.25 (m, 1H), 7.12 (m, 1H), 4.47 (m, 1H), 3.07 (s, 3H), 3.02 (s, 3H).

B. 4-Chlorobenzo[b]thiophene and 6-Chlorobenzo[b]thiophene.

A solution containing polyphosphoric acid (8 g) and chlorobenzene (50 mL) is heated at reflux. A solution containing 1-chloro-3-(2,2-dimethoxyethylsulfanyl)benzene (2.7 g, 11.6 mmol) in chlorobenzene (5 mL) is added dropwise to the refluxing polyphosphoric acid solution. After 6 hours, the solution is cooled to ambient temperature. The solution is diluted with CH_2Cl_2 and washed with water and saturated NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with hexanes to yield the title compounds (2.4 g, 9.0 mmol) as a 1:1 isomeric mixture. ^1H NMR ($CDCl_3$, 300MHz) δ 7.88 (m, 1H), 7.75 (m, 2H), 7.42 (m, 2H). MS (EI): m/z 168, 170 (M+), Cl pattern.

C. 4-Chlorobenzo[b]thiophene-2-sulfonyl chloride and 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.

To a solution of 4-chloro-benzo[b]thiophene and 6-chlorobenzo[b]thiophene (11.8 g, 88.1 mmol), in 400 mL of THF at -78°C is added n-BuLi (55 mL of a 1.6M solution in hexanes, 88.1 mmol). After 15 minutes, the solution is added by cannula to a precooled (-78°C) solution of SO_2 (200 g) in 100 mL of THF. After addition, the solution is allowed to warm to ambient temperature. After 0.5 hour, the solution is concentrated. The residue is suspended in hexanes (400 mL) and is cooled to 0°C. To the solution is added SO_2Cl_2 (12.5 g, 92.5 mmol). After stirring for 15 minutes, the solution is concentrated. The residue is dissolved in EtOAc. The organic solution is washed with saturated NH_4Cl (aq.), H_2O and saturated NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is dissolved in CH_2Cl_2 and filtered through a plug of silica gel. The crude product is purified by column

chromatography eluting with hexanes to yield the title compound as well as 4-chlorobenzo[b]thiophene-2-sulfonyl chloride as white solids.

4-Chlorobenzo[b]thiophene-2-sulfonyl chloride: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.32 (m, 1H), 7.81 (m, 1H), 7.53 (m, 2H).

6-Chlorobenzo[b]thiophene-2-sulfonyl chloride: ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.11 (s, 1H), 7.88 (m, 2H), 7.50 (m, 1H).

EXAMPLE 2. 5'-Chloro-[2,2']bithiophenyl-5-sulfonyl chloride.

A. 5-Chloro-[2,2']bithiophene.

The title compound is prepared from 2-chloro-thiophene according to the procedure described in Bull. Chem. Soc. Japan, 1979, 1126. The crude product is purified by column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to afford a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.24 (m, 1H), 7.11 (d, 1H), 7.03 (dd, 1H), 6.94 (d, 1H), 6.83 (d, 1H). MS (EI) [M+]= 200, 202, Cl pattern.

B. 5'-Chloro-[2,2']bithiophenyl-5-sulfonyl chloride.

The title compound is prepared as described in Example 1, Part C using 5-chloro-[2,2']bithiophene in place of 6-chloro-benzo[b]thiophene. The crude product is purified by column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to give a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.76 (d, 1H), 7.14 (d, 1H), 7.09 (d, 1H), 6.92 (d, 1H). MS (EI): m/z 298, 300 (M+), Cl pattern.

EXAMPLE 3. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride.

A. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonic acid ethyl ester.

n-Butyllithium (53.1 mL, 2.5M solution in hexanes) is added dropwise to a solution of ethylmethanesulfonate (12.9 mL, 0.12 mol) in THF (300 mL) at -78°C. The reaction mixture is stirred for 15 min then ethylchlorophosphonate (9.9 mL, 0.07 mol) is added dropwise. The solution is stirred at -78°C for 30 minutes and then heated to 50°C for 1 hour. The reaction mixture is then cooled to -78°C and stirred for 1 h then 5-chlorothiophenecarboxaldehyde (7.1 mL, 0.07 mol) is added dropwise. The reaction mixture is allowed to slowly warm to RT overnight. Water (30 mL) is added to the mixture and stirred for 15 min then concentrated in vacuo. The residue is taken up in CH_2Cl_2 and washed with water, brine, dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is purified by column chromatography eluting with 5% EtOAc/hexanes to give title product (11.3 g, 0.04 mol) as an oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.51 (d, 1H), 7.10 (d, 1H), 6.91 (d, 1H), 6.42 (d, 1H), 4.20 (q, 2H), 1.40 (t, 3H).

B. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride.

Tetrabutylammonium iodide (16.3 g, (44.2 mmol) is added to a solution of 2-(5-chloro-thiophen-2-yl)-ethenesulfonic acid ethyl ester (11.3 g, 40.2 mmol) in acetone (100 mL) at room temperature. The mixture is heated to reflux and stirred overnight then cooled to RT and conconcentrated in vacuo. The residue is taken up in CH_2Cl_2 then washed with water and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness to give an oil (18.74 g, 40.2 mmol) which is taken on to the next step without further purification. Sulfuryl chloride (7.1 mL, 88.5 mmol) is added to a solution of triphenylphosphine (21.0 g, 86.42 mmol) in CH_2Cl_2 at 0°C . The ice bath is then removed and the product (18.74 g, 40.2 mmol) from the above reaction is added. After 2 h, the reaction mixture is concentrated in vacuo and the product purified by column chromatography eluting with 10% EtOAc/Hexanes to give the title compound (6.4 g, 26.3 mmol) as an off-white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, 1H), 7.23 (d, 1H), 7.00 (d, 1H), 6.91 (d, 1H).

EXAMPLE 4. 3-Chlorobenzyl sulfamyl catechol.

To a solution of 3-chlorobenzylamine (0.14 g, 1.0 mmol) in 3 mL of DMF is added Et_3N (0.10 g, 1.5 mmol). The solution is cooled to 0°C. Catechol sulfate (0.172 g, 1.0 mmol) is added. The solution is warmed to ambient temperatures. After 2.5 h, 30 mL of EtOAc is added. The solution is washed with 5% HCl, H_2O and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the title compound (0.30 g, 0.97 mmol). ^1H NMR (d6-DMSO, 300 MHz) δ 9.94 (s, 1H), 8.82 (m, 1H), 7.41 (m, 4H), 7.19 (d, 1H), 7.10 (m, 1H), 6.95 (d, 1H), 6.79 (m, 1H), 4.32 (AB, 2H).

EXAMPLE 5. 2-Bromomethyl-6-chlorobenzo[b]thiophene.

A. 6-Chlorobenzo[b]thiophene-2-carboxaldehyde.

To a solution of 6-chlorobenzo[b]thiophene (1.0 g, 5.93 mmol) in THF (60 mL) at -78°C is added a 1.6 M solution of n-BuLi in THF (3.9 mL, 6.23 mmol). After 10 minutes, 0.5 mL of DMF is added. The solution is stirred for 0.5 hours, then allowed to warm to ambient temperature. The solution is poured into a solution of saturated NH_4Cl. The solution is diluted with ether and the layers are separated. The organic layer is washed with H_2O and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The title compound is obtained as a white solid. MS (EI): m/z 196 (M+).

B. 6-Chlorobenzo[b]thiophen-2-yl)methanol.

To a solution of 6-chlorobenzo[b]thiophene-2-carboxaldehyde in THF at 0°C is added $NaBH_4$. After 1 hour, the solution is diluted with saturated NH_4Cl and ether. The organic layer

is washed with H_2O and saturated NaCl, dried over $MgSO_4$, filtered and concentrated. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1H), 7.60 (d, 1H), 7.40 (m, 2H), 4.91 (AB, 2H).

C. 2-Bromomethyl-6-chlorobenzo[b]thiophene.

To a solution of 6-chlorobenzo[b]thiophen-2-yl)-methanol (0.2 g, 1.01 mmol) in THF (10 mL) is added triphenyl phosphine (0.34 g, 1.31 mmol) followed by CBr_4 (0.42g, 1.26 mmol). After 3 hours, the solution is concentrated. The product is purified by column chromatography eluting in a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes. The product is obtained as a white solid (0.25 g, 0.53 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1H), 7.62 (d, 1H), 7.40 (m, 2H), 4.76 (s, 2H).

EXAMPLE 6. 5-Bromomethyl-5'-chloro-[2,2']bithiophenyl.

A. (5'-Chloro-[2,2']bithiophenyl-5-yl)-methanol.

To a solution of 5-chloro-[2,2']bithiophenyl (3.00 g, 14.9 mmol) in 30 mL of THF at 0°C is added n-BuLi (9.8 mL of a 1.6M solution in hexanes, 15.7 mmol) dropwise. DMF (2.30 mL, 30 mmol) is added dropwise and the resulting solution is heated at reflux for 1 hour. The solution is diluted with H_2O and extracted with Et_2O. The organic layer is washed with H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude aldehyde is dissolved in 40 mL of anhydrous MeOH and sodium borohydride (0.85 g, 22.5 mmol) is added portionwise. The mixture is stirred at room temperature for 10 min, then quenched with water. The mixture is diluted with Et_2O and the layers separated. The organic layer is washed with H_2O, then dried over $MgSO_4$, filtered and concentrated to yield the title compound (2.23 g, 9.66 mmol) which is used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300MHz) δ 6.95 (d, 1H), 6.90 (m, 2H), 6.86 (d, 1H), 4.82 (s, 2H), 1.88 (bs, 1H).

B. 5-Bromomethyl-5'-chloro-[2,2']bithiophenyl.

To a solution of (5'-chloro-[2,2']bithiophenyl-5-yl)-methanol (2.23 g, 9.66 mmol) in 65 mL of CH_2Cl_2 is added bromotrimethylsilane (3.82 mL, 29.0 mmol). After 4 h, the solution is concentrated in vacuo. The crude product is stirred in hot hexanes and filtered. The filtrate is concentrated and the title compound (1.67 g, 5.69 mmol) is obtained as a green solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.00 (d, 1H), 6.94 (m, 2H), 6.85 (d, 2H), 4.71 (s, 2H).

EXAMPLE 7. 7-Bromomethyl-4-chloroquinazoline.

A. 7-Methyl-3H-quinazolin-4-one.

A solution of 2-amino-4-methylbenzoic acid (31.6 g, 206 mmol) in formamide (60mL) is heated to 130°C for 1 hour, then at 175°C for 3 hours. The solution is poured into 500 mL of ice

water. The resulting solid is collected by filtration and further dried under reduced pressure. The title compound (26.2 g, 170 mmol) is obtained as a white solid. MS (EI): m/z 159 (M+).

B. 4-Chloro-7-methyl-quinazoline.

To a solution of 7-methyl-3H-quinazolin-4-one (10.6 g, 69 mmol) in toluene (350mL) is added triethylamine (17.5 g, 173 mmol) followed by phosphorous oxychloride (12.3 g, 80 mmol). The resulting solution is heated to 80°C. After 4 hours, the solution is cooled to ambient temperature. The reaction mixture is poured into 500 mL of water. The layers are separated and the organic layer is washed with H_2O, saturated $NaHCO_3$, and saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The resulting crude product is purified by recrystallization from EtOAc. The title compound is obtained as a white solid (10g, 56 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.02 (s, 1H), 8.16 (d, 1H), 7.87 (s, 1H), 7.55 (d, 1H), 2.62 (s, 3H).

C. 7-Bromomethyl-4-chloroquinazoline.

To a solution of 4-chloro-7-methylquinazoline (7.0 g, 39 mmol) in carbon tetrachloride (140 mL) is added N-bromosuccinimide (8.0 g, 45 mmol), and benzoyl peroxide (0.8 g, 3.3 mmol). The solution is refluxed for 8 hours. After this time, the solution is filtered. The filtrate is concentrated and the residue is stirred with ether to give the title compound as an off-white solid (5.1 g, 20 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.10 (s, 1H), 8.30 (d, 1H), 8.10 (s, 1H), 7.82 (d, 1H), 4.68 (s, 2H). MS (EI): m/z 237 (M+).

EXAMPLE 8. 3-Bromomethyl-7-chloro-1H-quinolin-2-one.

A. N-(3-Chlorophenyl)-2-methyl-3-phenylacrylamide.

To a solution of 3-chloroaniline (0.98 mL, 9.3 mmol) in CH_2Cl_2 (25 mL) at 0°C is added pyridine (0.78mL, 9.5 mmol). To the resulting solution is added dropwise a solution of α-methyl cinnamic acid chloride (1.6 g, 9.3 mmol) in CH_2Cl_2 (8 mL). After 3 hours, the solution is concentrated. The crude product is purified by column chromatography eluting with 5%EtOAc/hexanes to 10%EtOAc/hexanes. The title compound is obtained as a solid (2.5 g, 9.2 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 1H), 7.73 (s, 1H), 7.46 (m, 1H), 7.33 (m, 6H), 7.22 (m, 1H), 7.03 (m, 1H), 2.13 (s, 3H).

B. 7-Chloro-3-methyl-1H-quinolin-2-one.

To a solution of N-(3-chlorophenyl)-2-methyl-3-phenylacrylamide (2.5 g, 9.2 mmol) in chlorobenzene (50 mL) is added $AlCl_3$ (6.2 g, 46 mmol). The solution is heated to 120°C. After 4 hours, the solution is poured onto ice. The solution is filtered. The organic layer is washed with 1N HCl, H_2O and saturated NaCl. The crude product is purified by column chromatography eluting with 2% MeOH/CH_2Cl_2. The title compound is obtained as a white solid

(1.5 g, 7.74 mmol). ^{1}H NMR (d6-DMSO, 300 MHz) δ 11.82 (bs, 1H), 7.73 (s, 1H), 7.52 (m, 1H), 7.21 (m, 2H), 2.08 (s, 3H).

C. 3-Bromomethyl-7-chloro-1H-quinolin-2-one.

The title compound is prepared as described in Example 7, Part C, substituting 7-chloro-3-methyl-1H-quinoline-2-one for 7-methyl-4-chloroquinazoline. The title compound is obtained as a white solid. ^{1}H NMR (d6-DMSO, 300 MHz) δ 12.00 (bs, 1H), 8.17 (s, 1H), 7.72 (d, 1H), 7.29 (m, 2H), 4.58 (s, 2H).

EXAMPLE 4. 6-Bromomethyl-2-chloro-quinoline.

A. 6-Methyl-1H-quinolin-2-one.

The title compound is prepared from p-toluidine and cinnamoyl chloride according to the procedure described in Synthesis 1975, 739. The crude product obtained is triturated in Et_2O/hexanes and filtered to give the title compound as a beige solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.60 (bs, 1H), 7.82 (d, 1H), 7.41 (s, 1H), 7.30 (d, 1H), 7.18 (d, 1H), 6.45 (d, 1H), 2.30 (s, 3H).

B. 2-Chloro-6-methylquinoline.

6-Methyl-1H-isoquinolin-2-one (14.6 g, 91.7 mmol) in phosphorus oxychloride (160 mL) is heated at 60°C for 17 hours. The mixture is cooled to room temperature, then concentrated to a beige residue. The residue is diluted with ice water and the pH is adjusted to about 8 by slow addition of 10 N NaOH. The crude product is precipitated out during neutralization of the aqueous solution and the solid is filtered, washed with water and dried. The solid is recrystallize from MeOH to afford the title compound (12.0 g, 67.5 mmol) as a beige solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, 1H), 7.92 (d, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.33 (d, 1H), 2.53 (s, 3H).

C. 6-Bromomethyl-2-chloro-quinoline.

N-Bromosuccinimide (12.9 g, 72.5 mmol) and benzoyl peroxide (0.33 g, 1.30 mmol) are added to a solution of 2-chloro-6-methyl-quinoline (12.0 g, 67.5 mmol) in carbon tetrachloride (300 mL). The mixture is heated at reflux for 6 hours. At this time, the resulting mixture is cooled to room temperature, filtered, washed with CH_2Cl_2 and concentrated in vacuo. The crude residue is recrystallized from 50% EtOAc/hexanes to yield the title compound (8.80 g, 34.3 mmol) as a beige crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H), 8.02 (d, 1H), 7.83 (s, 1H), 7.77 (dd, 1H), 7.40 (d, 1H), 4.65 (s, 2H). MS (EI): m/z 256, 258 (M+), Cl pattern.

EXAMPLE 10. 3-Bromomethyl-1,7-dichloro-2H-isoquinoline.

A. 3-(4-Chlorophenyl)-2-methyl-acryloyl azide.

To a solution of 3-(4-chlorophenyl)-2-methyl-acrylic acid (11.2 g, 57 mmol) in 500 mL of acetone at 0°C is added triethyl amine (9.6 mL, 68 mmol) followed by ethyl chloroformate (6.2 mL, 63 mmol). The solution is allowed to warm to ambient temperatures. After 2 h, sodium azide (5.6 g, 86 mmol) in 35 mL of H_2O is added. After addition, the solution is stirred for 2 hours. The solution is diluted with H_2O (100 mL). The resulting solid is collected by filtration giving the title compound as a white solid (11.1 g, 50mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (s, 1H), 3.38 (m, 4H), 2.10 9s, 3H).

B. 7-Chloro-3-methyl-2H-isoquinoline-1-one.

3-(4-Chlorophenyl)-2-methyl-acryloyl azide (11.0 g, 50 mmol) is dissolved in 80 mL of diphenyl ether. The solution is added dropwise to a solution of tributyl amine (11.8 mL, 50mmol) in 170 mL of diphenyl ether at 210°C. After 4 hours., the solution is cooled 50°C and diluted with 1.5 L of hexanes. The resulting solid is collected by filtration giving the title compound as a white solid (7.2 g, 37 mmol). ^1H NMR (d6-DMSO, 300 MHz) δ 11.4 (bs, 1H), 8.02 (s, 1H), 7.67 (d, 1H), 7.55 (d, 1H), 6.34 (s, 1H), 2.18 (s, 3H).

C. 1,7-Dichloro-3-methyl-isoquinoline.

A solution of 7-chloro-3-methyl-2H-isoquinoline-1-one (7.1 g, 36.7 mmol) in 100 mL of phosporous oxychloride is heated to 100°C. After 5 h, the solution is concentrated to dryness. The residue is dissolved in CH_2Cl_2. The solution is washed with H_2O. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with a gradient of 3%EtOAc/hexanes to 5% EtOAc/hexanes. The title compound is obtained as a white solid (6.0g, 28 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (s, 1H), 7.68 (m, 1H), 7.63 (m, 1H), 7.40 (s, 1H), 2.64 (s, 3H).

D. 3-Bromomethyl-1,7-dichloro-2H-isoquinoline.

The title compound is prepared as described in Example 7, part C, substituting 1,7-dichloro-3-methyl-isoquinoline for 4-chloro-7-methylquinazoline. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.82 (m, 1H), 7.76 (m, 2H), 4.68 (s, 2H).

EXAMPLE 11. 3-Bromomethyl-7-chloroisoquinoline.

A. 7-Chloro-3-methyl-isoquinoline.

To a solution of 1,7-dichloro-3-methyl-isoquinoline (0.50 g, 2.36 mmol), Example 10, part C, in 5.5 mL of 9:1 acetic acid:H_2O at 75°C is added zinc (0.23 g, 3.54 mmol) After 75 minutes, the solution is cooled to ambient temperatures. The solution is diluted with a 4:1 EtOAc:CH_2Cl_2 solution. To the solution is added 100mL of a 1N NaOH solution. The aqueous solution is extracted with 4:1 EtOAc:CH_2Cl_2. The combined organic layers are washed with a saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated. The

crude product is purified by column chromatography eluting with a gradient of 5%EtOAc/hexanes to 15% EtOAc/hexanes. The title compound is obtained as a white solid (0.36 g, 1.97 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H), 7.89 (s, 1H), 7.61 (d, 1H), 7.55 (d, 1H), 7.44 (s, 1H) 2.68 (s, 3H). MS (EI): m/z 177, 179 (M+), Cl pattern.

B. 3-Bromomethyl-7-chloroisoquinoline.

The title compound is prepared as described in Example 7, part C, substituting 7-chloro-3-methyl-isoquinoline for 4-chloro-7-methylquinazoline. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.18 (s, 1H), 7.97 (s, 1H), 7.75 (m, 2H), 7.67 (m, 1H), 4.71 (s, 2H).

EXAMPLE 12. 2-Bromomethyl-6-chloronaphthalene.

A. 6-Chloro-3,4-dihydro-1H-naphthalene-2-one.

To a solution of (4-chlorophenyl)-acetyl chloride (17.3 g, 92 mmol) in 50 mL of CH_2Cl_2 at -20°C is added a solution of $AlCl_3$ (24.4 g, 184 mmol) in 200 mL CH_2Cl_2 dropwise. After 20 minutes, ethylene (g) is bubbled through the solution for 30 minutes. The solution is stirred at -10°C for 15 minutes. The reaction mixture is poured into 300 g of ice. The layers are separated. The organic layer is washed with H_2O, saturated $NaHCO_3$ and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting solid is triturated with pentane (2x20mL). The solid is then dried to give the title compound as a solid (15.2 g, 84.2 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 2H), 7.06 (m, 1H), 3.52 (s, 2H), 3.04 (m, 2H), 2.56 (m, 2H).

B. 6-Chloro-2-methyl-1,2,3,4-tetrahydronaphthalene-2-ol.

To a solution of $TiCl_4$ (95 mL, 1M in toluene) at -45°C is added a solution of CH_3MgBr (4.2 mL 3M in THF). The solution is stirred for 20 minutes. After this time, 6-chloro-3,4-dihydro-1H-naphthalene-2-one (11.3 g, 63 mmol) in 80 mL of CH_2Cl_2 is added dropwise over 15 minutes. The reaction is stirred for an additional 15 min at -45°C. The solution is warmed to 0°C. After 2 h, the solution is diluted with H_2O and CH_2Cl_2. The organic layer is dried over $MgSO_4$, filtered and concentrated. The title compound is obtained as an oil (11.3 g, 57.5 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (m, 2H), 6.97 (m, 1H), 3.02 (m, 2H), 2.80 (s, 3H), 1.85 (m, 2H), 1.80 (m, 2H).

C. 2-Chloro-6-methyl naphthalene.

A solution of 6-chloro-2-methyl-1,2,3,4-tetrahydronaphthalene-2-ol (11.3 g, 57.5 mmol) and Ph_3COH (16.5 g, 63 mmol) in 80 mL of TFA is stirred for 2.5 days. After this time, the solution is concentrated to dryness. The residue is dissolved in CH_2Cl_2. The organic layer is washed with H_2O, saturated $NaHCO_3$, and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography

eluting with hexanes. The title compound is obtained as a white solid (4.05 g, 22.9 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (s, 1H), 7.69 (m, 2H), 7.58 (s, 1H), 7.50 (m, 2H), 2.49 (s, 3H).

D. 2-Bromomethyl-6-chloronaphthalene.

The title compound is prepared as described in Example 7, part C, substituting 2-chloro-6-methyl naphthalene for 4-chloro-7-methylquinazoline. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (m, 2H), 7.78 (s, 1H), 7.76 (m, 2H), 7.52 (d, 1H), 7.42 (d, 1H), 4.62 (s, 2H).

EXAMPLE 13. 2-(Benzhydrylidene-amino)-4-bromomethyl-benzonitrile.

A. 2-(Benzhydrylidene-amino)-4-methyl-benzonitrile.

To a solution of 2-amino-4-methyl benzonitrile (20 g, 151 mmol) in 1000mL of dichloroethane is added benzophenone imine (30g, 166mmol). The solution is refluxed for 48 hours After this time, the solution is cooled to ambient temperatures. The solution is washed with sat. $NaHCO_3$, water and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The product is further purified by recrystallization from t-butyl ether. The title compound (25.5g, 118mmol) is obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.88 (m, 2H), 7.42 (m, 3H), 7.32 (m, 7H), 6.79 (d, 1H), 6.58 (s, 1H), 2.23 (s, 3H).

B. 2-(Benzhydrylidene-amino)-4-bromomethyl-benzonitrile.

To a solution of 2-(benzhydrylidene-amino)-4-methyl-benzonitrile (11.2g, 37.8mmol) in 500mL of CCl_4 is added N-bromosuccinimide (7.06g, 39.7mmol), and benzoyl peroxide (0.92g, 3.8mmol). The solution is heated to reflux for 16 hours. After this time, the solution is filtered and the organic solution is concentrated under vacuum. The residue is purified by column chromatography eluting with a gradient of 20%t-butyl ether/hexanes to 25% t-butyl ether/hexanes. The product is obtained as an oil containing a mixture of the desired monobromide, dibromide and unreacted starting material. The mixture is assayed by proton NMR and is found to have a purity between 60-75%. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (m, 2H), 7.42 (m, 9H), 6.92 (d, 1H), 6.81 (s, 1H), 4.29 (s, 2H).

EXAMPLE 14. 7-Bromomethyl-4-chloroquinoline.

A. 7-Methyloxycarbonyl-4-chloroquinoline.

4-Chloro-7-trifluoromethylquinoline (5.0 g, 21.6 mmol) in 100 mL 80% H_2SO_4 is heated to 200°C for 24 hours in a sealed tube. The solution is cooled, poured into water and neutralized with sodium hydroxide to pH ~ 3-4. The precipitated solid is collected, washed with water and dissolved in 2 N sodium hydroxide. The aqueous solution is washed with ethyl acetate then acidified to pH~3-4. The precipitate is collected, washed with water and dried in a vacuum oven overnight to yield 7-carboxy-4-chloroquinoline as a solid (5.1 g, 24.6 mmol). A portion of this material (2.0 g, 9.6 mmol) is treated with anhydrous THF (200 mL) and DMF (2

mL) and 2 M oxalyl chloride in methylene chloride (14.5 mL, 29 mmol). The resulting suspension is stirred at room temperature for 2 h then treated with methanol (10 mL). After stirring 30 minutes the solution is concentrated and the residue is taken up in methylene chloride. The solution is washed with saturated sodium bicarbonate and dried (sodium sulfate) and concentrated to yield the title compound as a solid (2.1 g, 9.5 mmol). MS m/z: M^+ = 221; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.6 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.65 (d, 1H), 7.45 (s, 1H), 3.95 (s. 3H).

B. 7-Hydroxymethyl-4-chloroquinoline.

7-Methyloxycarbonyl-4-chloroquinoline (2.1 g, 9.5 mmol) is dissolved in anhydrous THF (25 mL) and anhydrous ether (200 mL). The solution is cooled in a dry ice/acetone bath and treated 1M lithium aluminum hydride in THF (11.0 mL, 11 mmol). The solution is warmed (approximately -45°C) for 20 minutes and quenched with ethyl acetate. The solution is diluted with ether (100 mL) and treated with water (36 mL), 15% NaOH (36 mL) and water (36 mL) in succession. The mixture is filtered and evaporated to yield the title compound as a residue (2.0 g, 9.7 mmol) which is dried under vacuum and used without further purification. MS m/z: M^+ = 193; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 7.6 (d, 1H), 7.45 (d, 1H), 4.8 (s, 2H).

C. 7-Bromomethyl-4-chloroquinoline.

7-Hydroxymethyl-4-chloroquinoline (0.2 g, 0.97 mmol) is treated with 48 % HBr and heated to 120°C for 1 hours. The resulting solution is cooled with ice, diluted with water and treated with ethyl acetate and sodium bicarbonate until basic to pH paper. The layers are separated and the organic layer is washed with water, dried (Na_2SO_4) and concentrated to give 7-bromomethyl-4-chloroquinoline (0.23 g, 0.9 mmol). MS m/z: M^+ = 255; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (d, 1H), 8.25 (d, 1H), 8.1 (s, 1H), 7.7 (d, 1H), 7.5 (d, 1H), 4.7 (s. 2H).

EXAMPLE 15. 7-Bromomethyl-4-chlorocinnoline.

A. 4-methyl-2-nitrophenylethanone.

4-Fluro-3-nitrotoluene (7.5 g, 48.4 mmol) is treated with a solution of nitroethane (15.2 mL, 200 mmol) in ethyl acetate (100 mL) and DBU (21 mL, 145 mmol) and stirred overnight at ambient temperature. The solution is concentrated under vacuum, diluted with methanol, treated with 30% H_2O_2 (25 mL) and 10% sodium bicarbonate (25 ml) and stirred overnight at ambient temperature. The reaction mixture is concentrated in vacuo, acidified with 5% HCl and extracted with methylene chloride. The organic layer is dried (sodium sulfate) and chromatographed (35% ethyl acetate/hexane) to give the title compound (7.2 g, 40.2 mmol).

MS m/z: M^+ = 279; ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.8 (s, 1H), 7.48 (d, 1H), 7.32 (d, 1H), 2.5 (s, 3H), 2.4 (s, 3H).

B. 2-Amino-4-methylphenylethanone.

A solution of 4-methyl-2-nitrophenylethanone (5.0 g, 28 mmol) in methanol (100 mL) is treated with ammonium formate (9.6 g, 140 mmol) and 5% palladium on carbon (1.5 g). The mixture is heated to 60°C for 6 h then stirred at ambient temperature for 16 hours. The reaction mixture is filtered through Celite and the filtrate is concentrated in vacuo. The concentrate is treated with sodium bicarbonate and partitioned between water and ethyl acetate. The organic layer is separated, dried with sodium sulfate and concentrated to give crude title compound (4.5 g, 30.2 mmol) which is used without further purification. MS m/z:M^+ = 149; ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.05 (d, 1H), 7.4 (d, 1H), 7.25 (s, 1H), 2.8 (s, 3H), 2.45 (s, 3H).

C. 7-Methyl-1-H-cinnolin-4-one.

A solution of 2-amino-4-methylphenylethanone (5.0 g, 33.6 mmol) in concentrated HCl (100 mL) is treated, in portions, with a solution of sodium nitrite (5.7 g, 82.6 mmol) in water (~ 10 mL). The resulting solution is stirred at 60°C for 2 hr, cooled to ambient temperature and diluted with a saturated solution of sodium acetate (~ 200 mL). Solid sodium acetate is added portionwise until the solution tested basic to pH paper. Upon stirring, the title compound precipitated as a white solid which is collected and air dried (2.3 g, 14.3 mmol). MS m/z: $[M+H]^+$ = 161; ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.1 (d, 1H), 7.85 (s, 1H), 7.45 (s, 1H) 7.3 (d, 1H), 2.55 (s, 3H).

D. 4-Chloro-7-methylcinnoline.

7-Methyl-1-H-cinnolin-4-one (1.3 g, 8.1 mmol) is treated with about 80 mL of chlorobenzene and heated until the solid dissolves. The resulting solution is cooled and treated with pyridine (0.16 mL, 2 mmol) and $POCl_3$ (1.13 mL, 12.2 mmol). The solution is heated to reflux for 1 h then concentrated to dryness. The residue is chromatographed (20 % ethyl acetate/hexane) to yield the title compound as a tan solid (~ 1 g, 5.6 mmol). MS m/z (M+=178); ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.3 (s, 1H), 8.35 (s, 1H), 8.1 (d, 1H), 7.7 (d, 1H), 2.68 (s, 3H).

E. 7-Bromomethyl-4-chlorocinnoline.

A solution of 4-chloro-7-methylcinnoline (0.6 g, 3.37 mmol) in carbon tetrachloride (30 mL) is treated with N-bromosuccinimide (0.64 g, 3.4 mmol) and a catalytic amount of 70 % benzoyl peroxide (0.22 g, 0.63 mmol). The solution is heated to 80 °C overnight, then filtered. The filtrate is concentrated in vacuo and the resulting residue is chromatographed (20 % ethyl acetate/ methyl chloride) to give the title compound (0.3 g, 1.2 mmol) and some unreacted

starting material (0.1 g, 0.56 mmol). MS m/z: $[M+H]^+$ = 257; ^1H NMR ($CDCl_3$, 300MHz) δ 9.35 (s, 1H), 8.55 (s, 1H), 8.2 (d, 1H), 8.85 (d, 1H), 4.75 (s, 2H).

EXAMPLE 16. 6-Bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole.

A. 1H-Indole-6-carboxylic acid methyl ester.

To a solution of 6-indole carboxylic acid (0.91 g, 5.67 mmol) in 33 mL of 2:1 THF/MeOH is added (trimethylsilyl)diazomethane (5.0 mL of a 2.0M solution in hexanes, 10.0 mmol). The mixture is stirred for 3 h and concentrated in vacuo to give the title compound (0.87 g, 4.97 mmol). The crude product is used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (bs, 1H), 8.20 (s, 1H), 7.82 (dd, 1H), 7.67 (d, 1H), 7.45 (m, 1H), 6.60 (m, 1H), 3.95 (s, 3H).

B. 3-Chloro-1H-indole-6-carboxylic acid methyl ester.

To a solution of 1H-indole-6-carboxylic acid methyl ester (5.86 g, 33.5 mmol) in 30 mL of CH_2Cl_2 is added N-chlorosuccinimide (0.58, 4.33 mmol) portionwise over 1.5 hours. The mixture is stirred for 2 h, then diluted with water. The layers are separated and the organic phase is washed with water and saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound (5.74 g, 27.3 mmol). The crude product is used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (bs, 1H), 8.19 (s, 1H), 7.90 (dd, 1H), 7.69 (d, 1H), 7.36 (d, 1H), 3.97 (s, 3H).

C. 3-Chloro-1-(toluene-4-sulfonyl)-1H-Indole-6-carboxylic acid methyl ester.

To a solution of 3-chloro-1H-indole-6-carboxylic acid methyl ester (3.00 g, 17.1 mmol) in 40 mL of THF at -78°C is added LDA(8.55 mL of a 2.0M solution in hexanes, 17.1 mmol) dropwise. The solution is stirred at -78°C for 30 minutes p-Toluenesulfonyl chloride (3.43 g, 18.0 mmol) in 15 mL of THF is added dropwise and the resulting solution is stirred at -78°C for 3 hours. The mixture is warmed to 0°C , quenched with saturated $NaHCO_3$ solution and diluted with H_2O and Et_2O. The layers are separated. The organic phase is washed with saturated $NaHCO_3$ solution, H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes to provide the title compound (3.64 g, 10.0 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 8.70 (s, 1H), 8.01 (dd, 1H), 7.80 (d, 2H), 7.70 (s, 1H), 7.60 (d, 1H), 7.38 (m, 2H), 4.00 (s, 3H), 2.49 (s, 3H).

D. [3-Chloro-1-(toluene-1-sulfonyl)-1H-indol-6-yl]-methanol.

To a solution of 3-chloro-1-(toluene-4-sulfonyl)-1H-Indole-6-carboxylic acid methyl ester (3.10 g, 8.53 mmol) in 50 mL of toluene at -78°C is added DIBAL (13.8 mL of a 1.5M solution in toluene, 20.8 mmol) dropwise. The mixture is stirred at -78°C for 2 h, then warmed to room

temperature and stirred for 2 hours. The reaction mixture is quenched by the addition of MeOH and washed with saturated disodium tartrate solution. The aqueuos layer is extracted with Et_2O. The combined organics are washed with saturated disodium tartrate solution, water and saturated NaCl solution. The organic phase is then dried over anhydrous $MgSO_4$, filtered and concentrated to give the title compound (2.88 g). The crude product is used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), 7.79 (d, 2H), 7.56 (s, 1H), 7.53 (d, 1H), 7.31 (d, 1H), 7.25 (d, 2H), 4.84 (s, 2H), 2.37 (s, 3H), 1.88 (bs, 1H).

E. 6-Bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole.

To a solution of [3-chloro-1-(toluene-1-sulfonyl)-1H-indol-6-yl]-methanol (0.45 g, 1.34 mmol) in 13 mL of Et_2O at 0°C is added phosphorous tribromide (0.04 mL, 0.40 mmol). The mixture is stirred at 0°C for 15 min, then at room temperature for 2 hours. The mixture is quenched by the addition of water/ice and diluted with Et_2O. The layers are separated and the organic phase is washed with saturated $NaHCO_3$ solution, water and saturated NaCl solution. The organic layer is dried over anhydrous $MgSO_4$, filtered and concentrated to provide the title compound (0.47 g, 1.18 mmol) as an oil. The crude product is used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H), 7.79 (d, 2H), 7.59 (s, 1H), 7.50 (d, 1H), 7.35 (d, 1H), 7.27 (m, 2H), 4.66 (s, 2H), 2.39 (s, 3H).

EXAMPLE 17. 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene.

A. 3-(5-Chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester.

To a solution of 5-chloro-2-thiophene-carboxaldehyde (5.10 g, 34.8 mmol) in 100 mL of dry CH_2Cl_2 is added methyl (triphenylphosphoranylidene)acetate (11.8 g, 35.3 mmol). The resulting brown-green mixture is stirred for 19 h at room temperature. The mixture is filtered through a Celite pad, concentrated in vacuo and triturated with hexane. The white precipitate (triphenylphosphine oxide) is filtered off and the filtrate is concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to provide the title compound (6.20 g, 30.6 mmol) as a yellow solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.65 (d, 1H), 7.05 (d, 1H), 6.89 (d, 1H), 6.10 (d, 1H), 3.80 (s, 3H).

B. 3-(5-Chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol.

To a solution of 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester (5.00 g, 24.7 mmol) in 80 mL of CH_2Cl_2 at 0°C is added slowly a solution of DIBAL (36.2 mL of a 1.5M solution in toluene, 54.3 mmol). The mixture is stirred at 0°C for 15 min, then quenched by the addition of 6 mL of MeOH. The mixture is allowed to warm to room temperature, diluted with water/ice and stirred for 15 minutes. The mixture is filtered through a pad of Celite and washed with CH_2Cl_2. The layers are separated and the aqueous layer is extracted with CH_2Cl_2. The

combined organics are washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue is purified via flash column chromatography eluting with a gradient of 15% EtOAc/hexanes to 25% EtOAc/hexanes to afford the title compound (4.18 g, 23.9 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.77 (d, 1H), 6.71 (d, 1H), 6.60 (d, 1H), 6.10 (m, 1H), 4.30 (d, 2H), 1.79 (bs, 1H).

C. 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene.

To a solution of 3-(5-chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol (4.18 g, 23.9 mmol) in 140 mL of Et_2O at 0°C is added phosphorous tribromide (1.34 mL, 14.3 mmol) in 10 mL of Et_2O. The mixture is stirred at 0°C for 45 min, then at room temperature for 1.5 hours. The mixture is quenched by the addition of water/ice and diluted with Et_2O. The layers are separated and the organic phase is washed with water until neutral (3x) and once with saturated NaCl solution. The organic layer is dried over anhydrous $MgSO_4$, filtered and concentrated to provide the title compound (5.46 g, 23.0 mmol) as an oil. The crude material solidified upon storage in the freezer and can be used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.80 (m, 2H), 6.65 (d, 1H), 6.10 (m, 1H), 4.10 (d, 2H).

EXAMPLE 18. 3-(4-Bromo-furan-2-yl)-(E)-propenal.

To a solution of 4-bromo-2-furfuraldehyde (0.5 g, 2.86 mmol) in 30 mL of dry CH_2Cl_2 is added (triphenylphosphoranylidene)acetaldehyde (0.87 g, 2.86 mmol). The resulting mixture is stirred for 16 h at room temperature. The crude mixture is concentrated in vacuo and the residue is purified via flash column chromatography eluting with CH_2Cl_2 to provide the title compound (0.15 g, 0.75 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.62(d, 1H), 7.59 (s, 1H), 7.18 (d, 1H), 6.81 (s, 1H), 6.60 (m, 1H).

EXAMPLE 19. Acetic acid 3-(6-methoxy-pyridin-3-yl)-(E)-allyl ester.

To a solution of 3-(6-methoxy-pyridin-3-yl)-prop-2-(E)-en-1-ol (0.39 g, 2.36 mmol, prepared as described in EXAMPLE 17 from 6-methoxy-pyridine-3-carbaldehyde (J. Org. Chem. 1990, 72)) in 8 mL of CH_2Cl_2 at 0°C is added triethylamine (0.66 mL, 4.72 mmol), DMAP (0.05 g, 0.40 mmol) and Ac_2O (0.33 mL, 3.54 mmol). The mixture is stirred at 0°C for 45 min, then at room temperature for 16 hours. The mixture is diluted with Et_2O and washed with 1N HCl, water, saturated $NaHCO_3$ solution and saturated NaCl solution. The organic layer is dried over anhydrous $MgSO_4$, filtered and concentrated. The residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to afford the title compound (0.25 g, 1.21 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d,

1H), 7.68 (dd, 1H), 6.72 (d, 1H), 6.60 (d, 1H), 6.18 (dt, 1H), 4.73 (d, 2H), 3.95 (s, 3H), 2.10 (s, 3H).

EXAMPLE 20. 2-(3-Bromo-prop-1-ynyl)-5-chloro-thiophene.

A. 3-(5-Chloro-thiophen-2-yl)-prop-2-yn-1-ol.

Nitrogen (g) is bubbled through a solution of 5-bromo-2-chloro-thiophene (1.00 g, 5.06 mmol) in 8 mL of piperidine. After 5 min, propargyl alcohol (0.32 mL, 5.56 mmol), tetrakis(triphenylphosphine) palladium(0) (0.06 g) and CuI (catalytic amount) are added to the solution. The mixture is heated at 80°C for 1 h in a sealed glass vessel. At this time, the mixture is cooled and diluted with EtOAc/Et_2O. The organic layer is washed 3N HCl, water, saturated $NaHCO_3$ solution and saturated NaCl solution. The organic layer is dried, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to give the title compound (0.8 g, 0.46 mmol) as an oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.99 (d, 1H), 6.80 (d, 1H), 4.49 (s, 2H), 1.90 (bs, 1H). EI MS, $[M]^+$=172, 174 (Cl pattern).

B. 2-(3-Bromo-prop-1-ynyl)-5-chloro-thiophene.

The title compound is prepared as described in EXAMPLE 17, Part C, using 3-(5-chloro-thiophen-2-yl)-prop-2-yn-1-ol in place of 3-(5-chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol. The crude product is used in the subsequent step without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, 1H), 6.80 (d, 1H), 4.98 (d, 2H).

EXAMPLE 21. 2-Bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A. 5-Chloro-2-methyl-indole-1-carboxylic acid tert-butyl ester.

A solution containing 5-chloro-2-methylindole (4.0 g, 24.1 mmol) and DMAP (295 mg, 2.42 mmol) in anhydrous THF (100 mL) is cooled to 0°C. A solution containing $(Boc)_2O$ (5.27 g, 24.1 mmol) in anhydrous THF (100 mL) is then added over a 20 min period. The reaction mixture is stirred for 2 h at 0°C and then at ambient temperature for 16 hours. The reaction mixture is concentrated and the crude residue is purified by flash silica gel chromatography (2% EtOAc/hexane to 5% EtOAc/hexane) to provide 5.2 g (81%) of title compound as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.57 (s, 3H), 6.24 (t, J = 0.9 Hz, 1H), 7.16 (dd, J = 8.8, 2.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H) ppm; MS (EI): m/z 265 (M+).

B. 2-Bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A solution containing 5-chloro-2-methyl-indole-1-carboxylic acid tert-butyl ester (3.0 g, 11.3 mmol), NBS (1.33 g, 11.3 mmol), and benzoyl peroxide (0.4 g, 1.13 mmol) in CCl_4 (100

mL) is heated at 80°C for 3 hours. An additional portion of NBS (0.65 g, 5.65 mmol), and benzoyl peroxide (0.2 g, 0.56 mmol) is then added and the reaction mixture is heated for an additional 3 hours. After cooling to ambient temperature, the reaction mixture is filtered. The filtrate is concentrated to a brown oil which is triturated with hexane to remove residual succinimide, filtered, and concentrated. The resultant oil (4.5 g, >100%) is used directly in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 9H), 4.88 (s, 2H), 6.63 (s, 1H), 7.27 (dd, J = 9.0, 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H) ppm; MS (EI): m/z 343 (M+).

EXAMPLE 22. 3-Bromomethyl-5-iodo-2-methoxy-pyridine

A. 5-Iodo-3-methyl-2-methoxy-pyridine.

To a solution containing 2-bromo-5-iodo-3-methyl-pyridine (4.80 g, 16.0 mmol) in DMSO (15 mL) is added methanolic NaOMe (3.33 M, 5.3 mL, 17.7 mmol) at 0 °C. The solution is allowed to warm to ambient temperature and then heated at 70°C for 1 hour. The reaction mixture is diluted with diethyl ether (300 mL) and water (200 mL) and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 2.86 g (71%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.90 (s, 3H), 7.60 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H) ppm; MS (EI): m/z 249 (M+).

B. 3-Bromomethyl-5-iodo-2-methoxy-pyridine.

A solution containing 5-iodo-3-methyl-2-methoxy-pyridine (1.00 g, 4.00 mmol) and NBS (0.78 g, 4.40 mmol) in CCl_4 (20 mL) is warmed to reflux. AIBN is added in 5 mg portions (0.03 mmol) every hour. After 3 h, the reaction mixture is cooled and then concentrated in vacuo. The residue is dissolved in EtOAc (150 mL) and washed successively with aqueous $Na_2S_2O_3$ (100 mL), water (100 mL), brine then dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product ispurified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 0.72 g (55%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.38 (s, 2H), 7.83 (d, J = 2.2 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H) ppm; MS (EI): m/z 327 (M+).

EXAMPLE 23. 5-Bromomethyl-6-methoxy -nicotinic acid methyl ester.

A. 6-Methoxy-5-methyl-nicotinic acid methyl ester.

A solution containing 5-iodo-3-methyl-2-methoxy-pyridine (10.0 g, 40.0 mmol), Et_3N (8.0 g, 80.0 mmol), and $(Ph_3P)_4PdCl_2$ (2.80 g, 4.00 mmol) in 1:1 DMF/MeOH (100 mL) is cooled to

0°C. Carbon monoxide is bubbled into the cooled solution for approx. 5 min at which time the reaction mixture is sealed under a balloon of CO. The reaction mixture is allowed to warm to ambient temperature and then stirred for 16 hours. The reaction mixture is concentrated in vacuo and the residue is partitioned between water (300 mL) and EtOAc (300 mL) and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 4.10 g (57%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.88 (s, 3H), 4.00 (s, 2H), 7.96 (d, J = 2.2 Hz, 1H), 8.65 (d, J = 2.2 Hz, 1H) ppm; MS (ISP loop): m/z 182 (M+H).

B. 5-Bromomethyl-6-methoxy -nicotinic acid methyl ester.

A solution containing 6-methoxy-5-methyl-nicotinic acid methyl ester (4.00 g, 22.1 mmol), NBS (5.11 g, 28.7 mmol), and AIBN (0.90 g, 5.5 mmol) in CCl_4 (100 mL) is warmed to reflux. After 5 h, the reaction mixture is cooled and then concentrated in vacuo. The residue is dissolved in EtOAc (500 mL) and washed successively with aqueous $Na_2S_2O_3$ (300 mL), water (100 mL), brine then dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 9:1) to provide 3.10 g (54%) of the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.07 (s, 3H), 4.46 (s, 2H), 8.19 (d, J = 2.2 Hz, 1H), 8.79 (d, J = 2.2 Hz, 1H) ppm; MS (EI): m/z 259 (M+).

EXAMPLE 24. 5-Chloro-2-thienyloxyacetic acid.

A. 2-Hydroxy-thiophene.

Thiophene (42g, 500mmol) is dissolved in ether (250mL). To the solution is added n-BuLi (200mL of a 2.5N solution in hexanes, 500mmol) at a rate which maintains a gentle reflux. After addition, the solution is stirred for 0.5 hour. The solution is then cooled to -78°C and triethyl borate (102 g, 700mL) is added dropwise. The solution is stirred for 3 hours. The cold bath is removed and 130mL of a 30% H_2O_2 is added dropwise with rapid stirring. After addition, the solution is allowed to refluxed for an additional 20 minutes. The solution is then cooled to 0°C and acidified to pH=3 with 6N HCl. The resulting solution is extracted with ether. The organic solution is washed with 10% ferric ammonium sulfate, water and saturated NaCl. The solution is dried over $MgSO_4$, filtered and concentrated under vacuum. The title compound (32g, 320mmol) is obtained as an oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.60 (m, 1H),6.35 (m, 1H), 4.12 (d, 2H).

B. Ethyl 2-thienyloxyacetate.

To a solution of 2-hydroxy-thiophene (32g, 320 mmol) in $CHCl_3$ (500mL) is added ethyl bromoacetate (53.4 g, 320 mmol). To the resulting solution is added a solution containing n-Bu_4NHSO_4 (25g, 74mmol) and NaOH (15.8g, 394 mmol) in water (500mL). After addition, the solution is stirred vigorously using mechanical stirring. The reaction is stirred for 12 hours. After this time, the layers are separated. The aqueous layer is extracted with $CHCl_3$. The combined organic layers are washed with water and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 30%CH_2Cl_2:hexanes to 60%CH_2Cl_2:hexanes. The title compound (11.5g, 62mmol) is obtained as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 6.68 (dd, 1H), 6.60 (d, 1H), 6.22 (d, 1H), 4.62 (s, 2H), 4.30 (q, 2H), 1.31 (t, 3H).

C. Ethyl 5-chloro-2-thienyloxyacetate.

To a solution of ethyl 2-thienyloxyacetate (1.1g, 5.9mmol) in acetic acid (15mL) is added N-chlorosuccinimide (0.78g, 5.9mmol). The solution is stirred for 1.5 hour. After this time the solution is concentrated. The resulting oil is dissolved in ether and washed with 1N NaOH, water and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The title compound (1.26g, 5.7mmol) is obtained as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 6.52 (d, 1H), 6.06 (d, 1H), 4.60 (s, 2H), 4.24 (q, 2H), 1.31 (t, 3H).

D. 5-Chloro-2-thienyloxyacetic acid.

To a solution of ethyl 5-chloro-2-thienyloxyacetate (0.39g, 1.77mmol) in 9mL of a 1:1:1 mixture of CH_3OH:THF:water is added LiOH (0.38g, 9.0 mmol). The solution is stirred for 16 hours. After this time, the solution is concentrated to 1/3 its volume. The resulting solution is acidified to pH=3 with 1N HCl. The aqueous solution is extracted with CH_2Cl_2. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The title compound (0.32g, 1.66mmol) is obtained as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 6.50 (d, 1H), 6.07 (d, 1H), 4.66 (s, 2H).

EXAMPLE 25. 3-(5-Chloro-thiophen-2-yl)-(E)-acrylic acid.

To a mixture of 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester (0.60 g, 2.96 mmol) in 15 mL of 1:1:1 THF/MeOH/H_2O at 0°C is added lithium hydroxide monohydrate (0.62 g, 14.7 mmol). The mixture is stirred at 0°C for 1 h, then at room temperature for 1 h and concentrated in vacuo. The residue is diluted with EtOAc and washed with 1N HCl. The aqueous layer is extracted with EtOAc and the combined organics are washed with water (2x), dried, filtered and concentrated to provide the title compound (0.54 g, 2.86 mmol) as a white

solid. The crude material can be used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.65 (d, 1H), 7.05 (d, 1H), 6.90 (d, 1H), 6.10 (d, 1H).

EXAMPLE 26. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid.

A. 4-Chloro-2-thiophene-carboxaldehyde.

To a solution of 2-thiophene-carboxaldehyde (6.33 g, 56.4 mmol) in 100 mL of $CHCl_3$ at 0°C is added aluminum trichloride (16.8 g, 126 mmol) portionwise over a few minutes. In a separate vessel, chlorine gas (4.00 g) is bubbled for about 2 min into 100 mL of CCl_4 at 0°C and then added to the former mixture slowly at 0°C . The resulting mixture is stirred at 0°C for 45 min, then allowed to warm to room temperature and stirred overnight. After 16 h, the reaction mixture is poured slowly into 6N HCl at 0°C , then stirred at room temperature for 2 hours. The layers are separated. The aqueous layer is extracted with $CHCl_3$. The combined organic layers are washed with H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with 10% EtOAc/hexanes to yield the title compound (6.70 g, 45.9 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.87 (s, 1H), 7.64 (s, 1H), 7.63 (s, 1H).

B. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester.

The title compound is prepared as described in EXAMPLE 1, Part A from 4-chloro-2-thiophene-carboxaldehyde. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 6.25 (d, 1H), 3.82 (s, 3H).

C. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid.

The title compound is prepared as described in EXAMPLE 1, Part B from 3-(4-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, 1H), 7.19 (d, 2H), 6.25 (d, 1H).

EXAMPLE 27. (5-Chloro-thiophen-2-yl)-acetic acid.

A. [2-(5-Chloro-thiophen-2-yl)-1-dimethylaminovinyl]phosphonic acid diethyl ester.

To a suspension of sodium hydride (0.25 g, 6.25 mmol, 60% mineral oil dispersion) in 10 mL of THF is added slowly a solution of tetraethyl dimethylaminomethylenediphosphonate (2.03 g, 6.14 mmol, prepared according to the procedure described in Psaume, Montury, and Cosmetic Comm. 1982, 12, 415) in 10 mL of THF. After stirring 1 h, a solution of 5-chloro-2-thiophene carboxaldehyde (0.90 g, 6.14 mmol) in 10 mL of THF is added. The resulting mixture is heated at reflux for 1 h, then cooled to room temperature. The reaction mixture is partitioned between Et_2O and water. The organic layer is washed sequentially with 1N HCl, water and

saturated NaCl, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified via flash column chromatography eluting with a gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to afford the title compound (1.52 g, 4.69 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 1H), 6.95 (d, 1H), 6.82 (d, 1H), 4.15 (m, 4H), 2.62 (s, 6H), 1.60 (t, 6H).

B. (5-Chloro-thiophen-2-yl)-acetic acid.

A mixture of [2-(5-chloro-thiophen-2-yl)-1-dimethylaminovinyl]phosphonic acid diethyl ester (1.52 g, 4.69 mmol) and 30 mL of 6N HCl is heated at reflux for 2 hours. After cooling to room temperature, ice water is added and the mixture is partitioned between Et_2O and water. The organic layer is washed with water (2x), dried over $MgSO_4$, filtered and concentrated to give the title compound (0.62 g, 3.51 mmol) as a brown solid. The crude material can be used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (bs, 1H), 7.79 (d, 1H), 6.71 (d, 1H), 3.81 (s, 2H).

EXAMPLE 28. 3-(5-Chloro-thiophen-2-yl)-propionic acid.

A. 3-(5-Chloro-thiophen-2-yl)-propionaldehyde.

To a mixture of $Pd(OAc)_2$ (0.12 g, 0.53 mmol), $NaHCO_3$ (0.52 g, 6.19 mmol) and NaI (0.28 g, 1.87 mmol) in 5 mL of HMPA is added 5-bromo-2-chloro-thiophene (1.00 g, 5.06 mmol) and allyl alcohol (1.03 mL, 15.2 mmol). The mixture is heated to 90°C and stirred for 16 hours. The reaction mixture is cooled to room temperature, diluted with Et_2O and washed with water. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue is purified by flash column chromatography eluting with a gradient of 10% Et_2O/hexanes to 20% Et_2O/hexanes to provide the product (0.18 g, 1.03 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, 1H), 6.71 (d, 1H), 6.58 (d, 1H), 3.07 (t, 2H), 2.81 (t, 2H).

B. 3-(5-Chloro-thiophen-2-yl)-propionic acid.

Silver nitrate (117 mg, 0.69 mmol) in 1 mL of H_2O is added to 1.36 mL of 1N NaOH at 0°C and stirred for 5 minutes. To the brown suspension is added 3-(5-chloro-thiophen-2-yl)-propionaldehyde (60 mg, 0.34 mmol) and the resulting mixture is allowed to warm to room temperature over 2 hours. The precipitate is filtered and washed with hot water (2x). The combined aqueous layers are acidified with 6 N HCl and extracted with EtOAc (2x). The combined organic layers are washed with water (2x), then dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound (50 mg, 0.26 mmol) as a beige solid. The crude material can be used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.72 (d, 1H), 6.60 (d, 1H), 3.07 (t, 2H), 2.71 (t, 2H).

EXAMPLE 29. 3-Fluorophenoxy-acetic acid.

A. 3-Fluorophenoxy-acetic acid ethyl ester.

To a solution of 3-fluorophenol (1.2g, 11.8mmol) in 20mL of DMF at 0°C is added sodium hydride (0.47g, 10.7mmol). After stirring for 10 minutes Ethyl bromoacetate (1.2g, 10.7 mmol) is added dropwise. The reaction is allowed to warm to ambient temperatures and is stirred for 16 hours. To the reaction is added a saturated solution NH_4Cl (aq.). The resulting mixture is diluted with EtOAc and H_2O. The layers are separted. The organic layer is washed with H_2O and a saturated solution NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product (2g, 10mmol) as an oil. ^1H NMR ($CDCl_3$, 300MHz) δ 7.22 (m, 1H), 6.65 (m, 3H), 4.61 (s, 2H), 4.27 (q, 2H), 1.24 (t, 3H).

B. 3-Fluorophenoxy-acetic acid.

To a solution of ethyl 3-fluorophenoxy-acetate (2g, 10mmol) in 24mL of a 1:1:1 solution of MeOH:H_2O:THF is added lithium hydroxide monohydrate (2.25g, 54mmol). The solution is stirred for 16 hours. After this time, the solution is concentrated under reduced pressure to 1/3 of its volume. The remaining solution is acidified to pH=3 with 1N HCl (aq.). The aqueous solution is extracted with EtOAc. The organic layer is washed with a saturated solution NaCl (aq.). The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product (1.65g, 9.7mmol) as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 9.8 (bs, 1H), 7.28 (m, 1H), 6.69 (m, 3H), 4.70 (s, 2H).

EXAMPLE 30. 2-Chloropyrdin-3-ylamino-acetic acid.

To a solution of 3-amino-2-chloropyridine (1.0g, 7.8mmol) in 20mL of MeOH is added glyoxylic acid (0.86mL of a 50% by weight solution in H_2O, 7.8mmol). After stirring for 10 minutes, $NaCNBH_3$ (1.54 g, 23mmol) is added. The reaction is stirred for 16 hours., then is concentrated under reduced pressure. The resulting residue is dissolved in H_2O. The solution is acidified to pH=3 with 1N HCl (aq.). The solution is extracted with EtOAc/CH_2Cl_2 (2:1). The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting product is obtained as a white solid (0.95g, 5.1mmol). ^1H NMR (d6-DMSO, 300MHz) δ 12.7 (bs, 1H), 7.62 (m, 1H), 7.44 (m, 1H), 6.90 (m, 1H), 5.8 (bs, 1H), 3.95 (AB, 2H).4.70 (s, 2H).

EXAMPLE 31. 5-Chlorothiophen-2-yl-sulfanyl acetic acid.

A. Thiophen-2-yl-sulfanyl acetic acid ethyl ester.

To a solution of thiophene-2-thiol (1.49g, 116mmol) in 40mL of CH_3CN is added ethyl bromoacetate (2.14g, 167mmol) followed by K_2CO_3 (3.54g, 138mmol). The solution is stirred for 16 hours. After this time, the solution is filtered. The solvent is evaporate to give the

product as an oil (2.4g, 118mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.37 (m, 1H), 7.21 (m, 1H), 6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H). MS (EI): m/z 202 (M+).

B. 5-Chlorothiophen-2-yl sulfanyl acetic acid.

To a solution of thiophen-2-yl-sulfanyl acetic acid ethy (0.52g, 2.6mmol) in 25 mL of CH_2Cl_2 is added N-chlorosuccinimide (0.35g, 2.6mmol). The solution is stirred for 10 minutes. After this time, 1 drop of TFA is added. The solution is stirred for 16 hours. The reaction mixture is then diluted with 25 mL of CH_2Cl_2. The resulting solution is washed with 1N NaOH and a saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting product is obtained as an oil which is determined to contain 45% of the desired product. The oil is then dissolved in 60 mL of 1:1:1 THF:MeOH:H_2O. To the solution is added lithium hydroxide monohydrate (1.26g, 30mmol). The solution is stirred for 16 hours. After this time, the solution is acidified to pH=3 with 1N HCl. The aqueous solution is washed with H_2O and saturated NaCl solution. The solution is extracted with EtOAc/CH_2Cl_2 (2:1). The organic layer is dried over $MgSO_4$, filtered and concentrated. The resulting crude product is purified by column chromatography eluting with 20% MeOH:Et_2O to give the product as a white solid (0.4g, 1.9mmol). MS (EI): m/z 208, 210 (M+), Cl pattern.

EXAMPLE 32. 5'-Chloro-[2,2']bithiophenyl-5-carboxylic acid.

A. 5'-Chloro-[2,2']bithiophenyl-5-carbaldehyde.

To a solution of 5-chloro-[2,2']bithiophene (1.06 g, 5.28 mmol) in 12 mL of THF at -78°C is added n-BuLi (4.4 mL of a 1.6M solution in hexanes, 6.99 mmol). After 15 minutes, DMF (0.97 mL, 14 mmol) is added and the resulting solution is allowed to warm to 0°C. After 15 min, the solution diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. The organic solution is washed with H_2O and saturated NaCl solution, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified by flash column chromatography eluting with a gradient of 10% Et_2O/hexanes to 20% Et_2O/hexanes to yield the title compound (0.89 g, 3.89 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.87 (s, 1H), 7.70 (d, 1H), 7.20 (d, 1H), 7.15 (d, 1H), 6.91 (d, 1H).

B. 5'-Chloro-[2,2']bithiophenyl-5-carboxylic acid.

The title compound is prepared as described in EXAMPLE 28, Part B using 5'-chloro-[2,2']bithiophenyl-5-carbaldehyde. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 1H), 7.09 (d, 1H), 7.06 (d, 1H), 6.89 (d, 1H). EI MS, $[M]^+$=243,245 (Cl pattern).

EXAMPLE 33. 7-Chloro-isoquinoline-3-carboxylic acid.

A. 7-Chloro-isoquinoline-3-carbaldehyde.

A 20mL of 80% H_2SO_4 is added 7-chloro-3,3-dibromomethyl isoquinoline (0.69g, 2.06mmol) is heated to 150°C for 16 hours. The solution is then cooled to ambient temperatures and diluted with 40 mL of H_2O. The resulting solution is basified to pH=11 with 1N NaOH. The aqueous solution is extracted with CH_2Cl_2. The organic solution is washed with H_2O and a saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product as an oil (0.25g, 1.3 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 10.0 (s, 1H), 9.30 (s, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 7.95 (d, 1H), 7.78 (d, 1H). MS (EI): m/z 191, 193 (M+), Cl pattern.

B. 7-Chloro-isoquinoline-3-carboxylic acid.

To 4.5 mL of a 1N NaOH solution at 0°C is added a solution of $AgNO_3$ (0.31g, 1.8mmol) in 3 mL of H_2O, followed by a solution of of 7-chloro-isoquinoline-3-carbaldehyde (0.25g, 1.3mmol) in 3 mL of EtOH. The solution is stirred at 0°C for 10 minutes, then at room temp. For 3 hours. The solution is acidified to pH=3 with 1H HCl. The resulting solution is extracted with $CHCl_3$. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product as a white solid (0.2g, 0.96mmol). ^1H NMR (CD_3OD, 300MHz) δ 9.18 (s, 1H), 8..63 (s, 1H), 8.18 (m, 1H), 7.80 (m, 2H). 6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H). MS (EI): m/z 208, 210 (M+), Cl pattern.

EXAMPLE 34. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid.

A. 4-(5-Chloro-thiophen-2-ylmethylene)-2-methyl-4H-oxazol-5-one.

A mixture consisting of 5-chlorothiophene-2-carboxaldehyde (1.00 g, 6.82 mmol), N-acetylglycine (0.96 g, 8.18 mmol), NaOAc (0.67 g, 8.18 mmol) in Ac_2O (5 mL) is warmed at reflux for 16 hours. The reaction mixture is cooled to ambient temperature and diluted with dilute aqueous NaOH (0.5 M, 100 mL) and CH_2Cl_2 (100 mL). The layers are separated and the organic phase is washed with aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 1.5 g (100%) of the title compound as a colorless oil which is used without further purification in the next reaction. ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 6.94 (d, J = 4.0 Hz, 1H), 7.21 (s, 1H), 7.26 (d, J = 4.0 Hz, 1H) ppm.

B. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid.

To a solution containing 4-(5-chloro-thiophen-2-ylmethylene)-2-methyl-4H-oxazol-5-one (1.5 g, 6.82 mmol) in MeOH (18 mL) is added 1.0 M NaOH (12.0 mL, 12 mmol) at ambient temperature. After 3 h, the reaction mixture is diluted with water (100 mL) and CH_2Cl_2 (100 mL) and the layers are separated. The basic, aqueous layer is washed with CH_2Cl_2 and then acidified using 1.0 M HCl (20 mL) to provide a crude solid which is collected on a Buchner

funnel. Drying in vacuo provided 1.2 g (75%) of the title compound as a pale brown solid which is used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H), 7.14 (d, J = 4.01 Hz, 1H), 7.38 (d, J = 4.01 Hz, 1H), 7.63 (s, 1H), 9.28 (s, 1H), 12.73 (br s, 1H) ppm; MS (EI): m/z 245 (M+).

EXAMPLE 35. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-propionic acid.

To a solution containing 2-acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid (1.00 g, 4.08 mmol) and K_2CO_3 (1.70 g, 12.1 mmol) in DMF (20 mL) is added MeI (0.87 g, 6.12 mmol) at ambient temperature. After 2 h, the reaction mixture is diluted with water (100 mL) and EtOAc (100 mL) and the layers are separated. The aqueous layer is extracted with EtOAc (50 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 0.92 g (83%) of the methyl ester which is used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.77 (s, 3H), 6.86 (d, J = 4.02 Hz, 1H), 6.99 (m, 1H), 7.05 (d, J = 4.02 Hz, 1H), 7.64 (s, 1H) ppm.

A small Parr® vessel is charged with the crude ester (0.85 g, 3.13 mmol) and $(Ph_3P)_3RhCl$ (0.10 g, 0.10 mmol) in MeOH (50 mL). The vessel is pressurized to 50 PSI H_2 pressure and agitated for 7 h at ambient temperature. The reaction mixture is then filtered and concentrated to provide the desired compound, which is used without further purification. MS (EI): m/z 261 (M+).

The above-prepared saturated ester is dissolved in a 1:1:1 solution of water/THF/MeOH (15 mL). LiOH monohydrate (0.14 g, 3.23 mmol) is added and the heterogeneous mixture is stirred for 16 hours. The reaction mixture is diluted with water (100 mL) and EtOAc (100 mL) and the layers are separated. The aqueous layer is extracted with EtOAc (50 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 0.62 g (81%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.30 (m, 2H), 4.81 (m, 1H), 6.45 (br d, J = 6.45 Hz, 1H), 6.58 (d, J = 3.68 Hz, 1H), 6.71(d, J = 3.68 Hz, 1H), 9.79 (br s, 1H) ppm; MS (EI): m/z 247 (M+).

EXAMPLE 36. 3-(6-Amino-pyridin-3-yl)-acrylic acid.

A. N-(5-Bromo-pyridin-2-yl)-acetamide.

Triethylamine(17.7mL, 75 mmol) is added to a mixture of 2-amino-5-bromopyridine (5.0 g, 29 mmol) and acetic acid (7.1 mL, 75 mmol). The solution is heated to reflux for 48 hours. After this time, the solution is concentrated. The reside is dissolved in water and the pH is adjusted to 10 with 1N NaOH. The solids are collected by filtration. The crude product is

recrystallized from boiling water to give the title compound (2.6 g 12.0 mmol) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (1H, bs), 8.42 (s, 1H), 8.01 (m, 2H), 2.05 (s, 3H).

B. 3-(6-Acetylamino-pyridin-3-yl)-acrylic acid

To a mixture of N-(5-bromo-pyridin-2-yl)-acetamide (1.26 g, 5.86 mmol) and tri-n-butylamine in xylenes (10 mL)is added $Pd(OAc)_2$ (1.4 mg, 0.006 mmol) and triphenyl phosphine (15.4mg, 0.06 mmol). Acrylic acid (0.48 mL, 7.03 mmol) is then added dropwise over 5 minutes. The mixture is heated to reflux for 5 hours. The solution is cooled to ambient temperatures. The mixture is diluted with water and the pH is adjusted to 4 with 1N HCl. The solution is extracted with EtOAc/CH_2Cl_2 (2:1). The resulting suspension is filtred to give the title compound (0.80 g, 3.88 mmol) as a white solid. MS (ion spray) 207, (M+H).

C. 3-(6-Amino-pyridin-3-yl)-acrylic acid

To 3-(6-acetylamino-pyridin-3-yl)-acrylic acid (0.80 g, 3.88 mmol) in ethanol (10 mL) is added 1N NaOH (20mL). The solution is heated to reflux. After 16 h, the solution is concentrated to 1/3 its volume. The aqueous solution is diluted with water and acidified to pH=2 with 6N HCl. The solution is concentrated to dryness. The residue is dissolved in methanol. The solution is filtered. The organic solution is concentrated. The crude product is purified by RP-HPLC eluting with a gradient of 5%CH3CN/H2O (0.1% TFA) to 30% CH3CN/H2O (0.1%TFA) to give the product as a white solid (0.54 g, 1.93 mmol). ^{1}H NMR (300 MHz, CD_3OD) δ 8.34 (d, 1H), 8.07 (s, 1H), 7.54 (d, 2H), 7.06 (d, 1H), 6.47 (d, 1H). MS (ion spray) 165, (M+H).

EXAMPLE 37. 4-Chloro-benzyl isocyanate.

To a solution of triphosgene (0.54 g, 1.85 mmol) in 10 mL of dry CH_2Cl_2 at 0°C is added 4-chloro-benzylamine (0.61 mL, 5.00 mmol) dropwise as a white precipitate forms. Et_3N (1.39 mL, 10.0 mmol) in 5 mL of CH_2Cl_2 is added immediately and the resulting mixture is stirred at 0°C for 5 min, then at room temperature for 3 hours. The mixture is concentrated in vacuo and triturated with EtOAc. The white precipitate (triethylamine hydrochloride) is filtered off and the filtrate is concentrated. The title compound (6.20 g, 30.6 mmol) is isolated as a crude yellow residue and used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, 2H), 7.25 (d, 2H), 4.50 (s, 2H).

EXAMPLE 38. 5-Chloro-thiophene-2-carbonyl azide.

To a solution of 5-chloro-2-thiophene-carboxylic acid (5.00 g, 30.7 mmol) in 130 mL of acetone is added Et_3N (4.29 mL, 30.7 mmol). The mixture is cooled to 0°C and ethyl chloroformate (3.23 mL, 33.8 mmol) is added. The mixture is stirred at 0°C for 1h and sodium

azide (3.40 g, 52.3 mmol) is added. The mixture is stirred at 0°C for 2 h, then poured into 300 mL of ice water and the aqueous layer is extracted with CH_2Cl_2 (2x). The combined organics are washed with water (2x) and brine, then dried, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with 10% EtOAc/hexanes to provide the title compound (3.00 g, 16.0 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, 1H), 6.99 (d, 1H).

EXAMPLE 39. 4-Nitro-2,3,5,6-tetrachloropyridine.

Pentachloropyridine (80 g, 320 mmol) is treated with benzyl amine (104 mL, 96 mmol), dissolved in dioxane (1 L) and refluxed for 16 hours. The reaction mixture is cooled to ambient temperature and the precipitated white solid is removed by filtration. The filtrate is concentrated to a brown residue and triturated with 4 % ethyl acetate in hexane (3 X 250 mL) to give 4-benzylamino-2,3,5,6-tetrachloropyridine as an off-white solid (40 g, 124 mmol). This material is dissolved in chloroform (400 mL), cooled in an ice bath and treated with trifluoroacetic acid (500 mL) and 30% hydrogen peroxide (100 mL). The reaction mixture is warmed to room temperature overnight and treated with additional trifluoroacetic acid (500 mL) and 30% hydrogen peroxide (100 mL). After stirring 24 hours the reaction is treated with water (1L). The lower organic layer is separated and the aqueous layer is extracted with chloroform. The combined organic layers are concentrated to a solid residue and redissolved in ethyl acetate/hexane (30 mL). The suspended orange solid is removed and the filtrate is loaded on a silica flash column. The column is eluted with hexane and the title compound is collected as a white solid (15.6 g, 60 mmol). EI MS m/z 260, 262, 264 [M+].

EXAMPLE 40. 4-(tert-Butyloxycarbonyl)-piperazin-2-one

4-(Benzyloxycarbonyl)-piperazin-2-one (2.2 g, 9.4 mmol) and Boc anhydride (2.5 g, 11.3 mmol) are dissolved in methanol (100 mL), treated with 5% Pd /C and shaken 16 h under hydrogen gas (30 PSI). The reaction vessel contents are filtered through Celite and the filtrate is concentrated to yield 4-(tert-Butyloxycarbonyl)-2-oxopiperazine (1.9 g, 9.4 mmol) which is used without further purification. EI MS m/z 200, M^+; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.17 (br, 1H), 4.20 (s, 2H), 3.55 (t, 2H), 3.38 (m, 2H), 1.48 (s, 9H).

EXAMPLE 41. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. N-Cbz-O-methylserine-aminoacetaldehyde dimethyl acetal.

To a solution of N-Cbz-O-methylserine (10.8g, 41.8mmol) in 500mL of CH_2Cl_2 is added Et_3N (12.7 g, 125mmol). The solution is cooled to 0°C and TBTU (13.5g, 42mmol) and

aminoacetaldehyde dimethyl acetal (4.83g, 46mmol) are added. The solution is stirred for 16 hours. The solution is diluted with 500mL of ether. The resulting solution is washed with water, 1N $KHSO_4$, and sat. NaCl. The title compound (13.7g, 41.8mmol) is obtained as a white foam. ^1H NMR ($CDCl_3$, 300MHz) δ 7.40 (m, 5H),6.55 (bs, 1H), 5.66 (bs, 1H), 5.32 (m, 1H), 5.13 (s, 2H), 4.32 (m, 2H), 3.79 (dd, 1H), 3.44 (m, 2H), 3.40 (m, 9H).

B. N-Cbz-2-Oxo-3-(S)-methoxymethyl-(4,5-dihydro)piperazine.

To a solution of N-Cbz-O-methylserine-aminoacetaldehyde dimethyl acetal (13.7g, 41.8mmol) in 300mL of toluene is added TsOH.H2O (0.80g, 4.2mmol). The solution is heated to 60°C. After 5h, the solution is diluted with ether. The resulting organic solution is washed with water, sat. NaHCO3, and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 10%EtOAc:CH_2Cl_2 to 20%EtOAc:CH_2Cl_2. The title compound (10.7g, 38mmol) is obtained as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H), 6.45 and 6.30 (d, 1H rotational isomers), 5.61 and 5.50 (d, 1H rotational isomers), 5.20 (s, 2H), 4.92 and 4.83 (bs, 1H rotational isomers), 3.63 (m, 3H), 3.32 and 3.20 (s, 1H rotational isomers).

C. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of N-Cbz-2-oxo-3-(S)-methoxymethyl-(4,5-dihydro)piperidine (10.7g, 38mmol) in 50mL of methanol is added Pt/C (1gm, 10% by weight). The atmosphere above the reaction is replaced by hydrogen. After 24h, the solution is filtered and the filtrate is washed with methanol. The collected organic solutions are concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH/CH_2Cl_2 to 5%MeOH/CH_2Cl_2. The title compound (6.0g, 22mmol) is obtained as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.35 (m, 5H),6.42 (bs, 1H), 5.20 (AB, 2H), 4.58 (m, 1H), 4.18 (m, 1H), 3.95 (m, 1H), 3.50 (m, 4H), 3.27 (s, 3H).

EXAMPLE 42. 2-Butyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-norleucine for Cbz-O-methyl-serine. ^1H NMR ($CDCl_3$, 300mHz) δ 7.32 (m, 5H), 5.13 (AB, 2H), 4.60 (m, 1H), 4.13 (m, 1H), 3.38 (m, 2H), 3.23 (m, 2H), 1.90 (m, 1H), 1.66 (m, 1H), 1.29 (m, 4H), 0.89 (m, 3H). MS (ion spray) m/z 291, (M+H).

EXAMPLE 43. 2-Ethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-2-amino-butric acid for Cbz-O-methyl-serine. ^1H NMR ($CDCl_3$, 300mHz) δ 7.37 (m, 5H), 6.55 (bs, 1H), 5.10 (AB,

2H), 4.57 (m, 1H), 4.24 (m, 1H), 3.42 (m, 1H), 3.26 (m, 2H), 2.20 (m, 1H), 1.81 (m, 1H), 0.96 (m, 3H).

EXAMPLE 44. 2-Propyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-norvaline for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300mHz) δ 7.32 (m, 5H), 7.00 (bs, 1H), 5.12 (AB, 2H), 4.58 (m, 1H), 4.21 (m, 1H), 3.40 (m, 1H), 3.19 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 1.37 (m, 2H), 0.91 (m, 3H). MS (ion spray) m/z 277, (M+H).

EXAMPLE 45. 2-Ethoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-ethyl-serine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 5H),6.96 (bs, 1H), 5.17 (AB, 2H), 4.58 (m, 1H), 4.18 (m, 1H), 4.03 (m, 1H), 3.66 (m, 2H), 3.44 (m, 3H), 3.27 (s, 1H), 1.06 (m, 3H). MS (ion spray) m/z 293, (M+H).

EXAMPLE 46. 2-Methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-alanine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.34 (m, 5H),7.02 (bs, 1H), 5.17 (AB, 2H), 4.65 (m, 1H), 4.17 (m, 1H), 3.42 (m, 1H), 3.23 (m, 2H), 1.41 (d, 3H). MS (EI) m/z 248, (M+).

EXAMPLE 47. 2-Benzyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

The title compound is prepared as in EXAMPLE 41, substituting Cbz-phenylalanine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.22 (m, 10H), 7.00 (bs, 1H), 5.10 (AB, 2H), 4.10 (m, 1H), 3.27 (m, 2H), 3.10 (m, 2H), 2.55 (m, 2H). MS (EI) m/z 324, (M+).

EXAMPLE 48. 2-(1-Methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-methyl-threonine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.52 (bs, 1H), 7.22 (m, 5H), 5.12 (AB, 2H), 4.33 (m, 1H), 4.05 (m, 2H), 3.60 (m, 1H), 3.14 (s, 3H), 3.10 (m, 1H), 2.82 (m, 1H), 1.10 (d, 3H). MS (ion spray) m/z 293, (M+H).

EXAMPLE 49. 2,2-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-2-amino-isobutryic acid for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H),6.52 (bs, 1H), 5.12 (s, 2H), 3.72 (m, 2H), 3.33 (m, 2H), 1.68 (s, 3H), 1.64 (s, 3H). MS (EI) m/z 262, (M+).

EXAMPLE 50. 2-Isopropyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-valine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H),5.88 (bs, 1H), 5.10 (s, 2H), 4.35 (m, 1H), 3.44 (m, 1H), 3.27 (m, 2H), 2.31 (m, 1H), 1.00 (d, 3H), 0.94 (d, 2H).

EXAMPLE 51. 2-Isobutyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-leucine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.35 (m, 5H), 6.50 (m, 1H), 5.15 (s, @H), 4.18 (m, 1H), 3.42 (m, 2H), 3.21 (m, 2H), 1.50 (m, 3H), 0.90 (m, 6H).

EXAMPLE 52. 2-(2-Methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-methyl-homo-serine for Cbz-O-methyl-serine. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 5H), 6.85 (bs, 1H), 5.14 (s, 2H), 4.75 (m, 2H), 4.20 (m, 2H), 3.42 (m, 1H), 3.21 (m, 3H), 2.12 (m, 4H).

EXAMPLE 53. 2-Methoxymethyl-5-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting 2-amino-propionaldehyde dimethyl acetal for aminoacetaldehyde dimethyl acetal. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.42 (m, 5H), 6.96 (bs, 1H), 5.12 (AB, 2H), 4.52 (m, 1H), 4.21 (m, 1H), 3.92 (m, 1H), 3.58 (m, 2H), 3.22 (s, 3H), 3.10 (m, 1H), 0.95 (m, 3H).

EXAMPLE 54. 3-(R)-(tert-Butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester.

A. 2-tert-Butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propionic acid.

tert-Butyldimethylchlorosilane (32.3 g, 0.214 mol) in THF (50 mL) is added dropwise via cannula to a solution of BOC serine (20.0g, 0.098 mol) and imidazole (15.3 g, 0.224 mol) in THF (360 mL) at RT. The resulting slurry is stirred for 2.5 h then the solvent is removed in vacuo. The crude product is dissolved in MeOH (180 mL) and 5N NaOH (58 mL) is slowly added at RT. The mixture is stirred for 3 h then diluted with water (180 mL) after which time the aqueous layer is washed with ether (180 mLx2). The aqueous layer is acidified to pH 4-5 with 2N HCl and extracted with diethyl ether. The organic layer is washed with saturated $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated to dryness. The crude product (12.67g, 0.040 mol) is used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.35 (bs, 1H), 4.30 (bs, 1H), 4.13 (dd, 1H), 3.80 (dd, 1H), 1.45 (s, 9H), 0.98 (s, 9H), 0.10 (s, 6H). EI MS, $[M+H]^+$=320.

B. [2-(tert-Butyl-dimethyl-silanyloxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester.

N,N-Dimethylaminopyridine (2.60 g, 21.3 mmol) and BOP reagent (18.15 g, 41.0 mmol) are added to a solution of 2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propionic acid (12.37 g, 38.7 mmol), diisopropylethylamine (8.1 mL, 46.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (4.53 g, 46.4 mmol) in THF (260 mL) at RT. The resulting suspension is stirred at RT overnight then concentrated to dryness. The residue is diluted with EtOAc and washed with saturated NH_4Cl, saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product which is purified by flash chromatography eluting with 10-30% EtOAc/Hexanes to yield the title compound (11.86 g, 30.37 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.35 (bd, 1H), 4.71 (bs, 1H), 3.78-3.85 (m, 2H), 3.72 (s, 3H), 3.20 (s, 3H), 1.42 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H).

C. [1-(tert-Butyl-dimethyl-silanyloxymethyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester.

A solution of [2-(tert-butyl-dimethyl-silanyloxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester (11.86, 30.37 mmol) in Et_2O (100 mL) is added dropwise to a 1.0M solution of LAH in ether (35.5 mL) at -5°C-0°C . The resulting mixture is stirred for 2.5 h then an aqueous solution of $KHSO_4$ is slowly added. The reaction mixture is stirred for 30 minutes and then washed with saturated NH_4Cl, saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product which is purified by flash chromatography eluting with 30% EtOAc/Hexanes to yield the title compound (6.04 g, 19.9 mmol) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.65 (s, 1H), 5.30 (bs, 1H), 4.20 (m, 1H), 3.65 (4.90 (m, 2H), 1.48 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H). Ion spray MS, $[M+H]^+$=304.

D. [2-tert-Butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propylamino]-acetic acid methyl ester.

Sodium cyanoborohydride (2.63 g, 41.9 mmol) is added to a solution of [1-(tert-butyl-dimethyl-silanyloxymethyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (6.04 g, 19.9 mmol) and glycine methyl ester hydrochloride (2.75 g, 32.9 mmol) in MeOH (500 mL). The mixture is stirred for 2 days at RT then concentrated to dryness. The crude product is purifed by flash chromatography eluting with 1-5% MeOH/CH_2Cl_2 to yield the title compound (3.06, 8.12 mmol) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.00 (bs, 1H), 3.75 (s, 3H), 3.60-3.70 (m, 4H), 3.40 (d, 1H), 2.80 (dd, 1H), 2.68 (dd, 1H), 1.40 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H). Ion spray MS, $[M+H]^+$=377.

E. (Benzyloxycarbonyl-[2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propyl]-amino)-acetic acid methyl ester.

Benzylchloroformate (1.4 mL, 9.81 mmol) is added dropwise to a solution of N,N-dimethylaminopyridine (1.09 g, 8.93 mmol) and [2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propylamino]-acetic acid methyl ester (3.06 g, 8.12 mmol) in CH_2Cl_2 at RT. The resulting mixture is stirred overnight then concentrated to dryness. The crude product is purifed by flash chromatography eluting with 1% MeOH/CH_2Cl_2 to yield the title compound (3.52 g, 6.89 mmol) as a colorless oil. Ion spray MS, $[M+H]^+$=511.

F. 3-(tert-Butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester

(Benzyloxycarbonyl-[2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silanyloxy)-propyl]-amino)-acetic acid methyl ester (3.52 g, 6.89 mmol) is stirred in 50% TFA/CH_2Cl_2 (40 mL) at RT for 40 minutes. The reaction mixture is concentrated in vacuo and the crude product is purifed by flash chromatography eluting with 1% MeOH/CH_2Cl_2 to yield the title compound (1.1 g, 2.9 mmol) as a colorless oil. Ion spray MS, $[M+H]^+$=379.

EXAMPLE 55. 5-Oxo-piperazine-1,3(R or S)-dicarboxylic acid 1-benzyl ester 3-methyl ester.

N,N-Dimethylaminopyridine (0.43 g, 3.5 mmol) and benzylchloroformate (0.55 g, 3.8 mmol) are added to a solution of methyl 6-oxopiperazine-2-carboxylate (0.50 g, 3.2 mmol) (Aebischer, B., Helv. Chim. Acta 1989, 72, 1043-1051) in CH_2Cl_2 at RT. After 1 h, the reaction mixture is poured into EtOAc and washed with saturated $NaHCO_3$ and brine then dried over $MgSO_4$, filtered and concentrated to dryness to give a solid (0.90 g, 3.1 mmol) which is used in subsequent reactions without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (bs, 5 H), 6.32 (bs, 1H), 5.15 (s, 2H), 4.00-4.30 (m, 3H), 4.23 (s, 3H), 3.70-3.80 (m, 2H). MS (EI) m/z 292 (M+).

EXAMPLE 56. (S)-5-Oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.

To a solution containing methyl (S)-6-oxopiperazine-2-carboxylate (1.32 g, 8.35 mmol), prepared by the method of Aebischer, in anhydrous dichloromethane (30 mL) at 0 °C is added triethylamine (1.26 g, 12.5 mmol) followed by allylchloroformate (1.20 g, 10.0 mmol). After 1 h, the reaction mixture is poured onto a 1:1 mixture of CH_2Cl_2/water (200 mL), acidified using 1 N HCl and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 1% MeOH/CH_2Cl_2) to provide 1.22 g (60%) of EXAMPLE 35 as a viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (bs, 1H), 5.90 (m, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 4.05-4.26 (m, 3H), 3.80 (s, 3H), 3.72 (m, 2H); MS (ISP loop): m/z 243 (M+H).

EXAMPLE 57. (2S, 6R)-4-(2,6-dimethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester and

EXAMPLE 58. (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester

N-(tert-Butoxycarbonyl)-L-alanine (10.0 g, 52.8 mmol) is dissolved in 150 mL of THF. Once the triethylamine (11.0 ml, 79.2 mmol) is added, the solution is cooled to 0°C . Isopropyl chloroformate in toluene (1M) (52.8 ml, 52.8 mmol) is added slowly followed by the addition of (2RS) 1-amino-2-propanol (6.1 ml, 79.2 mmol). After stirring overnight, the mixture is washed with 1N sodium hydroxide and 1N hydrochloric acid. Concentration of the organic solvent afforded (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester (9.92 g, 76% yield) as a clear oil.

B. (1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester

Dimethylsulfoxide (7.16 ml, 100.8 mmol) is added to a solution of oxalyl chloride (4.41 ml, 50.4 mmol) in 126 mL of methylene chloride at -78 °C . The mixture is left to stir for fifteen minutes, and a solution of (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester (9.92 g, 40.32 mmol) in 100 mL of CH_2Cl_2 is added dropwise. After stirring for 15 minutes at -78 °C , the reaction is quenched with triethylamine (28 mL, 381 mmol), and the temperature is allowed to rise to room temperature. The volatile solvents are removed, and the residue is purified by flash column (SiO_2, 60% EtOAc/Hexane). The product (1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester (5.93 g, 60 %) is isolated as a white solid. MS $C_{11}H_{20}N_2O_4$ MS m/z: 245.

C: (3S, 5RS)-3,5-dimethyl-piperazin-2-one.

(1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester (5.93 g, 24.3 mmol) is stirred in a solution of 30 % trifluoroacetic acid in methylene chloride (100 mL) for three hours. The solvents are removed in vacuo. The residue is dissolved in 50 mL of MeOH and transferred to a par bottle. Palladium on carbon (10 % , 1.0 g) is added, and the mixture is hydrogenated under pressure for 24 hours. The catalyst is filtered off ; the MeOH is removed in vacuo to afford (3S, 5RS)-3,5-dimethyl-piperazin-2-one which is directly protected with a benzyl carbamate without further purification.

D: (2S, 6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of (3S, 5RS)-3,5-dimethyl-piperazin-2-one (24.3 mmol) in 100 mL of methylenechloride is added triethylamine (8.45 mL, 60.75 mmol) and N-(benzyloxycarbonyloxy)succinimide (12.1 g, 48.6 mmol). After stirring overnight, the CH_2Cl_2 is removed, and the crude mixture is chromatographed (50 % EtOAc/Hexane). (2S, 6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (3.3 g, 52 % yield over three steps) is isolated as a white powder. MS $C_{14}H_{18}N_2O_3$ MS m/z: 263.

E. (2S, 6R)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

The two single enantiomers [(2S, 6R)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester] can be seperated by column chromatography from (2S, 6RS)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, which can also be used directly in combination or separation of its derivatives as shown below.

EXAMPLE 59. (2S, 6R)-4-(2,4-Dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. (2S, 2S)-N-(2, 4-dimethoxy-benzyl)-N-(2-hydroxy-propyl)-2-(2,2,2-trifluoroacetylamino)-propionamide.

To a slurry of (2S)-2-(2,2,2-trifluoroacetylamino)-propionic acid (15.3 g, 53.4 mmol) in 120 mL of methylene chloride is added triethylamine (5.6 mL, 40.0 mmol). The heterogeneous mixture is cooled to 0°C and isopropyl chloroformate (27 mL, 27.0 mmol) is added slowly. After stirring for 20 minutes at room temperature, a solution of the (2S)-1-(2,4-dimethoxy-benzylamino)-propan-2-ol (6.0 g, 26.7 mmol, obtained from the reductive amination of the corresponding aldehyde and aminoalcohol) in 5mL of methylene chloride is added. The resulting mixture is left to stir overnight. Ethyl acetate (500 mL) is added, and the organic solution is washed with 1N hydrochloric acid (50 mL) and 1N sodium hydroxide (50 mL). The ethyl acetate is dried with magnesium sulfate, filtered and condensed. The resulting residue is chromatographed on silica gel (25% ethyl acetate/hexane) to give (2S, 2S)-N-(2,4-dimethoxy-benzyl)-N-(2-hydroxy-propyl)-2-(2,2,2-trifluoroacetylamino)-propionamide (6.29g, 60% yield) as a clear oil. MS $C_{17}H_{23}F_3N_2O_5$ MS m/z: 393.

B. (3S, 5R)-1-(2,4-dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one.

(2S, 2S)-N-(2,4-Dimethoxy-benzyl)-N-(2-hydroxypropyl)-2-(2,2,2-trifluoroacetylamino)-propionamide (3.64 g, 9.29 mmol) is dissolved in 25 mL of tetrahydrofuran. Triphenylphosphate (3.65 g, 14.0 mmol) is added, and the resulting mixture is cooled to 0 °C before diethyl azodicarboxylate (2.2 mL, 14 mmol) is added slowly. The resulting mixture is left to stir overnight. The reaction mixture is condensed, and the residue is purified by column chromatography (SiO_2, 25% ethyl acetate/hexane). The desired product, (3S, 5R)-1-(2,4-dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one (1.5 g, 43% yield), is isolated as a clear oil.

C. (3S, 5R)-1-(2,4-Dimethoxy-benzyl)-3,5-dimethyl-piperazin-2-one.

(3S, 5R)-1-(2,4-Dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one (575 mg, 1.54 mmol) is dissolved in 30 mL of methanol and 3 mL of H_2O. Potassium carbonate (883 mg, 6.4 mmol) is added to the solution, and the reaction is refluxed for one and half hours before concentration. Ethyl acetate (3x 50 mL) is used to extract the aqueous layer. Removal of Ethyl acetate afforded the crude amine (387 mg, 91% yield) as a clear oil. $C_{15}H_{22}N_2O_3$ MS m/z: 279.

D. (2S, 6R)-4-(2,4-dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Triethylamine (0.4 mL, 2.8 mmol) and N-(benzyloxycarbonyloxy)-succinimide (1.04 g, 4.2 mmol) is added to a solution of the above crude amine (387 mg, 1.4 mmol) in 15 mL of methylene chloride. The reaction mixture is left to stir overnight. The residue after concentration is chromatographed on silica gel (30% ethyl acetate/hexane) to give (2S, 6R)-4-(2,4-dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (450 mg, 78 % yield) as a clear oil.

E. (2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6R)-4-(2,4-Dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.13 g, 2.74 mmol) is dissolved in 20 mL of acetonitrile. An aqueous solution of potassium persulfate (2.2 g, 8.23 mmol) and sodium phosphate (2.3 g, 16.5 mmol) in 12 mL of H_2O is added, and the resulting mixture is heated to 95-100 °C for two hours. After cooling to room temperature, ethyl acetate (200 mL) is used to extract the aqueous layer and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed (SiO_2, 60% ethyl acetate/hexane) to give (2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (480 mg, 67 % yield) as a yellow oil.

EXAMPLE 60. (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (380 mg, 1.45 mmol) is dissolved in 10 mL of THF and 1mL of DMF. Sodium hydride (60%, 72 mg, 3.14 mmol) is added at 0 °C and left to stir at room temperature for thirty minutes before 7-bromomethyl-4-chloro-quinoline (257 mg, 1.0 mmol) is added. The reaction is stirred for four hours. Ethyl acetate is added to the mixture, and the reaction is quenched with 3 mL of H_2O. The two layers are separated and ethyl acetate (2x 30 ml) is used to extract before dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (60% EtOAc/Hexane) to give (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (417 mg, 95 % yield).$C_{22}H_{20}ClN_3O_3$ MS m/z: 438, 440.

EXAMPLE 61. (3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and
EXAMPLE 62. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and
EXAMPLE 63 (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

(2S, 6RS)-4-(4-Chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (417 mg, 1.0 mmol) is taken up in 7 mL of acetonitrile, and iodotrimethylsilane (0.43 mL, 3.0 mmol) is added. The resulting mixture is stirred for one hour at room temperature before quenched with methanol (1 mL). The residue after concentration is taken up in 2N hydrochloric acid (3 mL) and is extracted with ether (2x 30 mL). The aqueous layer is condensed to dryness and the residue is recrystalized from isopropanol and ether to give a mixture (1:4 ratio) of (3S, 5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one as a yellow solid (290 mg). The two epimers are separated using a flash column (SiO_2, 1% triethylamine/3% methanol/methylene chloride). $C_{16}H_{18}ClN_3O$ MS m/z: 304, 306. The minor isomer (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.is (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one while the major isomer is (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one. Alternatively, (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one can be made via the same chemistry shown below from pure (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, respectively.

Alternative synthesis of (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.
A. (2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (750 mg, 2.86 mmol) is dissolved in 20 mL of THF and 2 mL of DMF. Sodium hydride (60%, 142.6 mg, 6.20 mmol) is added at 0 °C , and the reaction is left to stir at room temperature for thirty minutes at which time the 7-bromomethyl-4-chloro-quinoline (952 mg, 3.72 mmol) is added. The reaction is complete after stirring for four hours. Ethyl acetate (200 mL) is added to the mixture, and the reaction is quenched with 3 mL of H_2O . The two layers are separated, and ethyl acetate (2x 30 mL) is used to extract and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (60% EtOAc/Hexane) to give (2S,6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.04 g, 83 %).

B. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A 33 % solution of hydrogen bromide in acetic acid (10 mL) is added to (2S,6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.04 g, 2.38 mmol). The reaction is left to stir at room temperature for one hour. The reaction mixture is diluted with ethyl acetate and stirred vigorously to force the product to precipitate out of solution. The ethyl acetate is decanted off and the precipitate is purified on a silica gel column (1 % triethylamine/3 % methanol/methylene chloride) to 582 mg (81% yield) of (3S,5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one as a white solid.

EXAMPLE 64. (3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one and
EXAMPLE 65. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one.

The crude (3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (69 mg, 0.20 mmol) obtained from above is dissolved in 1 mL of DMF. Potassium carbonate (76 mg, 0.60 mmol) is added followed by the addition of 2-(3-bromopropenyl)-5-chloro-thiophene (56 mg, 0.24 mmol). The reaction is left to stir overnight. The potassium carbonate is filtered off, and the crude material is purified. The two epimers are separated at this stage by preparative thin layer chromatography (80 % EtOAc/hexane) to give a major epimer (3S, 5R)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one (25 mg, 26% yield) and a minor epimer (3S, 5S)-1-(4-chloro-quinolin-7-ylmethly)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one (7 mg, 7.5% yield).

EXAMPLE 66. 4-(2-Oxopiperazin-1-ylmethyl)benzamidine.

A. 4-(4-Cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxo-piperazine-1-carboxylic acid benzyl ester (3.0 g, 12.8 mmol) and 4-bromomethyl tolylnitrile (2.76 g, 14.1 mmol) in 135 mL of THF and 15 mL of DMF at 0°C is added a 60% dispersion in mineral oil of NaH (0.49 g, 12.8 mmol). After 5 hours, the solution is diluted with saturated NH_4Cl and EtOAc. The organic layer is washed with H_2O and saturated NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography over silcia gel eluting with 20% EtOAc/CH_2Cl_2. The title compound is obtained as a white solid (4.01 g, 11.4 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 7.62 (d, 2H), 7.39 (m, 7H), 5.14 (s, 2H), 4.68 (s, 2H), 4.27 (s, 2H), 3.73 (m, 2H), 3.30 (m, 2H).

B. 4-(4-Carbamimidoylbenzyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A solution of 4-(4-cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (2.4 g, 6.87 mmol) in 30mL of pyridine and 3 ml of Et_3N is saturated with H_2S. The resulting mixture is

sealed and stirred for 16 hours. After this time, the solution is concentrated. The residue is dissolved in 30 mL of acetone and methyl iodide (19.4 g, 137 mmol) is added. The solution is refluxed for 2 hours. After this time, the solution is concentrated. The residue is dissolved in MeOH (40 mL) and NH_4OAc (5.0 g, 65 mol) is added. The solution is reluxed for 3 hours. After this time, the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of CH_3CN to 60% CH_3CN/H_2O(0.1%TFA). The appropriate collected fractions are lyophilized to give the product as a white foam. MS (FAB) m/z 367, (M+H).

C. 4-(2-Oxopiperazin-1-ylmethyl)benzamidine.

To a solution of 4-(4-carbamimidoylbenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (2.0 g, 5.0 mmol) in 40 mL of MeOH and 4 mL of AcOH is added 10% Pd/C (0.4 g). The atmosphere above the reaction is replaced by hydrogen. After 4hours, the solution is filtered through a pad of Celite. The organic layer is concentrated. The resulting crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1%TFA) to 40% CH_3CN/H_2O (0.1% TFA). The title compound is obtained as a white foam. ^1H NMR (d^6-DMSO, 300 MHz) δ 9.3 (bs, 4H), 9.1 (bs, 2H), 7.83 (d, 2H), 7.42 (d, 2H), 4.78 (s, 2H), 3.80 (s, 2H), 3.44 (m, 2H), 3.32 (m, 2H).

EXAMPLE 67. 1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one.

A. 4-(2-Chloro-quinolin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid benzyl ester (4.65 g, 19.8 mmol) and 6-bromomethyl-2-chloroquinoline (5.40 g, 21.0 mmol) in 80 mL of a 3:1 mixture of THF:DMF at 0°C is added sodium hydride (0.81 g, 20.2 mmol, 60% mineral oil dispersion). The resulting mixture is stirred for 1 hour at 0°C then at room temperature for 18 hours. The reaction mixture is quenched with saturated NH_4Cl solution, then diluted with EtOAc. The organic layer is washed sequentially with 1N HCl, water, saturated $NaHCO_3$ and saturated NaCl, then dried over $MgSO_4$, filtered and concentrated. The crude product is triturated in Et_2O/hexanes/EtOAc and filtered to afford the title compound (6.96 g, 17.0 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H), 8.00 (d, 1H), 7.69 (s, 1H), 7.63 (dd, 1H), 7.41 (d, 1H), 7.35 (s, 5H), 5.15 (s, 2H), 4.78 (s, 2H), 4.28 (s, 2H), 3.70 (m, 2H), 3.32 (bs, 2H).

B. 4-(2-Phenoxyquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester.

A mixture of phenol (15.1 g, 160 mmol) and 4-(2-chloroquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (6.60 g, 16.1 mmol) is melted together at 70°C until a homogeneous mixture is obtained. Potassium hydroxide (3.15 g, 56.1 mmol) is added and the resulting mixture is heated overnight at 120°C. After 24 hours, the brown/black residue is cooled to room temperature, diluted with CH_2Cl_2 and stirred with 1N NaOH (100 mL) for 30

minutes. The two layers are separated and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with 1N NaOH, saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The crude title compound (6.92 g, 14.8 mmol) is obtained as a beige foam and used in the subsequent step without further purification.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, 1H), 7.76 (d, 1H), 7.63 (s, 1H), 7.50 (dd, 1H), 7.42 (m, 2H), 7.34 (m, 6H), 7.25 (m, 2), 7.09 (d, 1H), 5.14 (s, 2), 4.75 (s, 2H), 4.27 (s, 2H), 3.66 (m, 2H), 3.30 (bs, 2H).

C. 4-(2-Aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester

A mixture of ammonium acetate (18.7 g, 242 mmol) and 4-(2-phenoxyquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (6.92 g, 14.8 mmol) is heated overnight at 150°C. After 21 hours, an additional 3 g of ammonium acetate is added and the heating is continued. After 5 hours, the mixture is cooled to room temperature, diluted with CH_2Cl_2 and stirred with 1N NaOH (100 mL) for 30 minutes. The two layers are separated and the aqueous layer is extracted with CH_2Cl_2. The combined organic layers are washed with 1N NaOH, saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The crude mixture of the title compounds (5.50 g, 14.1 mmol) is obtained as a beige foam and used in the subsequent step without further purification.

Major component (4-(2-aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.45 (d, 1H), 7.35 (s, 5H), 6.74 (d, 1H), 5.14 (s, 2H), 4.79 (bs, 2H), 4.71 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H).

Minor component (3-oxo-4-(2-oxo-1,2-dihydroquinolin-6-ylmethyl)piperazine-1-carboxylic acid benzyl ester): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, 1H), 7.48 (m, 2H), 7.37 (m, 6H), 6.70 (d, 1H), 5.14 (s, 2H), 4.66 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H).

D. 1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one.

To a solution of a mixture of 4-(2-aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester and 3-oxo-4-(2-oxo-1,2-dihydro-quinolin-6-ylmethyl)piperazine-1-carboxylic acid benzyl ester (5.50 g, 14.1 mmol) in 100 mL of 10:1 MeOH/HOAc is added a catalytic amount of 10% palladium on activated carbon. The heterogenous mixture is hydrogenated at room temperature under a balloon of H_2 for 18 hours. The reaction mixture is filtered through a pad of Celite, washed with MeOH, and the filtrate is concentrated in vacuo. The crude mixture of products is purified by RP-HPLC eluting in a gradient of 2% CH_3CN/H_2O (0.1% TFA) to 20% CH_3CN/H_2O(0.1% TFA) and the appropriate product fractions are concentrated in vacuo to provide 1-(2-aminoquinolin-6-ylmethyl)-piperazin-2-one ditrifluoroacetate (2.64 g, 5.45 mmol) as the major product in the form of a white solid. ^1H NMR

(d^6-DMSO, 300 MHz) δ 8.78 (bs, 2H), 8.31 (d, 1H), 7.80 (s, 1H), 7.66 (m, 2H), 7.08 (d, 1H), 4.70 (s, 2H), 3.84 (s, 2H), 3.46 (bs, 4H). MS m/z 256, [M+]. Elemental analysis calculated with 0.25 mol of H_2O cal. C=44.25%, H=3.82%, N=11.47%, found C=44.23%, H=3.76%, N=11.23%. The minor by-product 6-(2-oxo-piperazin-1-ylmethyl)-1H-quinolin-2-one(0.62 g, 1.28 mmol) is also isolated from the RP-HPLC separation as a white solid ^{1}H NMR (d^6-DMSO, 300 MHz) δ 11.76 (bs, 1H), 9.30 (bs, 2H), 7.85 (d, 1H), 7.55 (s, 1H), 7.42 (d, 1H), 7.28 (d, 1H), 6.50 (d, 1H), 4.60 (s, 2H), 3.80 (s, 2H), 3.38 (bs, 4H). MS m/z 257, [M+]. Elemental analysis calculated with 0.5 mol of H_2O cal. C=43.72%, H=3.68%, N=8.50%, found C=43.70%, H=3.62%, N=8.61%.

EXAMPLE 68. 1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one.

The title compound is prepared as described in EXAMPLE 67 substituting 6-bromomethyl-1-chloroisoquinoline for bromomethyl-2-chloroquinoline. ^{1}H NMR (d6-DMSO, 300 MHz) δ (9.18 (bs, 2H), 8.53 (d, 1H), 7.81 (s, 1H), 7.63 (m, 2H), 7.14 (d, 1H), 4.77 (s, 2H), 3.88 (s, 2H), 3.50 (m, 4H).

EXAMPLE 69. 2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

A. 3-Iodopyridin-4ylamine.

A solution of potassium iodide (19.48 g, 117.4 mmol) and iodine (18.37 g, 72.3 mmol) in water (77 mL) is added dropwise via an addition funnel to a refluxing solution of 4-aminopyridine (9.21 g, 97.8 mmol) and sodium carbonate (6.12 g, 57.7 mmol) in water (35 mL). Upon complete addition the mixture is stirred for 2 hours at reflux then cooled to room temperature and extracted with ethyl acetate. The combined organic layers are washed with saturated sodium thiosulfate solution (3x) and brine then dried over $MgSO_4$, filtered and concentrated to give the title product (8.37 g, 38.0 mmol) and a trace of the di-iodo compound as an yellow/orange solid. This material is used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.10 (d, 1H), 6.55 (d, 1H), 4.60 (bs, 2H).

B. (3-Iodopyridin-4-yl)-carbamic acid tert-butyl ester.

Di-tert-butyl dicarbonate (20.7 g, 94.8 mmol) is added to a solution of 3-iodopyridin-4-ylamine (19.0 g, 86.4 mmol) in THF (86 mL). The resulting solution is stirred for 2 hours at room temperature then concentrated. The residue is diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated. The residue is purified by column chromatography eluting with 1% EtOAc/CH_2Cl_2 to give the title product and a small amount of the BOC-protected di-iodo compound. Trituration of the mixture with ether/hexane removes the undesired compound

leaving the title product in the solution. Filtration of the solid and concentration of the filtrate yields the title product (18.95 g, 59.2 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.0 (bs, 1H), 1.55 (s, 9H).

C. 3-Oxo-4-prop-2-ynylpiperazine-1-carboxylic acid benzyl ester.

Sodium hydride (0.82 g, 23.0 mmol, 60% mineral oil dispersion) is added to a solution of 4-benzyloxycarbonylpiperazin-2-one (5.13 g, 21.9 mmol) in THF/DMF (75 mL, 3/1 v/v) at 0°C . The mixture is stirred for 5 minutes, then propargyl bromide (3.7 mL, 41.5 mmol) is added dropwise. The resulting solution is stirred for 1 hour then brought to room temperature and stirred for 2 hours. The reaction is quenched with saturated ammonium chloride solution then diluted with ethyl acetate and washed with water (4x) and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The residue is purified by column chromatography eluting with 5% MeOH/CH_2Cl_2 to give the product (5.96 g, 21.9 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3 (m, 5H), 5.12 (s, 2H), 4.25 (s,2H), 4.16 (s, 2H), 3.75 (m, 2H), 3.47 (m, 2H), 2.22 (s, 1H).

D. 2-(4-Benzyloxycarbonyl-2-oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

$Pd(PPh_3)_2Cl_2$ (0.29 g, 0.41 mmol), CuI (0.05 g, 0.25 mmol) and triethylamine (4.6 mL, 32.9 mmol) is added to a solution of 3-oxo-4-prop-2-ynylpiperazine-1-carboxylic acid benzyl ester (2.24 g, 8.23 mmol) and (3-iodopyridin-4-yl)-carbamic acid tert-butyl ester (2.63 g, 8.23 mmol) in DMF (30 mL) at room temperature. The mixture is heated to 100°C and stirred for 1.5 hours. The reaction mixture is then cooled to 50°C and DBU (2.5 mL, 16.5 mmol) is added. After 30 minutes the solution is cooled to room temperature, diluted with ethyl acetate and washed with saturated ammonium chloride, water and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting solid is purified by column chromatography eluting with a gradient of 2% MeOH/$CH_2Cl_2$to 5% MeOH/ $CH_2Cl_2$to give the product (2.93 g, 6.31 mmol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.4 (d, 1H), 7.85 (d, 1H), 7.35 (m, 5H), 6.38 (s, 1H), 5.2 (s, 2H), 5.00 (s, 2H), 4.29 (s, 2H), 3.85 (m, 2H), 3.52 (m, 2H), 1.7 (s, 9H). Ion spray MS, $[M+H]^+$= 465.

E. 2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

Palladium black (1.1 g, 10.3 mmol) is added to a solution of 2-(4-benzyloxycarbonyl-2-oxo-piperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (1.7 g, 3.7 mmol) in HCO_2H/MeOH (45 mL, 4.4% solution). After 40 minutes the catalyst is filtered through Celite and washed with MeOH. The filtrate is concentrated in vacuo to remove methanol then the resulting solution is diluted with methylene chloride and washed with saturated sodium bicarbonate, and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to

dryness. The resulting solid is purified by column chromatography eluting with a gradient of 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to give the product (0.8 g, 2.5 mmol) as a pale yellow foamy solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.40 (d, 1H), 7.9 (d, 1H), 6.48 (s, 1H), 4.98 (s, 2H), 3.7 (s, 2H), 3.51 (t, 2H), 3.40 (t, 2H), 1.91 (bs, 1H), 1.70 (s, 9H).

EXAMPLE 70. 2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A. 2-Benzyloxycarbonylamino-3-(prop-2-ynylamino)-propionic acid methyl ester.

Propargyl bromide (1.6 mL, 14.4 mmol) is added to a solution of 3-amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride (4.0 g, 13.9 mmol) and triethylamine (4.1 mL, 29.4 mmol) in THF (46 mL). The resulting mixture is heated to 50°C and stirred overnight then cooled to RT and concentrated in vacuo. The crude residue is diluted with methylene chloride, washed with saturated $NaHCO_3$ and brine then the organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material (4.0 g) is taken on to the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.30 (m, 5H), 5.75 (bs, 1H), 5.20 (s, 2H), 4.45 (bs, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.31 (s, 2H), 3.08 (dd, 1H), 2.98 (dd, 1H), 2.20 (t, 1H). EI MS, $[M+H]^+$=291.

B. 2-Benzyloxycarbonylamino-3-(bromoactyl-prop-2-ynyl-amino)-propionic acid methyl ester.

DCC (2.27 g, 11.0 mmol) and bromoacetic acid (1.48 g, 10.7 mmol) is added to a solution of 2-benzyloxycarbonylamino-3-(prop-2-ynylamino)-propionic acid methyl ester (3.10 g, 10.7 mmol) in CH_2Cl_2 at RT. The mixture is stirred overnight then diluted with ether. The white solid which precipitates out is filtered and the filtrate is concentrated to give a yellow oil. The crude product is purified by chromatography eluting with a gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to yield the title product (2.1g, 5.12 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.70 (d, 1H), 5.10 (s, 2H), 4.63 (m, 1H), 4.15 (d, 2H), 4.00 (m, 1H), 3.80 (s, 3H), 3.75 (s, 2H), 3.70 (dd, 1H), 2.27 (bs, 1H). Ion spray MS, $[M+H]^+$=411, 413, Br pattern.

C. 5-Oxo-4-prop-2-ynyl-piperazine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester.

Sodium hydride (0.20 mg, 4.9 mmol) is added to a solution of 2-benzyloxycarbonylamino-3-(bromoactyl-prop-2-ynyl-amino)-propionic acid methyl ester (2.0 g, 4.8 mmol) in THF (50 mL) at 0°C. The solution is stirred for 40 minutes then quenched with saturated NH_4Cl solution. The reaction mixture is concentrated in vacuo then diluted with CH_2Cl_2 and washed with brine. The organic layer is dried over , filtered and concentrated in vacuo. The crude product is purified by chromatography eluting with 50% EtOAc/hexanes to give the title product (1.4 g, 4.1 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.20 (s, 2H),

5.10 (m, 1H), 4.30 (dd, 1H), 4.25 (d, 2H), 4.08 (m, 1H), 4.00 (dd, 1H), 3.78 (dd, 1H), 3.78 (s, 3H), 2.25 (t, 1H).

D. 2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.41 (d, 1H), 7.90 (d, 1H), 6.42 (s, 1H), 5.00 (AB, 2H), 3.85-3.93 (m, 2H), 3.78 (s, 3H), 3.70-3.81 (m, 3H), 1.65 (s, 9H). Ion spray MS, $[M+H]^+$=389.

EXAMPLE 71. 2-(2-(±)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (s, 1H), 8.43 (d, 1H), 7.90 (d, 1H), 6.48 (s, 1H), 5.63 (d, 1H), 4.40 (d, 1H), 4.20 (m, 1H), 3.78 (s, 3H), 3.70 (d, 1H), 3.52 (d, 1H), 3.33 (dd, 1H), 2.92 (s, 1H), 1.55 (s, 9H). Ion spray MS, $[M+H]^+$=389.

EXAMPLE 72. 1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one.

A. 4-(4-Chloroquinazoline-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid tert-butyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid tert-butyl ester (3.93 g, 19.6 mmol) and 7-bromomethyl-4-chloroquinazoline, EXAMPLE 7, (5.0 g, 19.6 mmol) in 150 mL of THF and 15 mL of DMF at 0°C is added a 60% dispersion in mineral oil of NaH (0.79 g, 19.6 mmol). The solution is stirred at 0°C for 0.5 hours and then is allowed to warm to ambient temperature. After 4 hours, the solution is poured into a saturated solution of NH_4Cl. The layers are separated and the organic layer is washed with H_2O, and saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The title compound is obtained as a white solid (5.1 g, 13.4 mmol). MS (FAB) m/z 377, 379, (M+H), chlorine pattern.

B. 4-(4-Aminoquinazoline-7-ylmethyl-3-oxopiperazine-1-carboxylic acid tert-butyl ester.

A solution of 4-(4-chloroquinazoline-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid tert-butyl ester (1.84 g, 4.9 mmol) in 120 mL of ethanol is saturated with NH_3 gas. To the resulting solution is added acetic acid (0.03 mL). The solution is heated to reflux. After 16 hours, the solution is concentrated. The resulting solid is dissolved in CH_2Cl_2 and the inorganic salts are filtered off. The organic solution is concentrated. The resulting solid is triturated with EtOAc. The title compound is obtained a a white solid (1.59 g, 4.5 mmol). MS (FAB) m/z 356, (M+H).

C. 1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one.

A solution of 4-(4-aminoquinazoline-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.92 g, 5.4 mmol) in EtOAc (200 mL) at 0 °C is saturated with HCl gas. The

solution is stirred at 0°C for 4 hours. After this time, the solution is concentrated. The title compound is obtained as a white solid (1.79 g, 5.4 mmol). ^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.9 (bs, 3H), 9.7 (bs, 2H), 8.8 (s, 1H), 8.46 (d, 1H), 7.72 (s, 1H), 7.61 (d, 1H), 4.78 (s, 2H), 3.83 (s, 2H), 3.4 (m, 4H).

Example 73. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one.

A. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 72, Part A, substituting 6-bromomethyl-4-chlorothieno[2,3-d]pyrimidine. for 7-bromomethyl-4-chloroquinazoline. Followed by treatment as described in EXAMPLE 72, Part B, the title compound is obtained. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.22 (s, 1H), 7.35 (s, 1H), 5.48 (s, 2H), 4.10 (s, 2H), 3.60 (m, 2H), 3.40 (m, 2H), 1.45 (s, 9H). MS (ion spray), 364, (M+H).

B. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one.

The title compound is obtained by treatment of 1-(4-amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester as described in EXAMPLE 72, Part C. MS (EI), 2634, (M+).

EXAMPLE 74. 4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester.

A. 4-[3-(1-tert-butoxycarbonyl-piperidin-4-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as described in EXAMPLE 72, Part A, substituting 3-oxopiperazine-1-carboxylic acid benzyl ester for 3-oxopiperazine-1-carboxylic acid tert-butyl ester and 4-(3-bromopropyl)-piperidine-1-carboxylic acid tert-butyl ester for 7-bromomethyl-4-chloroquinazoline. The title compound is obtained as a white foam. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.38 (m, 5H), 5.12 (s, 2H), 4.18 (m, 4H), 3.73 (m, 2H), 3.33 (m, 4H), 2.66 (m, 2H), 1.58 (m, 6H), 1.42 (s, 9H), 1.38 (m, 3H).

B. 4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester.

4-[3-(1-tert-butoxycarbonyl-piperidin-4-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester is treated as described in EXAMPLE 67, Part D, to give the title compound as an oil.

EXAMPLE 75. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one.

A. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 2-oxo-3-(S)-methoxymethylpiperidine (5.36g, 19.3mmol), EXAMPLE 41, in 200mL of 10:1 THF:DMF is added 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (12.6g, 60%purity, 19.3mmol), prepared as in EXAMPLE 13. The solution is cooled to 0°C. To the solution is added NaH (0.77g of a 60% dispersion in mineral oil, 19.3mmol). The solution is stirred for 16 hours. After this time, 1N HCl is added until the pH=1. The solution is stirred for 1 hour. After this time, the solution is diluted with EtOAc. The organic layer is washed with water and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 20%EtOAc/CH_2Cl_2 to 40%EtOAc/CH_2Cl_2. The title compound (6.8g, 16.7mmol) is obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.34 (m, 5H), 6.61 (m, 2H),5.13 (AB, 2H), 4.76 (m, 1H), 4.40 (AB, 2H), 4.08 (m, 5H), 3.74 (m, 2H), 3.32 (m, 1H), 3.30 (s, 3H), 3.10 (m, 1H).

B. 4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (6.8g, 16.7mmol) in 100mL of ethanol is added triazine (2.2g, 26.4mmol) and acetic acid (1.6g,26.4mmol). The solution is heated to a reflux. After 36h, the solution is concentrated. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2. The title compound (5.8g, 13.3mmol) is obtained as a white solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.55 (s, 1H), 7.72 (m, 2H), 7.48 (m, 1H), 7.35 (m, 5H), 6.40 (bs, 2H), 5.16 (AB, 2H), 5.06 (m, 1H),4.72 (m, 1H), 4.59 (m, 1H), 4.09 (m, 2H), 3.74 (m, 2H), 3.44 (m, 1H), 3.30 (s, 3H), 3.12 (m, 1H). MS (ion spray) m/z 436, (M+H).

C. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one.

To a solution of 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (5.8g, 13.3mmol) in 50mL of acetic acid is added dropwise, 20mL of a 30%HBr in AcOH solution. The solution is stirred for 1 hour. After this time, the solution is concentrated. The resulting crude product is purified by column chromatography eluting with CH_2Cl_2:MeOH:NH_4OH (20:5:1). The title compound (2.0g, 6.6mmol) is obtained as a white solid. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.60 (s, 1H), 7.72 (m, 2H),7.48 (d, 1H), 5.60 (bs, 2H), 4.72 (AB, 2H), 3.87 (m, 2H), 3.71 (m, 1H), 3,42 (m, 1H), 3.40 (s, 3H), 3.19 (m, 2H), 3.02 (m, 1H). MS (ion spray) m/z 302, (M+H).

EXAMPLE 76. 1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-butyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 42, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.35 (s, 1H), 8.09 (d,

1H), 7.54 (s, 1H), 7.41 (d, 1H), 4.74 (s, 2H), 3.43 (m, 2H), 3.28 (m, 1H), 3.09 (m, 1H), 2.95 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.39 (m, 4H), 0.93 (m, 3H). MS (ion spray) m/z 314, (M+H).

EXAMPLE 77. 1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-ethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester r, Example 43, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1H), 8.11 (d, 1H), 7.57 (s, 1H), 7.42 (d, 1H), 4.78 (s, 2H), 3.40 (m, 2H), 3.29 (m, 1H), 3.11 (m, 1H), 2.98 (m, 1H), 2.00 (m, 1H), 1.77 (m, 1H), 1.20 (m, 3H). MS (ion spray) m/z 286, (M+H).

EXAMPLE 78. 1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-propyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 44, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1H), 8.13 (d, 1H), 7.60 (s, 1H), 7.47 (d, 1H), 4.78 (s, 2H), 3.44 (m, 2H), 3.30 (m, 1H), 3.11 (m, 1H), 2.97 (m, 1H), 1.98 (m, 1H), 1.72 (m, 1H), 1.50 (m, 2H), 0.97 (m, 3H). MS (ion spray) m/z 300, (M+H).

EXAMPLE 79. 1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-ethoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 45, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.34 (s, 1H), 8.07 (d, 1H), 7.53 (s, 1H), 7.40 (d, 1H), 4.79 (AB, 2H), 3.90 (m, 1H), 3.72 (m, 1H), 3.68 (m, 1H), 3.52 (m, 2H), 3.36 (m, 2H), 3.20 (m, 1H), 3.00 (m, 1H), 1.92 (m, 3H). MS (ion spray) m/z 316, (M+H).

EXAMPLE 80. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 46, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1H), 8.11 (d, 1H), 7.57 (s, 1H), 7.44 (d, 1H), 4.79 (AB, 2H), 3.58 (m, 1H), 3.47 (m, 1H), 3.31 (m, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 1.41 (d, 3H). MS (ion spray) m/z 272, (M+H).

EXAMPLE 81. 1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-benzyl-3-oxo-piperazine-1-carboxylic acid benzyl, Example 47, ester for 2-methoxymethyl-3-oxo-

piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.35 (s, 1H), 8.09 (d, 1H), 7.57 (s, 1H), 7.38 (d, 1H), 7.27 (m, 5H), 4.74 (AB, 2H), 3.76 (m, 1H), 3.47 (m, 1H), 3.30 (m, 3H), 3.08 (m, 1H), 2.96 (m, 1H). MS (ion spray) m/z 348, (M+H).

EXAMPLE 82. 1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-(1-methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 48, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. This compound is isolated as the bis hydrobromide salt. ^{1}H NMR (CD_3OD, 300MHz) δ 8.70 (s, 1H), 8.40 (d, 1H), 7.88 (s, 1H), 7.71 (d, 1H), 4.94 (AB, 2H), 4.30 (m, 2H), 3.76 (m, 1H), 3.68 (m, 3H), 3.36 (s, 3H), 1.42 (d, 3H). MS (ion spray) m/z 316, (M+H).

EXAMPLE 83. 1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2,2-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 49, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.34 (s, 1H), 8.12 (d, 1H), 7.72 (bs, 2H), 7.41 (s, 1H), 7.26 (d, 1H), 4.60 (s, 2H), 3.33 (m, 2H), 2.98 (m, 2H), 1.27 (s, 6H).

EXAMPLE 84. 1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-isopropyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 50, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.32 (s, 1H), 8.12 (d, 1H), 7.66 (bs, 2H), 7.42 (s, 1H), 7.27 (d, 1H), 4.60 (AB, 2H), 3.23 (m, 2H), 3.05(m, 1H), 2.79 (m, 1H), 2.34 (m, 1H), 0.92 (s, 3H), 0.80 (s, 3H).

EXAMPLE 85. 1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-isobutyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 51, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.65 (s, 1H), 7.70 (m, 2H), 7.48 (m, 1H), 5.61 (m, 2H), 4.82 (m, 1H), 4.65 (m, 1H), 3.52 (dd, 1H), 3.37 (m, 1H), 3.18 (m, 2H), 2.98 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.59 (m, 2H), 0.95 (m, 6H).

EXAMPLE 86. 1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) l-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-(2-methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 52, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (d^6-DMSO, 300MHz) δ 8.32 (s, 1H), 8.13 (d, 1H), 7.70 (bs, 2H), 7.42 (s, 1H), 7.28 (m, 1H), 4.60 (m, 2H), 3.32 (m, 8H), 3.11 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H).

EXAMPLE 87. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-methoxymethyl-5-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 53, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.72 (s, 1H), 8.32 (d, 1H), 7.78 (m, 2H), 5.11 (m, 1H), 4.81 (m, 1H), 4.42 (m, 1H), 4.13 (m, 1H), 4.04 (m, 1H), 3.74 (m, 2H), 3.52 (m, 1H), 3.43 (s, 3H), 1.34 (d, 3H).

EXAMPLE 88. (3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A. (2S,6RS)-4-[3-(benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of the (2S,6RS)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.98 g, 7.56 mmol in 20 mL of tetrahydrofuran and 2 mL of DMF is added sodium hydride (60%, 289 mg, 12.6 mmol) at 0°C. The reaction is stirred for one hour at room temperature and the 2-benzhydrylidene-amino)-4-bromomethyl-benonitrile (4.24 mg, 11.34 mmol), Example 13, is added. After stirring at room temperature overnight, the tetrahydrofuran is removed. The residue is taken up in ethyl acetate. Excess sodium hydride is quenched with 5 mL of water, and normal aqueous work-up followed. The crude product is chromatographed on silica gel (50% EtOAc/Hexane) to give (2S,6RS)-4-[3-(benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.6 g, 65%). $C_{35}H_{32}N_4O_3$ MS m/z: 557.

B. (2S,6RS)-4-(3-amino)-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6RS)-4-[3-(Benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.6 g, 5.21 mmol) is dissolved in 100 mL of ethyl acetate and cooled to 0°C. A 12N solution of hydrochloric acid (0.5 ml, 6.0 mmol) is added dropwise. The deprotection is complete in thirty minutes. The reaction mixture is washed with 10 % sodium bicarbonate. The ethyl acetate layer is dried with magnesium sulfate, filtered and condensed. The resulting residue is purified by flash column (SiO_2, 60 % ethyl acetate/hexane) to give the

product (2S,6RS)-4-(3-amino)-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.03 g, 99 %).

C. (2S,6RS)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Glacial acetic acid (0.9 ml, 15.54 mmol) and 1,3,5-triazine (840 mg, 10.36 mmol) is added to a solution of (2S,6RS)-4-(3-amino-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.03 g, 5.18 mmol) in ethanol. The resulting mixture is heated to reflux overnight. Replaced the ethanol with ethyl acetate and washed with saturated sodium bicarbonate (5 mL). The ethyl acetate layer is dried with magnesium sulfate, filtered and condensed. The resulting residue is purified by flash column (SiO_2, 20% methanol/methylene chloride) to give the product (2S,6RS)-4-(4-amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.85 g, 85%) as a yellow solid. $C_{23}H_{25}N_5O_3$ MS m/z: 420.

D. (3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

Palladium on carbon (10 %, 700 mg) is added to a solution of (2S,6RS)-4-(4-amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.62 g, 3.87 mmol) in 20 mL of methanol and 2 mL of acetic acid. The reaction mixture is left to stir in an atmosphere of hydrogen for eight hours. The palladium is filtered off, and the volitale solvents are removed on the rotovap. The crude product (1.7 g, 95 %) is isolated as a white solid. The two epimers are separated on silica gel (1% triethylamine/15% methanol/methylene chloride). The minor epimer is assigned as (3S,5R)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and the major epimer is assigned as (3S,5S)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

EXAMPLE 89. 1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one.

4-(Benzyloxycarbonyl)-piperazin-2-one (1.1 g, 4.6 mmol) is dissolved in THF (50 mL), cooled in an ice bath and treated with tretrabutylammonium iodide (0.18 g, mmol) and 60% sodium hydride (0.24 g, 6.0 mmol). The reaction mixture is stirred at 0 C for 30 minutes then treated dropwise with a solution of 7-bromomethyl-4-chloroquinoline (1.2 g, 4.6 mmol), Example 14, in THF (50 mL). The resulting solution is stirred at 0 C for 2 h then quenched with ammonium chloride solution and concentrated. Dilution with ethyl acetate is followed by a water wash; the organic layer is dried (sodium sulfate) and concentrated. The residue is chromatographed (4% methanol/methylene chloride) to yield solid 4-(benzyloxycarbonyl)-1-(4-chloroquinolin-7-ylmethyl)-piperazin-2-one (1.2 g, 2.9 mmol). A portion of this material (0.75 g, 1.8 mmol) is dissolved in acetonitrile (20 mL) and treated with

iodo trimethylsilane (0.78 mL, 5.4 mmol) at room temperature for 3 hours. The reaction is quenched with methanol and concentrated to dryness. Methanol addition and concentration is repeated four times. The final residue is taken up is 2M aqueous HCl; the solution is washed with ether and concentrated. The residue is recrystallized from isopropanol and ether to yield the title compound (0.63 g, 2.3 mmol) MS m/z: M^+ = 275; ^{1}HNMR (CD_3OD, 300 MHz) δ 9.1 (d, 1H), 8.5 (d, 1H), 8.2-8.3 (m, 2H), 8.0 (d, 1H), 5.2 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H).

EXAMPLE 90. 1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one.

4-(t-Butyloxycarbonyl)-piperazin-2-one (0.6 g, 3.0 mmol), EXAMPLE 40, is dissolved in THF (80 mL), cooled in an ice bath and treated with tretrabutylammonium iodide (0.23 g, 0.62 mmol) and 60% sodium hydride (0.12 g, 3.0 mmol). The reaction mixture is stirred at °C for 40 minutes then treated dropwise with a solution of 7-bromomethyl-4-chlorocinnoline (10.7g, 2.7 mmol), Example 15, in THF (20 mL). The resulting solution is warmed to ambient temperature over 2 hours. The solution is evaporated to dryness and the residue is taken up in ethyl acetate and 10 % aqueous sodium bicarbonate solution. The organic layer is separated, washed with water, dried (sodium sulfate) and concentrated. The residue is chromatographed (ethyl acetate) to yield the title compound (0.6 g, 1.6 mmol). A portion of this material (0.21 g, 1.26 mmol) is dissolved in THF (~ 4 mL) and treated with a saturated solution of HCl in ethyl acetate (50 mL) at room temperature for 2 hours. The solution is filtered and concentrated to a residue (0.14 g, 0.4 mmol). MS m/z: M^+ = 275; ^{1}H NMR (CD_3OD, 300 MHz) δ 9.15 (d, 1H), 8.5 (d, 1H), 8.25 (s, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 5.0 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H).

EXAMPLE 91. 1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one.

4-(Benzyloxycarbonyl)-3-(S)-methylpiperazin-2-one (1.0 g, 4.0 mmol), EXAMPLE 46, is dissolved in THF (60 mL), cooled in an ice bath and treated with tretrabutylammonium iodide (0.10 g, 0.27 mmol) and 60% sodium hydride (0.18 g, 4.4 mmol). The reaction mixture is stirred at 0°C for 30 minutes then treated dropwise with a solution of 7-bromomethyl-4-chloroquinoline (1.12 g, 4.4 mmol), EXAMPLE 14, in THF (5 mL). The resulting solution warmed to room temperature over approximately 1 h then quenched with sodium bicarbonate solution and concentrated. The residue is partitioned between ethyl acetate and water; the organic layer is dried (sodium sulfate) and concentrated. The residue is chromatographed (5 % methanol/methylene chloride) to yield solid 4-(Benzyloxycarbonyl)-1-(4-chloroquinolin-7-ylmethyl)-3-(S)-methyl-piperazin-2-one (1.32 g, 3.1 mmol). A portion of this material (0.10 g, 0.23 mmol) is dissolved in acetonitrile (6 mL) and treated with iodotrimethyl-silane (0.1 mL, 0.75

mmol) at room temperature for 2 hours. The reaction is quenched with methanol and concentrated to dryness. Methanol addition and concentration is repeated six times. The final residue is taken up is 2M aqueous HCl; the solution is washed with ether and concentrated to yield the title compound. MS m/z: M^+ = 289; ^1H NMR (CD_3OD, 300 MHz) δ 9.2 (d, 1H), 8.6 (d, 1H), 8.2-8.3 (m,2H), 8.0 (d, 1H), 5.1 (q, 1H), 4.3-4.4 (m, 1H), 3.8-4.0 (m, 2H), 3.6-3.8 (m, 3H), 1.75 (d, 3H).

EXAMPLE 92. 1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one.

A. 4-(tert-Butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-piperazin-2-one (8.0 g, 40 mmol), EXAMPLE 40, is dissolved in THF (160 mL), cooled in an ice bath and treated with 60 % sodium hydride (1.9 g, 48 mmol). The reaction mixture is stirred 40 minutes, then treated with tetra-butylammonium iodide (0.35 g, 0.95 mmol) and bromoacetonitrile (3.4 mL, 48 mmol). After 2 h the reaction is quenched with water, concentrated to a small volume and extracted with methylene chloride (3 X). The combined organic extracts are concentrated and the residue is chromatographed (50 % ethyl acetate/hexane) to give 4-(tert-butyloxycarbonyl)-1-cyanomethyl-piperazin-2-one (5.2 g, 21.7 mmol). This material is dissolved in ethanol (140 mL) and treated with platinum oxide (0.83 g) at 50 PSI of hydrogen gas for 24 hours. The catalyst is removed by filtration and the solution is concentrated to yield 4-(tert-butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one (5.2 g, 21.6 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.08 (s, 2H), 3.62 (m, 2H), 3.44 (t, 2H), 3.38 (t, 2H), 2.89 (t, 2H).

B. 4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl]- piperazin-2-one.

4-(tert-Butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one (4.0 g, 16 mmol) is dissolved in methylene chloride (150 mL) and treated with 4-nitro-2,3,5,6-tetrachloro-pyridine (4.8 g, 18 mmol) and N-methylmorpholine (4.0 mL, 36 mmol). The reaction mixture is stirred for 5 h, concentrated and the residue is purified by chromatography (50% ethyl acetate/hexane) to give the title compound (4.8 g, 10.5 mmol). Fab MS m/z: 457, 469, 461, $[M+1]^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.00 (t, 1H), 4.10 (s, 2H), 3.97 (m, 2H), 3.66 (m, 2H), 3.38 (m, 2H).

C. 1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl-piperazin-2-one (3.5 g, 7.6 mmol) is dissolved in methanol (20 mL) and 0.5 M sodium methoxide in methanol (150 mL, 75 mmol). The solution is treated with Pd/C (0.5 g) and agitated under 50 PSI of hydrogen gas for 16 hours. The solvent is removed and the residue is extracted with methylene chloride which is filtered. The filtrate is concentrated and loaded onto a silica flash column. The column is eluted with 5% MeOH/CH_2Cl_2 followed by NH_4OH/MeOH/CH_2Cl_2 (1:5:95)

and NH_4OH/MeOH/ CH_2Cl_2 (1:10:70) to yield 4-(tert-Butyloxycarbonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one as a white foam (1.5 g, 4.7 mmol). This material (1.5 g, 4.7 mmol) is treated with 20% trifluoroacetic acid in methylene chloride (110mL) at ambient temperature for 2 hours. The solution is concentrated and the residue is treated with saturated bicarbonate solution and ammonium hydroxide until a basic solution is obtained. The solution is applied to a silica column and eluted with NH_4OH/MeOH/CH_2Cl_2 (1:10:60) and 1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one is isolated as a mixture of desired product and inorganic salts (estimate 25 % by weight) EI MS m/z: 220, M^+; ^1H NMR (CD_3OD, 300 MHz) δ 8.07 (d, 2H), 6.96 (d, 2H), 3.77 (s, 2H), 3,65 (m, 6H), 3.44 (t, 2H).

EXAMPLE 93. 1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one trifluroacetate.

4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl]-piperazin-2-one (0.19 g, 0.41 mmol), Example 92, Part B, is dissolved in DMF (3 ml) and treated with 60 % NaH (20 mg, 0.5 mmol). After 10 minutes methyl iodide (0.025 ml, 0.40 mmol) is added and the yellow solution is stirred at r.t. overnight. The solution is diluted with EtOAc and washed with H_2O (6 X). The organic layer is dried (MgSO4) and concentrated to a residue (0.19 g, 0.40 mmol). The residue is dissolved in methanol (2 ml) and treated with 0.5 M NaOMe in MeOH (8 ml, 4.0 mmol)). The solution is treated with Pd/C and agitated under 60 PSI of hydrogen gas overnight and filtered. The filtrate is concentrated and extracted several times with CH_2Cl_2; removal of solvent in vacuo gives 4-(tert-Butyloxycarbonyl)-1-[2-{(methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one as an amorphous residue (0.16 g). EI MS m/z: 335, $[M+1]^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, 2H), 6.56 (d, 2H), 3.99 (s, 2H), 3.60 (t, 2H), 3.53 (t, 2H), 3.47 (t, 2H), 3.28 (t, 2H), 2.98 (s, 3H), 1.46 (s, 9H). Treatment of the above product with 20% TFA/CH_2Cl_2 (10 mL) at r.t. for 1 h gives, after concentration, the title compound as a residue which is used without further purification. ^1H NMR (CD_3OD, 300 MHz) δ 8.14 (d, 2H), 7.30 (br, 1H), 7.00 (br, 1H), 3.88-3.67 (m, 8H), 3.53 (t, 2H), 2.26 (s, 3H).

EXAMPLE 94. 1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one.

A. 4-[2-(3-Methylpyridin-4-ylimino)-ethyl]-3-oxo-piperazine-1-carboxlic acid benzyl ester.

4-(Benzyloxycarbonyl)-piperazin-2-one (4.7 g, 20 mmol) is dissolved in THF (50 mL) and treated with 1.5M LDA (20 mL, 30 mmol) at 0°C. The reaction mixture is treated with condensed ethylene oxide (3 mL, 40 mmol) and stirred at r.t. overnight. The mixture is neutralized with 2N HCl, concentrated, and extracted with EtOAc. The EtOAc layer is washed with H_2O and concentrated to a crude residue. Further extraction of the crude with Et_2O and

concentration of the ethereal layer gives an oil (1.5 g). The above oil is dissolved in CH_2Cl_2 (25 mL) and added to the solution of 2M oxalyl chloride (7.5 mL, 15 mmol) and DMSO (2.3 mL, 29.7 mmol) in CH_2Cl_2 (25 mL) at -60°C. After 15 minutes, Et_3N (2.1 ml, 15 mmol) is added. The mixture is stirred at -50 °C for 10 minutes then warmed to r.t for 10 minutes. The reaction is quenched with 0.5 N HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer is washed with 0.5 N HCl, brine (2 X), H_2O, and concentrated to a residue. The residue is purified by chromatography (2% MeOH/CH_2Cl_2) to give 4-amino-3-methyl pyridine as an oil (0.5 g, 1.6 mmol). A solution of the oil (0.2 g, 2 mmol), and (1R)-(-)-10-camphorsulfonic acid (15 mg) in toluene (100 ml) is refluxed with a Dean Stark set up overnight. The mixture is concentrated and the residue is purified by chromatography (2-4% MeOH/CH2Cl2) to give the title imine as a white foam (0.20 g, 0.54 mmol). Ion spray MS m/z: 367, $[M+1]^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H), 8.14 (s, 1H), 7.35 (s, 5H), 6.60 (d, 1H), 6.18 (dd, 1H), 5.15 (s, 2H), 4.97 (d, 1H), 4.30 (s, 2H), 3.78 (t, 2H), 3.50 (bm, 2H), 2.15 (s, 3H).

B. 1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one.

4-[2-(3-Methylpyridin-4-ylimino)-ethyl]-3-oxo-piperazine-1-carboxlic acid benzyl ester (0.20 g, 0.54 mmol) is dissolved in anhydrous ethanol (20 mL) and hydrogenated at 50 PSI with 10% Pd/C overnight. After filtration, the filtrate is concentrated. The residue is treated with Pd black in 5% HCO_2H/CH_2Cl_2 (10 ml) for 10 minutes. Filtration and concentration gives crude residue, which is purified by chromatography using NH_4OH/MeOH/CH_2Cl_2 (1:5:95) to give the title compound as a clear syrup (0.078 g, 0.33 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17 (d, 1H), 8.03 (s, 1H), 7.35 (s, 5H), 6.36 (d, 1H), 5.30 (b, 1H), 3.74 (t, 2H), 3.53 (s, 2H), 3.38 (m, 4H), 3.08 (t, 2H), 2.02 (s, 3H).

EXAMPLE 95. 1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one.

1-(2-Aminoethyl)-4-(tert-butyloxycarbonyl)-piperazin-2-one from EXAMPLE 92, Part A (1.0 g, 4.1 mmol) is treated with 3,4,5-trichloropyridazine (0.81 g, 4.1 mmol), triethylamine (0.57 mL, 4.1 mmol), THF (25 mL) and heated to 120°C in a sealed tube for 3 hours. Upon cooling, the solution is diluted with ethyl acetate and washed with aqueous sodium bicarbonate (25 mL), water and dried over sodium sulfate. The organic layer is concentrated and chromatographed (5% methanol/methylene chloride) to give a mixture of isomers (0.8 g, 20 mmol). The mixture is dissolved in 0.5 M sodium methoxide in methanol (200 mL), treated with 10% Pd/C (0.5 g) and agitated under 50 PSI of hydrogen for 20 hours. The reaction mixture is filtered; the filtrate is concentrated to a residue which is chromatographed (NH_4OH/H_2O/MeOH/EtOAc, 1:1:2:90) to give crude 4-(tert-butyloxycarbonyl)-1-[2-(pyridazin-4-ylamino)-ethyl]-piperazin-2-one. This material is dissolved in a minimal amount of THF and treated with a saturated solution of HCl in

ethyl acetate (50 mL). The solution is stirred at ambient temperature for 2 h and diluted with diethyl ether (50 mL). The precipitated title compound is collected and air dried (0.5 g, 1.7 mmol). MS m/z: 367, $[M+1]^+$; ^1H NMR (CD_3OD, 300 MHz) δ 8.8 (d, 1H), 8.5 (s, 1H), 7.4 (d, 1H), 4.1 (s, 2H), 3.5-3.8 (m, 8H).

EXAMPLE 96. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

A. 1-Allyl-4-(tert-butyloxycarbonyl)-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-piperazin-2-one (1.0 g, 5.0 mmol), EXAMPLE 40, is alkylated with allyl bromide (0.48 ml, 5.5 mmol) in THF (20 ml) using the procedure described in Example 92, PartA. The title compound (0.92 g, 3.8 mmol) is obtained as a colorless liquid after chromatographed (50 % ethyl acetate/hexane). EI MS m/z 240 (M+); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80-5.68 (m, 1H), 5.23-5.15 (m, 2H), 4.09 (s, 2H), 4.03 (d, 2H), 3.63 (t, 2H), 3,30 (t, 2H), 1.45 (s, 9H).

B. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

1-Allyl-4-(tert-butyloxycarbonyl)-piperazin-2-one (0.49 g, 2.0 mmol) is treated with (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (0.64 g, 2.0 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), $P(o\text{-}tol)_3$ (37 mg, 0.12 mmol), and Et_3N (0.56 mmol) in a seal tube. The mixture is stirred at 100 °C overnight, then diluted with CH_2Cl_2 and washed H_2O (2 X). The CH_2Cl_2 layer is concentrated and the residue is chromatographed (5% MeOH/CH_2Cl_2) to give a mixture of two isomers (0.40 g, 0.92 mmol). The mixture is separated into its constituent isomers upon further chromatography (EtOAc) to give 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (90 mg, 0.21 mmol, higher R_f value) and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (0.24 g, 0.56 mmol, lower R_f value). For the former: MS m/z 433 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.38 (d, 1H), 8.28 (s, 1H), 7.93 (d, 1H), 7.48 (d, 1H), 6.67 (s, 1H), 5.10 (m, 1H), 4.15 (s, 2H), 3.70 (t, 2H), 3,46 (t, 2H), 3.39 (d, 2H), 1.48 (s, 9H), 1.45 (s, 9H). For the latter: MS m/z 433 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (s, 1H), 8.37 (d, 1H), 7.98 (d, 1H), 6.77 (s, 1H), 6.52 (d, 1H), 6.07 (m, 1H), 4.23 (d, 2H), 4.12 (s, 2H), 3,69 (t, 2H), 3.40 (t, 2H), 1.52 (s, 9H), 1.45 (s, 9H).

EXAMPLE 97. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

A mixture of the two isomers from EXAMPLE 96, Part B. (0.11 g, 0.25 mmol) is dissolved in MeOH (7 ml), treated with with 10% Pd/C and is stirred under a balloon of hydrogen for 4 hours. Filtration and concentration gives a white foam (80 mg, 0.18 mmol). EI MS m/z 434 (M+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (d, 1H), 8.30 (s, 1H), 8.05 (d, 1H), 4.08 (s, 2H), 3.64 (t, 2H), 3.50 (t, 2H), 3.35 (t, 2H), 2.58 (t, 2H), 1.90 (m, 2H), 1.57 (s, 9H), 1.48 (s, 9H).

EXAMPLE 98. 4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one

4-(Benzyloxycarbonyl)-1-(2-hydroxyethyl)-piperazin-2-one, prepared as described in EXAMPLE 94, part A. (0.26 g, 0.94 mmol) in methylene chloride (6 mL) is treated with triphenyl phosphine (0.60 g, 2.3 mmol), imidazole (0.16 g, 2.3 mmol), and iodine (0.47 g, 1.9 mmol) for 0.5 h at 0 °C. The reactin mixture is partitioned between water and methylene chloride; the organic layer is concentrated and the residue is chromatographed (15 % EtOAc/ methylene chloride) to give 4-(benzyloxycarbonyl)-1-(2-iodoethyl)-piperazin-2-one (0.24 g, 0.62 mmol). Pyrrolo[3,2-c]pyridine (0.073 g, g, 0.62 mmol) is dissolved in DMF (3 mL) and treated with 60 % sodium hydride (0.03 g, 0.74 mmol) and all of the 4-(benzyloxycarbonyl)-1-(2-iodoethyl)-piperazin-2-one from the previous step; the reaction mixture is stirred at r.t. for 16 g. The reaction mixture is concentrated to dryness and the residue is partitioned between water and methylene chloride. The organic layer is concentrated and subjected to chromatography (2-5 % MeOH/methylene chloride) to yield the title compound (0.028 g, 0.074 mmol) Ion Spray MS m/z: 379, $[M+1]^+$.

EXAMPLE 99. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester

A solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (55 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) is cooled to 0°C. DIPEA (24 mg, 0.18 mmol) is then added followed by the addition of 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (32 mg, 0.12 mmol), EXAMPLE 1. The reaction mixture is warmed to ambient temperature. After 16 h, the reaction mixture is absorbed directly onto silica gel and chromatographed (CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to provide 60 mg (73%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (dd, J = 12.3, 3.4 Hz, 1H), 3.50-3.72 (m, 3H), 3.79 (s, 3H), 4.15 (dd, J = 12.3, 1.4 Hz, 1H), 4.24 (d, J = 16.9 Hz, 1H), 5.41 (d, J = 15.3 Hz,

1H), 6.50 (s, 1H), 6.76 (dd, J = 7.9, 1.4 Hz, 1H), 7.11-7.86 (m, 15H) ppm; MS (ISP loop): m/z 683 (M+H).

B. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester

Concentrated HCl (12M, one drop) is added at 0°C to a mixture containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (60 mg, 0.08 mmol) in MeOH (5 mL). Added THF (2 mL) followed by a second drop of 12M HCl and warmed reaction mixture to ambient temperature. The reaction is quenched by pouring the reaction mixture onto a 1:1 mixture of CH_2Cl_2/aqueous $NaHCO_3$ and the layers are separated. The aqueous phase is washed with CH_2Cl_2 and then the combined organic phase is washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 4% MeOH/ CH_2Cl_2) to provide 42 mg (93%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98 (dd, J = 12.5, 3.5 Hz, 1H), 3.60 (d, J = 16.8 Hz, 1H), 3.69 (d, J = 15.3 Hz, 1H), 3.79 (s, 3H), 3.98 (m, 1H), 4.21-4.31 (m, 2H), 4.44 (br s, 2H), 5.36 (d, J = 15.3 Hz, 1H), 6.47 (dd, J = 8.0, 1.4 Hz, 1H), 6.54 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 8.5, 1.8 Hz, 1H), 7.80-7.86 (m, 3H) ppm; MS (ISP loop): m/z 519 (M+H).

EXAMPLE 100. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Water (5 drops) is added to a solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (30 mg, 0.05 mmol), EXAMPLE 99, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature, LiOH monohydrate (7 mg, 1.66 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 10 mg (34%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.18 (dd, J = 12.1, 3.5 Hz, 1H), 3.61 (d, J = 16.0 Hz, 1H), 3.77 (d, J = 16.0 Hz, 1H), 3.95 (d, J = 16.0 Hz, 1H), 4.06 (d, J = 12.1 Hz, 1H), 4.14 (m, 1H), 6.40 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.57 (dd, J = 8.6, 1.9 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 8.18 (s, 1H), 8.33 (s, 1H) ppm; MS (ISP loop): m/z 505 (M+H).

EXAMPLE 101. 4-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxo-piperazine-1-ylmethyl]benzamidine.

To a solution of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (0.38 g, 0.83mmol), EXAMPLE 66, in CH_2Cl_2 (5 mL) is added Et_3N (0.35 mL, 2.6 mmol) and 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.23 g, 0.85 mmol, EXAMPLE 1. After 6 hours, the solution is concentrated. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 70% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (0.37 g, 0.65 mmol). ^1H NMR (d^6-DMSO, 300MHz) δ 9.33 (bs, 2H), 8.96 (bs, 2H), 8.30 (s, 1H), 8.18 (s, 1H), 8.04 (d, 1H), 7.70 (m, 2H), 7.50 (m, 1H), 7.28 (m, 2H), 4.55 (s, 2H), 3.86 (s, 2H), 3.44 (m, 2H), 3.22 (m, 2H).

The following compounds are prepared from 1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, Example 77, and the appropriate sulfonyl chloride using the method of Example 101.

Example	Name	m/z (M+H)
102	4-[4-(4-Methoxy-benzenesulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	403
103	4-[4-(5-Chloro-thieno[3,2-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465
104	4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
105	4-[2-Oxo-4-(thieno[2,3-c]pyridine-2-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	430
106	4-[4-(7-Chloro-thieno[2,3-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
107	4-[4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	495, 497 Cl pattern
108	4-[4-(4-Chloro-thieno[3,2-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
109	4-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	387
110	4-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	429
111	4-Amino-3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	478, 480 Cl pattern
112	3-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	387
113	3-[4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-	447

	ylmethyl]-benzamidine	
114	3-[4-(4-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465 Cl pattern
115	3-[4-(5-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465 Cl pattern
116	3-[4-(6-Methoxy-naphthalene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	453
117	3-{4-[5-(5-Nitro-pyridine-2-sulfonyl)-thiophene-2-sulfonyl]-2-oxo-piperazin- 1-ylmethyl}-benzamidine	565
118	3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]- benzamidine	463, 465 Cl pattern
119	3-{4-[2-(3-Chloro-phenyl)-ethenesulfonyl]-2-oxo-piperazin-1-ylmethyl}- benzamidine	433, 435 Cl pattern
120	3-[2-Oxo-4-(4-phenylazo-benzenesulfonyl)-piperazin-1-ylmethyl]-benzamidine	477
121	3-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	429

EXAMPLE 122. 4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine.

Hydrogen chloride gas is bubbled into an ice-cooled solution of 4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile (100 mg, 0.264 mmol), (prepared by deprotecting 4-(4-cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester, EXAMPLE 66, Part A, followed by alkylation with 6-chloro-2-chloromethylbenzimidazole) in 15 mL of methanol. The solution contained 3Å molecular sieves. The reaction mixture is stored at -30°C. The methanol is removed on the rotovap. Fresh methanol (20 ml) is added folowed by a stream of ammonia gas. The resulting mixture is heated to reflux for three hours. The reaction mixture is filtered at room temperature. The mother liquor is condensed and the resulting residue is purified by reverse phase HPLC (0-50 % ACN/H_2O). The product is isolated as a white solid with a melting point of 91-95°C .

MS $C_{20}H_{21}ClN_6O$ m/z: 397, 399. Anal. cald. for $C_{20}H_{21}ClN_6O{\cdot}3C_2HF_3O_2$: C, 42.26; H, 3.27; N, 11.37. Found C, 42.20; H, 3.44; N, 11.36.

EXAMPLE 123. 4-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl}benzamidine.

To a solution of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (75 mg, 0.16 mmol), EXAMPLE 66, in 1.5 mL of DMF is added N,N-diisopropylethylamine (0.14 mL, 0.80 mmol). After stirring 10 min at room temperature, 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid (32 mg, 0.17 mmol), EXAMPLE 25, is added, followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (55 mg, 0.17 mmol). The resulting mixture is stirred at room temperature for 16 h and the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (77 mg, 0.15 mmol) as a white solid.

^1H NMR (d6-DMSO, 300 MHz) δ 9.27 (bs, 2H), 9.10 (bs, 2H), 7.77 (d, 2H), 7.65 (d, 1H), 7.49 (dd, 2H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1H), 4.65 (s, 2H), 4.45, 4.21 (m, 2H, rotamers), 3.80 (m, 2H), 3.35 (m, 2H). ESI MS, $[M+H]^+$=403,405 (Cl pattern).

EXAMPLE 124. 3-{4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl}benzamidine.

The title compound is prepared as described in EXAMPLE 123 using 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid (EXAMPLE 25) and 3-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (prepared from 3-bromomethyl toluylnitrile as described in EXAMPLE 66). ^1H NMR (DMSO-d_6, 300 MHz) δ 9.32 (bs, 2H), 9.16 (bs, 2H), 7.65 (m, 5H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1H), 4.64 (s, 2H), 4.44, 4.21 (m, 2H, rotamers), 3.93, 3.79 (m, 2H, rotamers), 3.36 (m, 2H). ESI MS, $[M+H]^+$=403,405 (Cl pattern).

EXAMPLE 125. 3-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine.

A white solid (13.0 mg, 13%). $C_{20}H_{21}ClN_6O$ MS m/z: 397, 399 Anal. cald. for $C_{20}H_{21}ClN_6O \cdot 3C_2HF_3O_2$: C, 42.26; H, 3.27; N, 11.37. Found C, 43.70; H, 3.71; N, 11.95.

EXAMPLE 126. 1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)piperazin-2-one.

The title compound is prepared as described in Example 101 using 1-(2-aminoquinolin-6-ylmethyl)piperazin-2-one, EXAMPLE 67, and 5'-chloro-[2,2']bithiophenyl-5-sulfonyl chloride, EXAMPLE 2. The crude product is triturated in CH_2Cl_2 and filtered to provide the title compound as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 7.82 (d, 1H), 7.68 (d, 1H), 7.42 (m, 3H), 7.36 (d,1H), 7.25 (d, 1H), 7.20 (d, 1H), 6.70 (d, 1H), 6.43 (bs, 2H), 4.53 (s, 2H), 3.78 (s, 2H), 3.31 (m, 4H). MS (ion spray) m/z 519, 521, (M+H), Cl pattern.

EXAMPLE 127. 6-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]-1H-quinolin-2-one.

The title compound is prepared as described in EXAMPLE 101,using 6-(2-oxopiperazin-1-ylmethyl)-1H-quinolin-2-one, minor product from EXAMPLE 67, Part D, and 6-chlorobenzo[b]thiophene-2-sulfonyl chloride, EXAMPLE 1. The crude product is triturated in CH_2Cl_2 and filtered to provide the title compound as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 11.72 (bs, 1H), 8.33 (s, 1H), 8.18 (s, 1H), 8.07 (d,1H), 7.78 (d,1H), 7.58 (dd, 1H), 7.45 (s, 1H), 7.30 (dd, 1H), 7.18 (d, 1H), 6.46 (d, 1H), 4.52 (s, 2H), 3.86 (s, 2H), 3.43 (m, 2H), 3.31 (m, 2H). MS (ion spray) m/z 488, 490, (M+H), Cl pattern.

The following compounds are prepared using starting materials prepared as described in Examples 67, 68 and 73 and the appropriate carboxylic acid according to the method of Example 123.

Example	Name	m/z (M+H)
128	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-3-ylmethyl-piperazin-2-one	478, 480 Cl pattern
129	1-(2-Amino-quinoxalin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	
130	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-one	478, 480 Cl pattern
131	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	478, 480 Cl pattern
132	1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	488, 490 Cl pattern
133	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-hydroxy-isoquinolin-6-ylmethyl)-piperazin-2-one	488, 490 Cl pattern
134	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-6-ylmethyl)-piperazin-2-one	506, 508 Cl pattern
135	7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-2H-isoquinolin-1-one	488, 490 Cl pattern
136	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-7-ylmethyl)-piperazin-2-one	506, 508 Cl pattern
137	1-(7-Amino-thieno[2,3-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern

138	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one	506, 508 Cl pattern
139	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-quinolin-6-ylmethyl-piperazin-2-one	472, 474 Cl pattern
140	7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-1H-quinolin-2-one	488, 490 Cl pattern
141	1-(2-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
142	1-(4-Amino-thieno[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
143	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1,2,3,4-tetrahydro-isoquinolin-6-ylmethyl)-piperazin-2-one	475, 477 Cl pattern
144	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-isoquinolin-6-ylmethyl-piperazin-2-one	472, 474 Cl pattern
145	1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
146	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-6-ylmethyl)-piperazin-2-one	482, 484 Cl pattern
147	1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
148	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-7-ylmethyl)-piperazin-2-one	482, 484 Cl pattern
149	1-(1-Amino-isoquinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 Cl pattern
150	1-(4-Amino-thieno[3,2-c]pyridin-3-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
151	(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid	536, 538 Cl pattern
152	(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid	536, 538 Cl pattern
153	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
154	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	475, 477 Cl pattern

155	(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-piperazin-2-one	494, 496, 498, Cl_2 pattern
156	(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-piperazin-2-one	490, 492, 494, Cl_2 pattern
157	(S)-4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
158	1-(2-Amino-quinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	427, 429 Cl pattern

The following compounds are prepared from starting materials prepared as described in Example 67 and the appropriate aryl-methyl bromide or allyl-methyl bromide using a K_2CO_3-mediated alkylation reaction.

Example	Name	m/z (M+H)
159	1-(2-Aminoquinolin-6-ylmethyl)-4-(4-methoxybenzyl)piperazin-2-one	377
160	1-(2-Aminoquinolin-6-ylmethyl)-4-6-chlorobenzo[b]thiophen-2-ylmethyl)piperazin-2-one	436, 438 Cl pattern
161	1-(2-Aminoquinolin-6-ylmethyl)-4-(5-methoxy-1H-benzoimidazol-2-ylmethyl)piperazin-2-one	417
162	1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)piperazin-2-one	469, 471 Cl pattern
163	1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	413, 415 Cl pattern
164	1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]piperazin-2-one	601, 603, 605 Br_2 pattern
165	3-[4-(2-Aminoquinolin-6-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one	431
166	1-(2-Aminoquinolin-6-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	430

The following compounds are prepared from starting materials prepared as described in Examples 66, 67, 68 and 73 and the appropriate aryl-methyl bromide or allyl-methyl bromide using a K_2CO_3-mediated alkylation reaction.

Example	Name	m/z (M+H)

167	3-(4-Biphenyl-3-ylmethyl-3-oxo-piperazin-1-ylmethyl)-benzamidine	399
168	4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
169	1,4-Bis-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	427
170	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
171	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	444, 446 Cl pattern
172	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	420, 422 Cl pattern
173	1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	401
174	1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	426
175	1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	443
176	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	413, 415 Cl pattern
177	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-benzamidine	413, 415 Cl pattern
178	4-(4-Cyclohexylmethyl-2-oxo-piperazin-1-ylmethyl)-benzamidine	329
179	1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	437, 439 Cl pattern
180	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one	457, 459 Cl pattern
181	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	468
182	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	454
183	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one	483
184	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one	453

EXAMPLE 185. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one.

The title compound is prepared as described in EXAMPLE 101, substituting 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, for 4-(2-oxopiperazin-1-ylmethyl)-benzamidine. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA). The appropriate collected fractions are lyopholized to afford the title compound as a white solid. MS (ion spray) m/z 488, 490, (M+H). ^1H NMR (d_6-DMSO, 300 MHz) δ 9.65 (s, 2H), 8.80 (s, 1H), 8.30 (m, 2H), 8.20 (s, 1H), 8.05 (d, 1H), 7.60 (m, 3H), 4.70 (s, 2H), 3.85 (s, 2H), 3.50-3.20 (m, 4H).

EXAMPLE 186. 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 3-chloro-benzylamide.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, (0.10g, 0.30mmol) is 9 mL of DMF is added 3-chlorobenzyl sulfamyl catechol (0.09g, 0.30mmol), EXAMPLE 4, Et_3N (0.08g, 0.75 mmol) and DMAP (0.001 g, 0.12 mmol). The solution is heated to 60°C. After 16 h, the solution is concentrated. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_20 (0.1%TFA) to 100% CH_3CN. The product fractions are lyophilized to give the title compound (0.077g, 0.17 mmol) as the TFA salt. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.82 (bs, 2H), 8.98 (s, 1H), 8.52 (d, 1H), 8.32 (d, 1H), 7.60 (m, 2H), 7.35 (m, 4H), 4.69 (AB, 2H), 4.11 (m, 2H), 3.77 (s, 2H), 3.38 (m, 2H), 3.27 (m, 2H). MS (ion spray) m/z 461, 463, (M+H), Cl pattern.

The following compounds are prepared from the compound of Example 72 and the appropriate sulfonyl choride using the method of Example 101.

Example	Name	m/z (M+H)
187	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	489, 491 Cl pattern
188	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-piperazin-2-one	520, 522 Cl pattern
189	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 4-chloro-benzylamide	460
190	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-isoxazol-3-yl-thiophene-2-sulfonyl)-piperazin-2-one	471
191	1-(4-Amino-quinazolin-7-ylmethyl)-4-(thieno[3,2-b]pyridine-2-	455

	sulfonyl)-piperazin-2-one	
192	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(3-chloro-phenyl)-ethyl]-amide	474
193	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(4-chloro-phenyl)-ethyl]-amide	474
194	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-piperazin-2-one	472
195	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	464, 466 Cl pattern
196	4-(3-Amino-benzenesulfonyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	413

The following compounds are prepared from starting materials obtained as described in Examples 75-88 and the appropriate sulfonyl chloride using the method of Example 101.

Example	Name	m/z (M+H)
197	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-ethyl-piperazin-2-one	492, 494 Cl pattern
198	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-ethyl-piperazin-2-one	516, 518 Cl pattern
199	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-ethyl-piperazin-2-one	548, 550 Cl pattern
200	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methyl-piperazin-2-one	534, 536 Cl pattern
201	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methyl-piperazin-2-one	502, 504 Cl pattern
202	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one	502, 504 Cl pattern
203	(+/-)-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-piperazin-2-yl]-acetic acid	546, 548 Cl pattern

The following compounds are prepared from starting materials obtained as described in Examples 72 and 73 and the appropriate sulfonyl chloride according to the method of Example 101 or the appropriate carboxylic acid according to the method of Example 123.

Example	Name	m/z (M+H)
204	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	470, 472 Cl pattern

205	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
206	1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	494, 496 Cl pattern
207	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-6-ylmethyl)-piperazin-2-one	489, 491 Cl pattern
208	1-(4-Amino-thieno[3,2-d]pyrimidin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	494, 496 Cl pattern
209	1-(4-Amino-quinazolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	488, 490 Cl pattern
210	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-7-ylmethyl)-piperazin-2-one	489, 491 Cl pattern
211	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one	478, 480 Br pattern
212	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	434, 436 Cl pattern

EXAMPLE 213. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-{4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-2-oxopiperazin-1-ylmethyl}pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

To a solution of 2-(2-oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (0.71 g, 2.1 mmol), EXAMPLE 69, in CH_3CN (7 mL) is added triethylamine (0.60 mL, 4.3 mmol) followed by 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride, EXAMPLE 3, (0.57 g, 2.1 mmol). The mixture is stirred overnight, then concentrated to dryness. The residue is diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound (1.2 g, 2.1 mmol) as a light yellow solid. The crude material can be used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.80 (s, 1H), 8.42 (d, 1H), 7.88 (d, 1H), 7.55 (d, 1H), 7.14 (d, 1H), 6.98 (d, 1H), 6.41 (s, 1H), 6.36 (d, 1H), 5.00 (s, 2H), 3.98 (s, 2H), 3.61 (m, 4H), 1.71 (s, 9H). Ion spray MS, $[M+H]^+$= 537, 539, Cl pattern.

B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

Trifluoroacetic acid (2.2 mL, 28.6 mmol) is added dropwise to a slurry of 2-[4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.32 g, 2.4 mmol) in CH_2Cl_2 (25 mL) at 0°C. After 1.5 hours, the ice bath is removed and the solution stirred at room temperature for 4 hours. The reaction mixture is diluted with methylene choride and washed with saturated sodium bicarbonate and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound as the free base. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are lyophilized to provide the title compound (1.29 g, 2.2 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 14.90 (bs, 1H), 12.81 (s, 2H), 9.12 (s, 1H), 8.41 (d, 1H), 7.89 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 6.95 (s, 1H), 4.80 (s, 2H), 3.98 (s, 2H), 3.48 (s, 4H). Ion spray MS, $[M+H]^+$= 437, 439, Cl pattern.

EXAMPLE 214. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.7 (s, 1H), 8.41 (d, 1H), 7.9-7.8 (m, 3H), 7.45 (d, 1H), 7.25 (d, 1H), 6.31 (s, 1H), 4.95 (s, 2H), 3.98 (s, 2H), 3.65 (m, 2H), 3.55 (m, 2H), 1.68 (s, 9H). Ion spray MS, $[M+H]^+$= 561, 563, Cl pattern.

B. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one trifluoroacetate.

^1H NMR (d6-DMSO, 300 MHz) δ 14.68 (bs, 1H), 12.6 (s, 1H), 9.1 (s, 1H), 8.36 (d, 1H), 8.29 (d, 1H), 8.17 (s, 1H), 8.05 (d, 1H), 7.82 (d, 1H), 7.56 (m, 2H), 6.83 (s, 1H), 4.1 (s, 2H), 3.84 (s, 2H), 3.38 (m, 4H). Ion spray MS, $[M+H]^+$= 461,463, Cl pattern.

EXAMPLE 215. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(5-oxy-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one (0.06 g, 0.13 mmol) is dissolved in anhydrous methylene chloride (20 ml), treated with m-chloroperbenzoic acid (0.03 g, mmol) and stirred at room temperature for 4 hours. The solution is diluted with methylene chloride, washed with $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (5-10 % $MeOH/CH_2Cl_2$) and converted to the TFA salt to provide the title compound (0.015 g, 0.032 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.14 (bs, 1H), 8.95 (d, 1H), 7.8- 7.87 (m, 3H), 7.57 (d, 1H), 7.48 (dd, 1H),

6.87 (s, 1H), 4.90 (s, 2H), 3.95 (s, 2H), 3.86 (s, 3H), 3.49 (s, 3H). EI MS, [M$^+$] = 474, 476, Cl pattern.

EXAMPLE 216. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one (0.59 g, 1.28 mmol), EXAMPLE 214, is dissolved in anhydrous DMF (30 ml), cooled in an ice bath, treated with 60 % sodium hydride (0.061 g, 1.53 mmol) and stirred at room temperature for 30 minutes. The solution is treated with methyl iodide (83 mL, 1.33 mmol) and warmed to room temperature over 4 hours. The reaction is quenched with ammonium chloride solution, diluted with ethyl acetate and separated. The organic layer is washed with brine (3x), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (5-10 % MeOH/CH_2Cl_2) to provide the title compound (0.31 g, 0.65 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.55 (d, 1H), 7.99 (dd, 1H), 7.82 (m, 3H), 7.49 (dd, 1H), 7.43 (d, 1H), 6.55 (s, 1H), 4.75 (s, 2H), 3.96 (s, 2H), 3.52 (m, 4H), 3.86 (s, 3H), 3.49 (s, 3H). Ion Spray MS, $[M+H]^+$=477.

The following compounds are prepared from starting materials obtained as described in Example 69 and the appropriate sulfonyl chlorides according to the method of Example 101.

Example	Name	m/z (M+H)
217	4-(3-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	460
218	4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.	462, 464 Cl pattern
219	4-(6-Bromobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	505
220	2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]-benzo[b]thiophene-6-carbonitrile	452
221	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	493
222	4-[2-(4-Chlorophenyl)ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	431
223	{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid	519, 521 Cl pattern

224	4-(5-Pyridin-4-ylthiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	454
225	{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid ethyl ester	547, 549 Cl pattern
226	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-methoxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one	519, 520 Cl pattern
227	4-(6-Chlorothieno[3,2-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	462, 464 Cl pattern
228	{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[2,3-c]pyridin-1-yl} acetic acid methyl ester	533, 535 Cl pattern
229	2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]benzo[b]thiophene-5-carbonitrile	452
230	4-(5-Aminomethylbenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	456
231	2-{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl}acetamide	518, 520 Cl pattern
232	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-hydroxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl]piperazin-2-one	505
233	4-(6-Chloro-1H-benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	445, 447 Cl pattern
234	4-(1H-Benzoimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	411
235	4-(6-Aminomethyl-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	456
236	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	428
237	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one	428
238	4-[2-(5-Chloro-thiophen-2-yl)-ethanesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
239	4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	453
240	4-[2-(5-Chloro-4-methoxy-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	467, 469

241	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	462, 464
242	4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	446
243	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one	460, 462 Cl pattern
244	4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one	462, 464 Cl pattern
245	{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[2,3-c]pyridin-1-yl}-acetic acid methyl ester	533, 535 Cl pattern
246	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one	461, 463 Cl pattern

EXAMPLE 247. 1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)piperazin-2-one.

A. (2-Chloro-pyridin-4-yl)-carbamic acid tert-butyl ester.

NaHMDS (61.7 mL, 1.0M solution in THF) is rapidly added to a solution of 2-chloro-pyridin-ylamine (4.0 g, 30.9 mmol) amd BOC anhydride (6.74 g, 30.9 mmol) in THF (28 mL) at RT. The reaction mixture is cooled in an ice water bath (0°C) for 1h then stirred for 3 hr at RT. The gelatinous mixture is concentrated in vacuo and diluted with ethyl acetate and saturated NH_4Cl solution. The organic layer is washed with 0.1N HCl, saturated $NaHCO_3$ and brine. The organic layer is then dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1% MeOH/CH_2Cl_2 to yield the title product (5.57 g, 24.4 mmol) as a yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, 1H), 7.48 (d, 1H), 7.12 (dd, 1H), 1.60 (s, 9H). EI MS $[M]^+$=228.

B. (2-Chloro-3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester.

tert-Butyllithium (36.3 mL, 1.7M in pentane) is added dropwise to a solution of (2-chloro-pyridin-4-yl)-carbamic acid tert-butyl ester (6.00 g, 26.2 mmol) in THF (46 mL) at -78 °C under Ar. The yellow/orange mixture is stirred for 2 h at -78°C then warmed to -40 °C for 1 h then cooled to -78°C before dropwise addition of I_2 (15.65 g, 61.7 mmol) in THF (49 mL). The reaction mixture is stirred for 1.5 h at -78°C then at -10°C for 30 minutes. The reaction is quenched with saturated NH_4Cl solution then diluted with CH_2Cl_2 and washed with saturated NH_4Cl, saturated sodium thiosulfate, water then brine. The organic layer is dried over $MgSO_4$, filtered and

concentrated to dryness. The crude product is chromatographed eluting with 1-2% MeOH/CH_2Cl_2 to yield the title product (7.96 g, 22.5 mmol) as a bright yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, 1H), 8.02 (d, 1H), 7.32 (bs, 1H), 1.60 (s, 9H). EI MS $[M]^+$=354, 356, Cl pattern.

C. 4-(4-Chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Trifluoroacetic acid (10 mL) is added to a solution of 2-(4-benzyloxycarbonyl-2-oxo-piperazin-1-ylmtheyl)-4-chloro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (5.66 g, 11.3 mmol, prepared in the same manner as described previously) in CH_2Cl_2 (10 mL). The solution is stirred overnight then diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH_2Cl_2 to yield the title product (3.81 g, 9.56 mmol) as a foamy yellow solid.

^1H NMR ($CDCl_3$, 300 MHz) δ 9.43 (bs, 1H), 8.08 (d, 1H), 7.38 (s, 5H), 7.18 (d, 1H), 6.51 (s, 1H), 5.15 (s, 2H), 4.58 (s, 2H), 4.20 (s, 2H), 3.71 (m, 2H), 3.50 (m, 2H). Ion spray $[M+H]^+$= 399, 401, Cl pattern.

D. 4-(1-Benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Powdered NaOH (0.96 g, 23.9 mmol) followed by nBu_4NHSO_4 (0.32 g, 0.96 mmol) and benzene sulfonyl chloride (1.8 mL, 14.1 mmol) is added to a solution of 4-(4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (3.81 g, 9.56 mmol) in CH_2Cl_2 (32 mL) at RT. The resulting slurry is stirred for 3.5 h then diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH_2Cl_2 to yield the title product (5.06 g, 9.38 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, 1H), 7.97 (d, 1H), 7.84 (d, 2H), 7.61 (d, 1H), 7.51 (m, 2H), 7.38 (s, 5H), 6.50 (s, 1H), 5.18 (s, 2H), 5.03 (s, 2H), 4.29 (s, 2H), 4.29 (s, 2H), 3.80 (m, 2H), 3.51 (m, 2H). Ion spray $[M+H]^+$= 539, 541, Cl pattern.

E. 1-(1-Benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

TMSI (2.7 mL, 19.0 mmol) is added to a solution of 4-(1-benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (5.06 g, 9.38 mmol) in CH_3CN (134 mL) at 0°C. The reaction mixture is warmed to RT and stirred for 5

hours. The reaction mixture is concentrated to dryness and the red residue is diluted with MeOH and concentrated to dryness (this is repeated twice). The mixture is diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH_2Cl_2 to yield the title product (0.70 g, 1.74 mmol) and unreacted starting material (3.58 g, 6.64 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H), 7.93 (d, 1H), 7.85 (d, 2H), 7.60 (d, 1H), 7.51 (m, 2H), 6.50 (s, 1H), 5.01 (s, 2H), 3.45 (m, 2H), 3.18 (m, 2H). Ion spray $[M+H]^+$= 405, 407, Cl pattern.

F. 1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one.

Anhydrous ammonium acetate (0.56 g, 7.2 mmol), phenol (0.45 g, 4.8 mmol) and 1-(1-benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one (0.31 g, 0.48 mmol, prepared as described previously) are heated to 100°C for 3.5 days. The mixture is cooled to RT then the crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN then the appropriate product fractions are lyophilized to provide the title compound (1.29 g, 2.2 mmol) as a white solid (22.4 mg, 0.038 mmol). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.40 (bs, 1H), 12.00 (bs, 1H), 8.31 (d, 1H), 8.20 (s, 1H), 8.06 (d, 1H), 8.02 (bs, 2H), 7.57 (dd, 1H), 7.48 (m, 1H), 6.89 (d, 1H), 6.81 (s, 1H), 4.60 (s, 2H), 3.81 (s, 2H), 3.40 (m, 4H). LR-FAB MS, $[M+H]^+$=476, 478.

EXAMPLE 248. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-{4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

Sodium borohydride (0.005 g, 0.13 mmol) is added to a solution of 2-{4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-methoxycarbonyl-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.04 g, 0.07 mmol), (prepared from 2-(2-(±)-methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester, EXAMPLE 71, and 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride, EXAMPLE 3, using the procedure described in EXAMPLE 214, Part A) in MeOH (3 mL) at RT. The reaction mixture is stirred for 6 h then quenched with water and concentrated in vacuo. The crude product (0.04 g) is taken onto the next step without further purification.

B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Trifluoroacetic acid (1.8 mL) is added to a solution of 2-{4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.04 g) in CH_2Cl_2 (4.2 mL) at RT. The reaction mixture is stirred for 4 h then concentrated in vacuo. The title compound is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and lyophilizing the appropriate product fractions. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.10 (s, 1H), 8.46 (d, 1H), 7.82 (d, 1H),7.50 (d, 1H) 7.43 (d, 1H), 7.14 (d, 1H), 7.01 (d, 1H), 6.94 (s, 1H), 5.12 (bs, 1H), 4.80 (AB, 2H), 3.98 (d, 2H0, 3.90 (m, 1H), 3.40-3.50 (m, 4H). APCI MS, $[M+H]^+$=467, 469.

The following compounds are prepared from starting materials obtained using the methods of Examples 69, 70 and 71 and the appropriate sulfonyl chorides according to the method of Example 101.

Example	Name	m/z
249	1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	519, 521 Cl pattern
250	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	495, 497 Cl pattern
251	1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	505, 507 Cl pattern
252	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	491, 493 Cl pattern

The following enantiomerically pure compounds are obtained by chiral resolution on a CHIRACEL OD prep column.

Example	Name	%ee	m/z
253	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid methyl ester	99% (-)	495, 497 Cl pattern

254	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid methyl ester	95% (+)	495, 497 Cl pattern

EXAMPLE 255. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 6-(R)-(tert-Butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Trifluoroacetic acid (0.25 mL) is added to a solution of 2-{2-(R)-(tert-butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.025 g, 0.037 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture is stirred for 2 h then concentrated to dryness. The residue is diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product (0.019 g, 0.033 mmol) is used in the subsequent step without further purification.

B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Glacial acetic acid (3 mL, 0.046 mmol) and tetrabutylammonium fluoride (92 mL, 0.092 mmol) is added to a solution of 6-(R)-(tert-butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one (0.019 g, 0.033 mmol) in THF (0.5 mL). The resulting solution is stirred for 4 h then concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are lyophilized to provide the title compound (0.009 g, 0.016 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 14.50 (bs, 1H), 12.60 (bs, 1H), 9.18 (s, 1H), 8.38 (d, 1H), 7.89 (d, 1H), 7.61 (d, 1H), 7.50 (d, 1H), 7.21 (d, 1H), 7.08 (d, 1H), 6.90 (s, 1H), 5.03 (s, 2H), 4.63 (d, 2H), 3.70-3.90 (AB, 2H), 3.75 (m, 1H), 3.21 (m, 2H). Ion spray MS, $[M+H]^+$=467, 469, Cl pattern.

The following compounds are prepared from starting materials obtained as described in Examples 69, 70 and 71 and the appropriate sulfonyl chloride according to the method of Example 101.

Example	Name	m/z
256	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-hydroxymethyl-1-(1H-	491, 493

	pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	
257	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	495, 497 Cl pattern
258	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	519, 521 Cl pattern
259	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	481, 483 Cl pattern
260	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	505, 507 Cl pattern
261	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	491, 493 Cl pattern
262	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	467, 469 Cl pattern
263	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid amide	504, 506 Cl pattern
264	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483
265	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	505, 507
266	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	537, 539
267	4-[2-(4-Chloro-phenyl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	475, 477

EXAMPLE 268. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-ylmethyl)piperazin-2-one.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride (1.84 g, 5.73 mmol), EXAMPLE 72, in DMF (20 mL) is added 2-bromomethyl-6-chloro-benzo[b]thiophene, EXAMPLE 5, (1.5 g, 5.73 mmol) and K_2CO_3 (4.0 g, 28.7 mmol). The

solution is stirred for 16 hours. After this time, the solution is diluted with water. The solution is acidified with trifluoroacetic acid. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 50% CH_3CN/H_2O (0:1% TFA). The appropriate collected fractions are lyopholized to afford the title compound as a white solid. ^1H NMR (d^6-DMSO, 300MHz) δ 9.78 (bs, 3H), 8.82 (s, 1H), 8.34 (d, 1H), 8.07 (s, 1H), 7.81 (d, 1H), 7.63 (d, 1H), 7.51 (s, 1H), 7.32 (m, 2H), 4.71 (s, 2H), 3.95 (s, 2H), 3.28 (m, 4H), 2.80 (m, 2H).

EXAMPLE 269. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)piperazin-2-one.

A mixture of 1-(4-aminoquinazolin-7-ylmethyl)piperazin-2-one (50 mg, 0.15 mmol), EXAMPLE 72, 6-chloro-2-chloromethylbenzimidazole (30.5 mg, 0.15 mmol) and potassium carbonate (83 mg, 0.6 mmol) in 2 mL of DMF is stirred at ambient temperature overnight. The mixture is purified on reverse phase HPLC (CH_3CN/H_2O/TFA) to give the trifluoroacetic acid salt of 1-(4-aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)piperazin-2-one (25 mg) as a solid. ^1H NMR (CD_3OD, 300 MHz) δ 8.69 (s, 1H), 8.33 (d, 1H), 7.79 (s, 1H), 7.75-7.69 (m, 3H), 7.57-7.54 (m, 1H), 4.86 (s, 2H), 4.22 (s, 2H), 3.31 (m, 4H), 2.99 (m, 2H). MS m/z 422 (M+H).

EXAMPLE 270. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (76 mg, 0.23 mmol), EXAMPLE 72, in 2 mLof DMF is added potassium carbonate (127 mg, 0.92 mmol) followed by 6-chloro-2-chloromethyl-benzothiazole (prepared according to the procedure of B.L.Mylari, Synthesis Comm. 1989, 16, 2921) (50 mg, 0.23 mmol). The resulting mixture is stirred overnight at room temperature. The undissolved potassium carbonate is removed by filtration and the mother liquor is purified by reverse phase HPLC (10-100% CH_3CN/H_2O). The desired is product is obtained as a white solid with a melting point of 123-126°C. $C_{21}H_{19}ClN_6OS$ MS m/z: 439, 441. Anal. cald. for $C_{21}H_{19}ClN_6OS \cdot 2C_2HF_3O_2$: C, 45.02; H, 3.17 N, 12.60. Found C, 44.15; H, 3.19; N, 11.79.

EXAMPLE 271. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one.

The desired product (10.0 mg, 7 %) is isolated as a white solid. $C_{21}H_{19}ClN_6O_2$ MS m/z: 423, 425.

EXAMPLE 272. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one.

The desired product (19.0 mg, 22%) is obtained as a white solid. $C_{21}H_{19}ClN_6OS$ MS m/z: 438,440. Anal. cald. for $C_{21}H_{19}ClN_6OS \cdot 2C_2HF_3O_2$: C, 45.02; H, 3.17 N, 12.60. Found C, 43.35; H, 3.26; N, 12.65.

EXAMPLE 273. 3-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxopiperazin-1-ylmethyl]-7-chloro-1H-quinolin-2-one.

The title compound is prepared as described in EXAMPLE 268, substituting 3-bromomethyl-7-chloro-1H-quinoline-2-one, EXAMPLE 8, for 2-bromomethyl-6-chlorobenzo[b]thiophene. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 50% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyopholized to afford the title compound as a white solid.
^1H NMR (d^6-DMSO, 300MHz) δ 12.18 (bs, 1H), 9.75 (m, 1H), 8.86 (s, 1H), 8.40 (m, 1H), 8.11 (d, 1H), 8.10 (s, 1H), 7.78 (m, 1H), 7.69 (m, 2H), 7.37 (m, 1H), 4.80 (s, 2H), 4.10 (m, 2H), 3.47 (m, 4H), 3.30 (m, 2H). MS (ion spray) m/z 449, (M+H).

EXAMPLE 274. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one.

A. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1-(toluene-4-sulfonyl)-1H-indol-6-ylmethyl)-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 268 using 6-bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole, EXAMPLE 16, in place of 2-bromomethyl-6-chloro-benzo[b]thiophene. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.75 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.64 (m, 2H), 7.60 (m, 2H), 7.40 (d, 1H), 7.23 (m, 1H), 7.19 (m, 2H), 6.99 (d, 2H), 5.09 (s, 2H), 4.78 (s, 2H), 4.10 (m, 2H), 3.40 (m, 4H), 2.49 (s, 3H).

B. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-(3-chloro-1-(toluene-4-sulfonyl)-1H-indol-6-ylmethyl)-piperazin-2-one ditrifluoroacetate (31 mg, 0.04 mmol) in 2 mL of MeOH is added 0.3 mL of 1N NaOH solution. The solution is heated at 100°C for 3 hours. After this time, the solution is diluted with water/acetonitrile and neutralized with trifluoroacetic acid. The

crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (21 mg, 0.03 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.71 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.63 (m, 3H), 7.53 (d, 1H), 7.50 (s, 1H), 7.20 (d, 1H), 4.78 (s, 2H), 4.30-3.10 (m, 8H). ESI MS, $[M+H]^+$=421, 423 (Cl pattern).

EXAMPLE 275. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one bishydrochloride (100 mg, 0.31 mmol), EXAMPLE 72, in 3 mL of DMF is added 2-(3-bromo-(E)-propenyl)-5-chloro-thiophene (73 mg, 0.31 mmol), prepared as described in EXAMPLE 17., and K_2CO_3 (0.21 g, 1.54 mmol). The solution is stirred at room temperature for 16 hours. After this time, the solution is diluted with water/acetonitrile and neutralized with trifluoroacetic acid. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (80 mg, 0.12 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.76 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.70 (s, 1H), 7.62 (dd, 1H), 7.10 (m, 2H), 6.90 (d, 1H), 6.05 (dt, 1H), 4.80 (s, 2H), 3.77 (m, 4H), 3.50 (m, 2H), 3.37 (m, 2H). ESI MS, $[M+H]^+$=414,416 (Cl pattern). Anal. ($C_{20}H_{20}ClN_5OS \cdot 2.0TFA \cdot 1.1H_2O$) C, H, N.

EXAMPLE 276. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-(E)-enyl]-piperazin-2-one ditrifluoroacetate.

^1H NMR (DMSO-d_6, 300 MHz) δ 9.70 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.68 (s, 1H), 7.61 (d, 1H), 7.10 (m, 2H), 5.88 (t, 1H), 4.79 (s, 2H), 3.75 (m, 4H), 3.49 (m, 2H), 3.29 (m, 2H), 2.09 (s, 3H). EI MS, $[M+H]^+$=427, 429 (Cl pattern).

EXAMPLE 277. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-2-methyl-(E)-allyl]-piperazin-2-one ditrifluoroacetate.

^1H NMR (DMSO-d_6, 300 MHz) δ 9.80 (bs, 2H), 8.85 (s, 1H), 8.41 (d, 1H), 7.70 (s, 1H), 7.68 (d, 1H), 7.06 (d, 1H), 7.05 (d, 1H), 6.70 (bs, 1H), 4.80 (s, 2H), 4.30 (bs, 2H), 3.45 (m, 4H), 3.10 (m, 2H), 1.99 (s, 3H). ESI MS, $[M+H]^+$=428, 430 (Cl pattern).

EXAMPLE 278. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-furan-2-yl)-(E)-allyl]-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (50 mg, 0.20 mmol), EXAMPLE 72.in 3 mL of acetonitrile is added 3-(4-bromo-furan-2-yl)-(E)-propenal (43 mg, 0.22 mmol), prepared as described in EXAMPLE 18, 2 drops of HOAc and sodium triacetoxyborohydride (62 mg, 0.29 mmol). The solution is stirred at room temperature for 16 hours. After this time, the solution is diluted with water/acetonitrile. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (48 mg, 0.07 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.75 (bs, 2H), 8.85 (s, 1H), 8.60 (d, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1H), 6.80 (s, 1H), 6.65 (d, 1H), 6.19 (dt, 1H), 4.80 (s, 2H), 3.70 (m, 4H), 3.50 (m, 2H), 3.28 (m, 2H). ESI MS, $[M+H]^+$=441,443 (Br pattern).

EXAMPLE 279. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-methoxy-pyridin-3-yl)-(E)-allyl]-piperazin-2-one.

Nitrogen (g) is bubbled through a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (100 mg, 0.39 mmol), EXAMPLE 72, in 2 mL of CH_3CN. After 5 min, acetic acid 3-(6-methoxy-pyridin-3-yl)-(E)-allyl ester (75 mg, 0.36 mmol, prepared as described in EXAMPLE 19 in 2 mL of CH_3CN, palladium(II) acetate (catalytic amount), triphenylphosphine (catalytic amount), 2 mL of H_2O and 0.5 mL of triethylamine are added to the solution. The mixture is heated at 80°C for 1 hours. At this time, the mixture is cooled, filtered and concentrated in vacuo. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound (44 mg, 0.07 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.86 (s, 1H), 9.79 (s, 1H), 8.83 (s, 1H), 8.40 (d, 1H), 8.25 (s, 1H), 7.95 (d, 1H), 7.75 (s, 1H), 7.63 (d, 1H), 6.86 (d, 1H), 6.82 (d, 1H), 6.32 (dt, 1H), 4.78 (s, 2H), 3.98 (s, 2H), 3.93 (m, 2H), 3.85 (s, 3H), 3.53 (m, 4H). ESI MS, $[M+H]^+$=405.

EXAMPLE 280. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-4-oxy-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one ditrifluoroacetate (0.60 g, 0.94 mmol), prepared as described in EXAMPLE 275, in 25 mL of CH_2Cl_2 is added m-chloroperoxybenzoic acid (0.30 g, 0.96 mmol, 55% pure grade). The mixture is stirred at room temperature for 3 h and then concentrated in vacuo. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are

combined and lyopholized to give the title compound (0.5 mg, 0.76 mmol) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.68 (bs, 2H), 8.79 (s, 1H), 8.39 (d, 1H), 7.68 (s, 1H), 7.60 (d, 1H), 7.17 (d, 1H), 7.12 (d, 1H), 7.06 (d, 1H), 6.17 (dt, 1H), 4.84 (s, 2H), 4.53 (m, 2H), 4.50 (AB, 2H), 4.04 (m, 2H), 3.78 (m, 1H), 3.60 (m, 1H). ESI MS, $[M+H]^+$=430,432 (Cl pattern).

Anal. ($C_{20}H_{20}ClN_5O_2S$·2.0TFA·1.4H_2O) C, H, N.

EXAMPLE 281. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-prop-2-ynyl]-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 275 using 2-(3-bromo-prop-1-ynyl)-5-chloro-thiophene (prepared as described in EXAMPLE 20) in place of 2-(3-bromo-(E)-propenyl)-5-chloro-thiophene. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1H), 8.38 (d, 1H), 7.63 (d, 1H), 7.58 (s, 1H), 7.25 (d, 1H), 7.13 (d, 1H), 4.74 (s, 2H), 3.74 (s, 2H), 3.32 (m, 4H), 2.85 (m, 2H). ESI MS, $[M+H]^+$=412, 414 (Cl pattern).

EXAMPLE 282. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one

The title compound is prepared as described in EXAMPLE 278 using 3-(5-chloro-thiophen-2-yl)-propionaldehyde (EXAMPLE 28, Part A) in place of 3-(4-bromo-furan-2-yl)-(E)-propenal. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to give the title compound as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1H), 8.39 (d, 1H), 7.71 (s, 1H), 7.60 (d, 1H), 6.95 (d, 1H), 6.77 (d, 1H), 4.78 (s, 2H), 3.88 (m, 2H), 3.50 (m, 2H), 3.42 (m, 2H), 3.05 (m, 2H), 2.80 (t, 2H), 1.96 (m, 2H). ESI MS, $[M+H]^+$=416,418 (Cl pattern).

EXAMPLE 283. 1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one.

A. 1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one.

Propargyl bromide (0.29 g, 1.95 mmol) is added to a solution containing 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (0.5 g, 1.95 mmol), EXAMPLE 72, and K_2CO_3 (0.40 g, 2.93 mmol) in DMSO (10 mL) at ambient temperature. After 15 min, the reaction mixture is partitioned between aqueous $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL) and the layers are separated. The aqueous phase is subsequently saturated with NaCl and extracted three times

with $CHCl_3$ (50 mL). The combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide 390 mg (68%) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (m, 1H), 3.13-3.37 (m, 6H), 4.07 (app q, J = 5.2 Hz, 1H), 4.63 (s, 2H), 7.28 (dd, J = 8.4, 1.4 Hz, 1H), 7.42 (s, 1H), 7.72 (br s, 2H), 8.14 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H) ppm; MS (ISP loop): m/z 296 (M+H).

EXAMPLE 284. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-2-yl-prop-2-ynyl)-piperazin-2-one.

A solution containing 1-(4-amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one (50 mg, 0.17 mmol), EXAMPLE 283, 2-bromobiphenyl (44 mg, 0.19 mmol), Et_3N (69 mg, 0.68 mmol), $(Ph_3P)_4PdCl_2$ (6 mg, 0.008 mmol), and CuI (1 mg, 0.005 mmol) in anhydrous DMF (2 mL) is warmed at 80°C for 1 hours. The reaction mixture is cooled to 50 °C and the solvent is removed over 16 h under a stream of nitrogen. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to afford a colorless gum which is triturated with ethyl alcohol to provide 4 mg (5%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.03 (s, 2H), 3.14 (m, 2H), 3.31 (m, 2H), 3.50 (s, 2H), 7.21-7.55 (m, 11H), 7.76 (br s, 2H), 8.18 (d, J = 8.6 Hz, 1H), 8.36 (s, 1H) ppm; MS (ion spray): m/z 448 (M+H).

EXAMPLE 285. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. (3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-prop-1-ynyl}-pyridin-4-yl)-carbamic acid tert-butyl ester.

A solution containing 1-(4-amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one (100 mg, 0.34 mmol), EXAMPLE 283, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester, EXAMPLE 69, Part B, (108 mg, 0.34 mmol), Et_3N (140 mg, 1.36 mmol), $(Ph_3P)_4PdCl_2$ (12 mg, 0.017 mmol), and CuI (2 mg, 0.01 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 59 mg (36%) of the title compound as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.84 (m, 2H), 3.35 (m, 2H), 3.44 (s, 2H), 3.71 (s, 2H), 4.75 (s, 2H), 6.19 (br s, 2H), 7.24 (d, J = 5.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.79 (d, J = 8.4

Hz, 1H), 8.05 (d, J = 5.5 Hz, 1H), 8.37 (s, 1H), 8.49 (s, 1H), 8.58 (s, 1H) ppm; MS (ISP loop): m/z 488 (M+H).

B. 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

1,8-Diazabicyclo[5.4.0]undec-7-ene (37 mg, 0.24 mmol) is added to a suspension containing (3-{3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-prop-1-ynyl}-pyridin-4-yl)-carbamic acid tert-butyl ester (59 mg, 0.12 mmol) in anhydrous CH_3CN (5 mL) and the mixture is warmed to 50 °C. Dimethylformamide (1 mL) is added to solubilize and the homogeneous solution is maintained for 5 h at 50°C. The reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 50 mg of the product as a crude solid which is used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 9H), 2.78 (m, 2H), 3.30 (m, 2H), 3.37 (s, 2H), 3.95 (s, 2H), 4.74 (s, 2H), 6.24 (br s, 2H), 6.63 (s, 1H), 7.40 (dd, J = 8.5, 1.6 Hz, 1H), 7.64 (s, 1H), 7.81 (d, J = 5.8 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.99 (s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 8.58 (s, 1H), 8.77 (s, 1H) ppm.

C. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (50 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 34 mg (73%, two steps) of the title compound as a white, lyophilized solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (s, 3H), 3.23 (s, 2H), 3.31 (m, 2H), 3.89 (s, 2H), 4.00 (br s, 3H), 4.71 (s, 2H), 6.94 (s, 1H), 7.60 (m, 2H), 7.84 (d, J = 6.5 Hz, 1H), 8.36 (m, 2H), 8.81 (s, 1H), 9.18 (s, 1H), 9.73 (br s, 2H), 12.87 (s, 1H) ppm; MS (ion spray): m/z 388 (M+H).

The following compounds are prepared from the compound of Example 72 using the procedures described above.

Example	Name	m/z (M+H)
286	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-piperazin-2-one	418, 420 Cl pattern
287	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-indol-2-	435, 437

	ylmethyl)-piperazin-2-one	CI pattern
288	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	414, 416 CI pattern
289	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-piperazin-2-one	464, 466 CI pattern
290	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-4-methyl-thiophen-2-yl)-allyl]-piperazin-2-one	428, 430 CI pattern
291	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-ylmethyl)-piperazin-2-one	422, 424 CI pattern
292	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-5-ylmethyl)-piperazin-2-one	421, 423 CI pattern
293	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	421, 423 CI pattern
294	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,7-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one	455, 457 CI pattern
295	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	421, 423 CI pattern
296	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-p-tolyl-prop-2-ynyl)-piperazin-2-one	386
297	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-m-tolyl-prop-2-ynyl)-piperazin-2-one	386
298	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406, 408 CI pattern
299	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406, 408 CI pattern
300	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406
301	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-4-yl-prop-2-ynyl)-piperazin-2-one	448
302	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4,5-dibromo-thiophen-2-yl)-allyl]-piperazin-2-one	536, 538, 540 Br_2 pattern
303	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-3-yl-prop-2-ynyl)-piperazin-2-one	448

304	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-thiophen-3-yl)-prop-2-ynyl]-piperazin-2-one	446, 448 Cl pattern
305	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-propyl]-piperazin-2-one	410, 412 Cl pattern
306	1,4-Bis-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	415
307	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one	388
308	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-nitro-thiophen-2-yl)-allyl]-piperazin-2-one	425
309	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-pyridin-3-yl)-allyl]-piperazin-2-one	409, 411 Cl pattern
310	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	388
311	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-allyl]-piperazin-2-one	414, 416 Cl pattern
312	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-allyl]-piperazin-2-one	442, 444 Br pattern
313	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-methyl-thiophen-2-yl)-penta-2,4-dienyl]-piperazin-2-one	420
314	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-5-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
315	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methyl-thiophen-2-yl)-allyl]-piperazin-2-one	394
316	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methoxy-thiophen-2-yl)-allyl]-piperazin-2-one	410
317	4-(1-Amino-7-chloro-isoquinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	448, 450 Cl pattern
318	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-acetamide	431
319	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one	433, 435 Cl pattern
320	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenyl)-2-(S)-hydroxy-ethyl]-piperazin-2-one	412, 414 Cl pattern
321	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenylsulfanyl)-	428, 430

	ethyl]-piperazin-2-one	Cl pattern
322	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-methylene-1,1-dioxo-2,3-dihydro-1H-1l 6-benzo[b]thiophen-3-yl)-piperazin-2-one	470
323	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-nitro-phenyl)-allyl]-piperazin-2-one	419
324	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-6-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
325	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(4-chloro-phenyl)-acetamide	425, 427 Cl pattern
326	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one	437, 439 Cl pattern
327	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethyl]-piperazin-2-one	402, 404 Cl patten
328	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propyl]-piperazin-2-one	410, 412 Cl pattern
329	2-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chlorophenyl)-acrylic acid	452, 454 Cl pattern
330	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-1-hydroxy-isoquinolin-3-ylmethyl)-piperazin-2-one	449, 451 Cl pattern
331	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	432, 434 Cl pattern
332	1-(4-Amino-quinazolin-7-ylmethyl)-4-isoquinolin-3-ylmethyl-piperazin-2-one	399
333	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(3-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one	437, 439 Cl pattern
334	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1,7-dichloro-isoquinolin-3-ylmethyl)-piperazin-2-one	467, 469 Cl pattern
335	4-(2-Amino-7-chloro-quinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	448, 450 Cl pattern
336	1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one.	438, 440 Cl pattern
337	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one	428, 430 Cl pattern
338	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(6-chloro-benzo[b]thiophen-	452, 454

	2-yl)-ethyl]-piperazin-2-one	Cl pattern
339	1-(4-Aminoquinazolin-7-ylmethyl)-4-[2-(4-chloro-phenoxy)-ethyl]-piperazine-2-one	412, 414 Cl pattern
340	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-4H-benzo[1,4]thiazin-3-one	469, 471 Cl pattern
341	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,7-dichloro-quinolin-3-ylmethyl)-piperazin-2-on	467, 469 Cl_2 pattern
342	2-[[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-(4-chloro-phenyl)-methyl]-acrylic acid ethyl ester	480, 482 Cl pattern
343	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chloro-phenyl)-acrylic acid ethyl ester	480, 482 Cl pattern
344	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazin-2-one	408, 410 Cl pattern
345	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazin-2-one	408, 410 Cl pattern
346	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-allyl]-piperazin-2-one	458, 460 Br pattern
347	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-allyl]-piperazin-2-one	458, 460 Br pattern
348	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one	433
349	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinoxalin-2-one	450, 452 Cl pattern
350	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	436, 438 Cl pattern
351	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-3H-quinazolin-4-one	492, 494 Cl pattern
352	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-thiophen-2-yl-propyl)-piperazin-2-one	382
353	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-quinolin-3-ylmethyl)-piperazin-2-one	432, 434 Cl pattern
354	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5,7-dichloro-1H-quinolin-2-one	483, 485 Cl pattern
355	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6,7-dichloro-	472, 474

	benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	Cl_2 pattern
356	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-1H-quinolin-2-one	449, 451 Cl pattern
357	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-[2,3']bithiophenyl-5'-ylmethyl)-piperazin-2-one	470, 472 Cl pattern
358	4-(6-Amino-benzo[b]thiophen-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	419
359	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one	433, 435 Cl pattern
360	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	466, 468 Br pattern
361	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-nitro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	449
362	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	464, 466 Cl pattern
363	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	468, 470 Cl pattern
364	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinolin-2-one	449, 451 Cl pattern
3653	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-trifluoromethyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	456
366	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	450
367	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418
368	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3,3'-dimethyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	498, 500 Cl pattern
369	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperazin-2-one	602, 604, 606 Br_2 pattern
370	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418
371	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418

372	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
373	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	484, 486 Cl pattern
374	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	388
375	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-bromo-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	514, 516 Br pattern
376	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-oxazol-2-ylmethyl]-piperazin-2-one	473
377	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	472, 474 Cl pattern
378	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4,5-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	472, 474 Cl pattern
379	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one	423, 425 Cl pattern
380	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
381	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
382	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	484, 486 Cl pattern
383	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
384	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	456
385	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-benzooxazol-2-yl-benzyl)-piperazin-2-one	464
386	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	464, 466 Cl pattern
387	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	402
388	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2,2']bithiophenyl-5-ylmethyl-piperazin-2-one	435

389	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	422
390	1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-fluoro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one.	422
391	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(1-methyl-5-trifluoro-methyl-1H-pyrazol-3-yl)-thiophen-2-ylmethyl]-piperazin-2-one	501
392	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,4-dimethyl-thieno[2,3-b]thiophen-2-ylmethyl)-piperazin-2-one	438
393	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	452, 454 Cl pattern
394	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	452, 454 Cl pattern
395	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophen-2-ylmethyl] piperazin-2-one	502
396	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-nitro-phenyl)-furan-2-ylmethyl]-piperazin-2-one	459
397	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-6-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
398	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-methoxy-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	460
399	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-hydroxy-2-pyridin-2-yl-pyrimidin-5-ylmethyl)-piperazin-2-one	443
400	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-fluoro-phenoxy)-benzyl]-piperazin-2-one	458
401	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one	465, 467 Cl pattern
402	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	482, 484 Br pattern
403	1-(4-Amino-quinazolin-7-ylmethyl)-4-benzo[b]thiophen-2-ylmethyl-piperazin-2-one	404
404	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	470, 472 Cl pattern
405	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-bis-trifluoromethyl-benzyl)-piperazin-2-one	488

406	1-(4-Amino-quinazolin-7-ylmethyl)-4-biphenyl-4-ylmethyl-piperazin-2-one	423 (M+)
407	1-(4-Amino-quinazolin-7-ylmethyl)-4-naphthalen-2-ylmethyl-piperazin-2-one	397 (M+)
408	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-3-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
409	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-piperazin-2-one	438, 440Cl pattern

EXAMPLE 410. 1-(4-Aminoquinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, in place of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1H), 8.40 (dd, 1H), 7.68 (d, 1H), 7.65 (s, 1H), 7.58 (d, 2H), 7.15 (d, 2H), 4.80 (s, 2H), 4.33, 4.15 (m, 2H, rotamers), 3.70 (m, 2H), 3.49 (m, 2H). ESI MS, $[M+H]^+$=456, 458 (Br pattern).

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example	Name	m/z [M+H]
411	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-thiophene-2-carbonyl)-piperazin-2-one	402, 404 Cl pattern
412	4-[3-(3-Amino-4-chloro-phenyl)-(E)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	437, 439 Cl pattern
413	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-piperazin-2-one	435, 437 Cl pattern
414	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]piperazin-2-one	432, 434 Cl pattern
415	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	472, 474 Br pattern
416	5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-amide	459, 461 Cl pattern
417	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-(E)-	428, 430

	acryloyl]-piperazin-2-one	Cl pattern
418	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-piperazin-2-one	435, 437 Cl pattern
419	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	478, 480 Cl pattern
420	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	472, 474 Br pattern
421	5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-methyl-2-oxo-ethyl}-amide	473, 475 Cl pattern
422	5-Chloro-thiophene-2-carboxylic acid {3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-amide	473, 475 Cl pattern
423	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one	426, 428 Cl pattern
424	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-piperazin-2-one	440, 442 Cl pattern
425	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-piperazin-2-one	484, 486 Cl pattern
426	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-piperazin-2-one	430, 432 Cl pattern
427	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one	422, 424 Cl pattern
428	N-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-(5-chloro-thiophen-2-ylmethyl)-2-oxo-ethyl]-benzamide	428, 430 Cl pattern
429	N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-benzamide	549, 550 Cl pattern
430	N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-acetamide	485, 487 Cl pattern
431	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one	422, 424 Cl pattern
432	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yl)-acetyl]-piperazin-2-one	415, 417 Cl pattern
433	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one	451, 453 Cl pattern
434	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-	483, 485

	6-chloro-4H-benzo[1,4]thiazin-3-one	Cl pattern
435	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-benzo[b]thiophen-2-yl)-acetyl]-piperazin-2-one	466, 468 Cl pattern

EXAMPLE 436. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid 4-chloro-benzylamide.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (25 mg, 0.097 mmol), EXAMPLE 72, in 1 mL of DMF is added 4-chloro-benzyl isocyanate (22 mg, 0.13 mmol, prepared as described in EXAMPLE 37). After stirring 1 h at room temperature, the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (36 mg, 0.067 mmol) as a white solid. ^1H NMR (d6-DMSO, 300 MHz) δ 9.76 (bs, 2H), 8.83 (s, 1H), 8.38 (d, 1H), 7.64 (d, 1H), 7.60 (s, 1H), 7.34 (d, 2H), 7.31 (m, 1H), 7.26 (d, 2H), 4.75 (s, 2H), 4.22 (d, 2H), 4.08 (s, 2H), 3.60 (m, 2H), 3.35 (m, 2H). ESI MS, $[M+H]^+$=425,427 (Cl pattern).

EXAMPLE 437. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-ylmethyl)amide.

To a solution of (5-chloro-thiophen-2-yl)-acetic acid (0.18 g, 1.04 mmol), prepared as described in EXAMPLE 27 in 6 mL of dry CH_2Cl_2 is added Et_3N (0.15 mL g, 1.04 mmol) and diphenylphosphoryl azide (0.24 mL, 1.04 mmol). The mixture is stirred at room temperature for 2.5 h, then heated at 50°C for 2 hours. To the solution is added 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (0.10 g, 0.41 mmol), EXAMPLE 72, and Et_3N (0.15 mL g, 1.04 mmol) and the mixture is heated at 50°C for 2 h, then stirred at room temperature for 16 hours. The resulting mixture is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (10 mg, 0.02 mmol) as a white solid. ^1H NMR (d6-DMSO, 300 MHz) δ 9.69 (bs, 2H), 8.80 (s, 1H), 8.48 (d, 1H), 7.61 (d, 1H), 7.60 (s, 1H), 7.41 (t, 1H), 6.90 (d, 1H), 6.80 (d, 1H), 4.77 (d, 2H), 4.30 (d, 2H), 4.10 (s, 2H), 3.61 (m, 2H), 3.38 (m, 2H). ESI MS, $[M+H]^+$=431,433 (Cl pattern).

EXAMPLE 438. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide.

A mixture of 5-chloro-thiophene-2-carbonyl azide (55 mg, 0.29 mmol, prepared as described in EXAMPLE 38) and 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (50 mg, 0.20 mmol), EXAMPLE 72, in 3 mL of dry toluene is heated at 105°C for 1 hours. The resulting

mixture is concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyopholized to provide the title compound (35 mg, 0.02 mmol) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 10.04 (s, 1H), 9.71 (bs, 2H), 8.81 (s, 1H), 8.38 (dd, 1H), 7.64 (d, 1H), 7.61 (s, 1H), 6.77 (d, 1H), 6.42 (d, 1H), 4.76 (s, 2H), 4.21 (s, 2H), 3.73 (m, 2H), 3.40 (m, 2H). ESI MS, $[M+H]^+$=417,419 (Cl pattern).

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example	Name	m/z [M+H]
439	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	417, 419 Cl pattern
440	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide	461, 463 Br pattern
441	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3-amino-4-chloro-phenyl)-amide	426, 428 Cl pattern
442	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	455, 457 Br pattern
443	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	411, 413 Cl pattern
444	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-methoxy-phenyl)-amide	407
445	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide	445, 447 Cl_2 pattern

EXAMPLE 446. 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester.

To a solution of 5-chloro-2-thiophene-methanol (0.10 g, 0.67 mmol, prepared by $NaBH_4$ reduction of 5-chloro-2-thiophene-carboxaldehyde) in 6 mL of CH_2Cl_2 is added 1,1'-carbonyldiimidazole (0.11 g, 0.67 mmol). The mixture is stirred at room temperature for 3 hours. Then 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (0.17 g, 0.67 mmol, EXAMPLE 72) and a catalytic amount of DMAP is added to the solution and the resulting mixture is heated at 35°C for 18 hours. The mixture is dissolved in water/MeOH and the crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100%

CH_3CN. The appropriate fractions are combined and lyopholized to provide the title compound as a white solid. ESI MS, $[M+H]^+$=432,434 (Cl pattern).

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example	Name	m/z [M+H]
447	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-carboxylic acid 6-chloro-benzooxazol -2-ylmethyl ester	467, 469 Cl pattern
448	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 1-(3-chloro-phenyl)-pyrrolidin-3-yl ester	481, 483 Cl pattern

EXAMPLE 449. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one.

To a solution of 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80, (0.06g, 0.2mmol) in 2 mL of DMF is added 3-bromomethyl-7-chloroisoquinoline, EXAMPLE 11, 0.052g, 0.20mmol), and K_2CO_3 (0.08 g, 0.06 mmol). After 16 h, the reaction mixture is concentrated to dryness. The crude product is purified by RP-HPLC eluting with a gradient of 5%CH_3CN/H_2O (0.1% TFA) to 50%CH_3CN/H_2O (0.1% TFA). The product fractions are lyophilized to give the title compound as a tristrisfluoroacetic acid salt (0.06g, 0.08 mmol) as a white solid. ^1H NMR (d6-DMSO, 300 MHz) δ 9.79 (bs, 2H), 9.40 (s, 1H), 8.73 (s, 1H), 8.33 (d, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 8.00 (d, 1H), 7.79 (d, 1H), 7.60 (m, 2H), 4.80 (AB, 2H), 4.72 (AB, 2H), 4.28 (m, 1H), 3.54 (m, 4H), 1.96 (d, 3H). MS (ion spray) 447, 449, (Cl pattern). Elemental analysis $C_{28}H_{25}ClF_6N_6O_6 \cdot 3CF_3CO_2H \cdot 0.28H_2O$, cal C=45.38%, H=3.35%, N=10.58%; found C=45.38, H=3.35%, N=10.63%.

EXAMPLE 450. 4-(4-Amino-quinazolin-7-ylmethyl)- 4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 274 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.79 (bs, 2H), 8.82 (s, 1H), 8.39 (d, 1H), 7.61 (m, 3H), 7.57 (d, 1H), 7.52 (d, 1H), 7.49 (d, 1H), 7.20 (d, 1H), 7.10 (d, 1H), 4.75 (AB, 2H), 4.57 (m, 1H), 4.23 (m, 1H), 3.97 (m, 1H), 3.50 (m, 3H), 1.65 (d, 3H). ESI MS, $[M+H]^+$= 435,437 (Cl pattern). Anal. ($C_{23}H_{23}ClN_6O \cdot 2.15TFA \cdot 0.25H_2O$) C, H, N.

The following compounds are prepared from the compound of Example 80 using the methods described above.

Example	Name	m/z [M+H]
451	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	428, 430 Cl pattern
452	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	478, 480 Cl pattern
453	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-methyl-piperazin-2-one	429, 431 Cl pattern
454	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	435, 437 Cl pattern
455	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-methyl-piperazin-2-one	442, 444 Cl pattern
456	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methyl-piperazin-2-one	483 (M+) (EI)
457	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-benzoimidazol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	536, 538 Cl pattern
458	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	428, 430 Cl pattern
459	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
460	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	453, 455 Cl pattern
461	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	452, 454 Cl pattern
462	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	452, 454 Cl pattern
463	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one	452, 454 Cl pattern
464	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one	452, 454 Cl pattern

EXAMPLE 465 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80, and 3-(4-chloro-thiophen-2-

yl)-(E)-acrylic acid, EXAMPLE 26. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.62 (m, 5H), 7.05 (d, 1H), 4.92 (m, 1H), 4.80 (m, 2H), 4.73 (m, 1H), 4.50 (m, 1H), 3.40 (m, 2H), 1.42 (m, 3H). ESI MS, $[M+H]^+$= 442, 444 (Cl pattern).

The following compounds are prepared from the compound of Example 80 using the methods described above.

Example	Name	m/z [M+H]
466	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
467	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
468	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	486, 488 Br pattern
469	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-3-(S)-methyl-piperazin-2-one	449, 451 Cl pattern
470	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methyl-piperazin-2-one	461, 463 Cl pattern
471	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
472	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	486, 488 Br pattern
473	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methyl-piperazin-2-one	440, 442 Cl pattern
474	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-3-(S)-methyl-piperazin-2-one	498, 500 Cl pattern
475	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-methyl-piperazin-2-one	456, 458 Cl pattern
476	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methyl-piperazin-2-one	466, 468 Cl pattern
477	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	442, 444 Cl pattern

EXAMPLE 478. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 278 using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, EXAMPLE 77 and 3-(5-chloro-

thiophen-2-yl)-propionaldehyde, EXAMPLE 28. ^{1}H NMR (d6-DMSO + 1 drop TFA, 300 MHz) δ 9.80 (bs, 2H), 8.79 (s, 1H), 8.32 (d, 1H), 7.58 (m, 2H), 6.88 (d, 1H), 6.70 (d, 1H), 4.72 (AB, 2H), 4.00 (m, 1H), 3.72 (m, 1H), 3.48 (m, 2H), 3.23 (m, 3H), 2.72 (m, 2H), 1.96 (m, 4H), 0.98 (m, 3H). MS (ion spray), m/z, (M+H) = 444, 446 (Cl pattern).

The following compounds are prepared from the compound of Example 77 using the methods described above.

Example	Name	m/z [M+H]
479	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one	442, 444 Cl pattern
480	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-ethyl-piperazin-2-one	456, 458 Cl pattern
481	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-ethyl-piperazin-2-one	461, 463 Cl pattern
482	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one	442, 444 Cl pattern
483	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	460, 462 Cl pattern
484	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	466, 468 Cl pattern
485	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	467, 469 Cl pattern

EXAMPLE 486. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, EXAMPLE 77 and 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid, EXAMPLE 25. ^{1}H NMR (d6-DMSO + 1 drop TFA, 300 MHz) δ 9.78 (bs, 2H), 8.79 (s, 1H), 8.37 (d, 1H), 7.65 (m, 2H), 7.50 (s, 1H), 7.41 (m, 1H), 7.11 (d, 1H), 6.98 (d, 1H), 4.88 (m, 2H), 4.60 (m, 1H), 4.31 (m, 1H), 3.52 (m, 1H), 3.30 (m, 2H), 1.96 (m, 2H), 0.88 (m, 3H). MS (ion spray), m/z, (M+H) = 456, 458 (Cl pattern). Elemental analysis, cal $C_{22}H_{22}ClN_5O_2S \cdot 1.5C_2HF_3O_2$ %C=47.89, %H=3.78, %N=11.17; found %C=47.34, %H=4.00, %N=11.12.

The following compounds are prepared from the compound of Example 77 using the methods described above.

Example	Name	m/z [M+H]
487	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one	460, 462 Cl pattern
488	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one	460, 462 Cl pattern
489	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(S)-3-ethyl-piperazin-2-one	456, 458 Cl pattern
490	2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetamide	517, 519 Cl pattern
491	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid	518, 520 Cl pattern
492	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one	514, 516, 518 Cl_2 pattern
493	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one	480, 482 Cl pattern
494	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester	546, 548 Cl pattern
495	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-ethyl-piperazin-2-one	494, 496 Cl pattern
496	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester	532, 534 Cl pattern
497	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-(3S)-ethyl-piperazin-2-one	463, 465
498	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-ethyl-piperazin-2-one	475, 477 Cl pattern
499	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one	460, 462 Cl pattern
500	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	500, 502 Br pattern

501	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	456, 458 Cl pattern
502	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	500, 502 Br pattern
503	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3-(S)-ethyl-piperazin-2-one	458, 460 Cl pattern
504	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-1H-pyrrole-2-carbonyl]-3-(S)-ethyl-piperazin-2-one	489, 491 Cl pattern
505	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-acetyl]-3-(S)-ethyl-piperazin-2-one	470, 472 Cl pattern
506	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-ethyl-piperazin-2-one	470, 472 Cl pattern
507	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-ethyl-piperazin-2-one	454, 456 Cl pattern
508	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	450, 452 Cl pattern
509	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-3-(S)-ethyl-piperazin-2-one	463, 465 Cl pattern
510	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propionyl]-3-(S)-ethyl-piperazin-2-one	452, 454 Cl pattern
511	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethyl-4-[3-(4-methoxy-phenyl)-propionyl]-piperazin-2-one	448
512	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-ethyl-piperazin-2-one	480, 482 Cl pattern

EXAMPLE 513. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one, EXAMPLE 78 and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.78 (bs, 2H), 8.81 (s, 1H), 8.35 (d, 1H), 7.60 (m, 2H), 7.51 (s, 1H), 6.69 (m, 1H), 6.21 (d, 1H), 4.91 (AB, 2H), 4.72 (m, 2H), 3.84 (m, 1H), 3.52 (m, 2H), 3.23 (m, 1H), 1.80 (m, 2H), 1.24 (m, 2H), 0.82 (m, 3H). MS (ion spray), m/z, 474, 476, (M+H) (Cl pattern). Elemental analysis, cal $C_{22}H_{22}ClN_5O_2S \cdot C_2HF_3O_2 \cdot 1.15H_2O$ %C=47.31, %H=4.52, %N=11.50; found %C=47.39, %H=4.140, %N=11.19.

EXAMPLE 514. 4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one, EXAMPLE 78 and 3-(6-amino-pyridin-3-yl)-acrylic acid, EXAMPLE 36. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1H), 8.36 (m, 2H), 8.22 (m, 3H), 7.62 (d, 1H), 7.52 (m, 1H), 7.39 (m, 1H), 7.21 (m, 1H), 6.91 (d, 1H), 5.00 (m, 1H), 4.78 (m, 1H), 4.60 (m, 2H), 4.34 (m, 1H), 3.30 (m, 2H), 1.87 (m, 2H), 1.24 (m, 2H), 0.90 (m, 3H). MS (ion spray), m/z, 446, 448 (M+H), (Cl pattern).

The following compounds are prepared from the compound of Example 78 using the methods described above.

Example	Name	m/z [M+H]
515	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	508, 509, 511, Cl_2 pattern
516	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	474, 476 Cl pattern
517	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	514, 516 Br pattern
518	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern
519	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one	468, 470 Cl pattern
520	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	474, 476 Cl pattern
521	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one	498, 500 Cl pattern
522	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern
523	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern

EXAMPLE 524. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 278 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one, EXAMPLE 75 and 2-(3-bromo-(E)-

propenyl)-5-chloro-thiophene EXAMPLE 17. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.80 (s, 1H), 8.38 (d, 1H), 7.69 (m, 2H), 7.02 (dd, 1H), 6.84 (d, 1H), 6.02 (m, 1H), 4.76 (AB, 2H), 3.86 (m, 4H), 3.30 (s, 3H), 3.23 (m, 2H), 3.02 (m, 2H). MS (ion spray), m/z, 458, 460, (M+H) (Cl pattern). Elemental analysis, cal $C_{22}H_{24}ClN_5O_2S \cdot 2C_2HF_3O_2 \cdot 1.45H_2O$ %C=43.85, %H=4.09, %N=9.83; found %C=43.92, %H=3.61, %N=9.63.

The following compounds are prepared from the compound of Example 75 using the methods described above.

Example	Name	m/z [M+H]
525	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	465, 467
526	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
527	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
528	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(R)-methoxymethyl-piperazin-2-one	477, 479 Cl pattern
529	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	477, 479 Cl pattern
530	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	476, 478 Cl pattern
531	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	482, 484 Cl pattern

EXAMPLE 532. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one.

To a solution of 4-(4-amino-quinazoline-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, EXAMPLE 75, (0.69g, 2.29mmol) in 9mL of DMF is added N,N-diisopropylethyl amine (0.89g, 6.87mmol), TBTU (0.76g, 2.36mmol), and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24, (0.40g, 2.08mmol). The solution is stirred for 16 hours. After this time the solution is concentrated. The crude material is purified by RP-HPLC eluting with a gradient of 10%CH_3CN/H_2O (0.1%TFA) to 80%CH_3CN/H_2O (0.1%TFA). The product fractions are lyophilized to give the product as a white solid (1.0g, 1.57mmol). ^{1}H NMR (d6-DMSO, 300MHz) δ 9.70 (bs, 2H), 8.78 (s, 1H), 8.29 (m, 1H), 7.55 (m, 2H), 6.72 (m, 1H), 6.22 (m, 1H), 4.80 (m, 4H),3.78 (m, 4H), 3.59 (m, 3H), 3.31and 3.2 (s, 3H rotational isomers).MS (ion

spray) M+H=476.Elemental Analysis: C21H22ClN5O4S·1.4CF3CO2H cal: C=45.03%, H=3.68%, N=11.04%; found C=44.98%, H=3.71%, N=11.02%.

EXAMPLE 533. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one.

To a solution of 4-(4-amino-quinazoline-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, EXAMPLE 75, (20 mg, 0.066 mml) in 1.5 mL of DMF is added TBTU (923.4 mg, 0.073 mmol), diisopropylethylamine (0.013 ml, 0.073 mmol) and 6-chloro-1H-benzoimidazole-2-carboxylic acid (prepared from literature in Eur.J.med.Chem. 1993, 28, 71) (14.3 mg, 0.073 mmol). The resulting mixture is left to stir at room temperature overnight. The crude mixture is directly purified by reverse phase HPLC (10-70% ACN/H_2O). The product (30.1 mg, 55%) is isolated as a white powder. $C_{23}H_{22}ClN_7O_3$ MS m/z: 480, 481. Anal. cald. for $C_{23}H_{22}ClN_7O_3 \cdot 2C_2HF_3O_2$: C, 45.81; H, 3.42; N, 13.85. Found C, 45.19; H, 3.59; N, 13.76.

The following compounds are prepared from the compound of Example 75 using the methods described above.

Example	Name	m/z [M+H]
534	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)- methoxymethyl-piperazin-2-one	476, 478 Cl pattern
535	4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	447
536	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-3H-imidazol-4-yl-acryloyl)-3-(S)-methoxymethyl-piperazin-2-one	
537	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512, Cl_2 pattern
538	(1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	480, 482 Cl pattern
539	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
540	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	500, 502 Br pattern
541	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512 Br pattern
542	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-	466, 468

	3-(S)-methoxymethyl-piperazin-2-one	Cl pattern
543	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	576, 578 Br pattern
544	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	466, 468 Cl pattern
545	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	576, 578 Br pattern
546	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)--methoxymethyl-piperazin-2-one	476, 478 Cl pattern
547	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
548	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
549	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	448
550	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	500, 502 Cl pattern
551	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
552	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl_2 pattern
553	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-fluoro-thiophen-2-yloxy)-acetyl]-3-(S)- methoxymethyl-piperazin-2-one	460
554	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	453
555	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenoxy)-propionyl]-3-(S)-methoxymethyl-piperazin-2-one	484, 486 Cl pattern
556	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
557	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-[(4-trifluoromethylsulfanyl-phenoxy)-acetyl]-piperazin-2-one	536
558	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	469, 471 Cl pattern

559	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	469, 471 Cl pattern
560	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
561	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid	534, 536 Cl pattern
562	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-ylsulfanyl)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	492, 494 Cl pattern
563	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern
564	2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)- acetic acid ethyl ester	533, 535 Cl pattern
565	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	496, 498 Cl pattern
566	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	530, 532, 534 Cl_2 pattern
567	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512, 514 Cl_2 pattern
568	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester	548, 550 Cl pattern
569	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester	562, 564 Cl pattern
570	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern
571	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,3-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl_2 pattern
572	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-fluoro-phenoxy)-acetyl]-3-	454

	(S)-methoxymethyl-piperazin-2-one	
573	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	484, 486 Cl pattern
574	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,4-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl_2 pattern
575	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	491, 493 Cl pattern
576	(1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	516, 518 Br pattern
577	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
578	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(R)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
579	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
580	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	496, 498 Cl pattern
581	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern

EXAMPLE 582. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one, EXAMPLE 79 and, (6-chloro-pyridin-3-yloxy)-acetic acid, prepared similary to the procedure descibed in EXAMPLE 29. ^{1}H NMR (d6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1H), 8.37 (m, 1H), 8.10 (m, 1H), 7.61 (m, 2H), 7.40 (m, 2H), 4.98 (m, 2H), 4.65 (m, 2H), 4.50 (m, 1H), 3.91 (m, 1H), 3.75 (m, 1H), 3.59 (m, 2H), 3.31 (m, 2H), 1.07 (m, 3H). MS (ion spray), m/z, 485, 487 (M+H), (Cl pattern).

The following compounds are prepared from the compound of Example 79 using the methods described above.

Example	Name	m/z [M+H]
583	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethoxymethyl-4-[(3-fluoro-phenoxy)-acetyl]-piperazin-2-one	454

584	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethoxymethyl-piperazin-2-one	486, 488 Cl pattern
585	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	484, 486 Cl pattern
586	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	484, 486 Cl pattern
587	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	490, 492 Cl pattern

The following compounds are prepared from the compounds of Examples 81-85 using the methods described above.

Example	Name	m/z [M+H]
588	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	518, 520 Cl pattern
589	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thio-phene-2-carbonyl)-piperazin-2-one	542, 544 Cl pattern
590	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	504, 506 Cl pattern
591	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	528, 530 Cl pattern
592	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one	516, 518 Cl pattern
593	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	522, 524 Cl pattern
594	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one	506, 508 Cl pattern
595	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	490, 492 Cl pattern
596	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	472, 474 Cl pattetn
597	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	486, 488 Cl pattern
598	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	530, 532 Br pattern
599	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-	491, 493

	ylmethyl)-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	CI pattern
600	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-isopropyl-piperazin-2-one	480, 482 CI, pattern
601	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,3-dimethyl-piperazin-2-one	466. 468 CI pattern
602	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,3-dimethyl-piperazin-2-one	442, 444 CI pattern
603	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,3-dimethyl-piperazin-2-one	456, 458 CI pattern
604	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3,3-dimethyl-piperazin-2-one	480, 482 CI pattern
605	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	490, 492 CI pattern
606	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469, 471 CI pattern
607	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	490, 492 CI pattern
608	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	510, 512 CI pattern

EXAMPLE 609. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 268, using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one, EXAMPLE 87, and 2-bromomethyl-6-chloronaphthalene, EXAMPLE 12. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 7.79 (d, 1H), 7.70-7.12 (m, 3H), 7.68-7.67 (m, 2H), 7.55 (d, 1H), 7.39 (d, 1H), 4.78 (d, 2H), 3.98 (d, 2H), 3.44 (s, 3H), 3.38 (t, 1H), 2.64 (m, 2H), 1.26 (d, 3H). MS (ISP) 490, 492, (M+H), CI pattern.

The following materials are prepared from starting materials obtained as described in Example 87 using the methods described above.

Example	Name	m/z [M+H]
610	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-6-methyl-piperazin-2-one	458, 460 CI pattern

611	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(R)-methyl-piperazin-2-one	490, 492 Cl pattern
612	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	472, 474 Cl pattern
613	(1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl pattern
614	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-6-dimethyl-piperazin-2-one	491, 493 Cl pattern
615	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-6-methyl-piperazin-2-one	442, 446 Cl pattern
616	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methyl-piperazin-2-one	428, 430 Cl pattern

EXAMPLE 617. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one, EXAMPLE 87, and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24. ^{1}H NMR (CD_3OD300 MHz) δ 8.68 (s, 1H), 8.27 (d, 1H), 7.62 (m, 2H), 6.54 (d, 1H), 6.18 (m, 1H), 7.39 (d, 1H), 4.94 (m, 4H), 4.15 (m, 2H), 3.76 (m, 2H), 3.44 (s, 3H), 3.10 (m, 2H), 1.28 (d, 3H).

The following compounds are prepared from compounds obtained as described Examples 75-87 using the methods described above.

Example	Name	m/z [M+H]
618	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(S)-3-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl pattern
619	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-3-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl_2 pattern
620	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-4-fluoro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	502, 504 Cl_2 pattern
621	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	502, 504 Cl pattern
622	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-phenyl)-acryloyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	514
623	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-2-methyl-phenoxy)-	498, 500

	acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	Cl_2 pattern
624	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	518
625	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	484
626	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3(S)-ethyl-6-methyl-piperazin-2-one	472, 474 Cl pattern
627	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-ethyl-6-methyl-piperazin-2-one	474
628	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	514, 516 Br pattern
629	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	470, 472 Cl pattern
630	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one	486, 488 Cl pattern
631	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one	530, 532 Br pattern
632	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3(S)-6-dimethyl-piperazin-2-one	480 Cl pattern
633	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one	500, 502 Br pattern
634	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one	456, 458 Cl pattern
635	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-6-methyl-piperazin-2-one	442, 444 Cl pattern

EXAMPLE 636. 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

The title compound is prepared as described in EXAMPLE 436 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one, EXAMPLE 75, and 4-chlorophenyl isocyanate. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1H), 8.70 (s, 1H), 8.40 (d, 1H), 7.64 (d, 1H), 7.61 (s, 1H), 7.49 (d, 2H), 7.28 (d, 2H), 4.88 (m, 1H), 4.80 (AB, 2H), 4.19 (m, 1H), 3.96 (m, 1H), 3.74-3.42 (m, 4H), 3.28 (s, 3H). ESI MS, $[M+H]^+$=455,457 (Cl pattern). Anal. ($C_{22}H_{23}ClN_6O_3 \cdot TFA \cdot 1.5H_2O$) C, H, N.

EXAMPLE 637. 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide.

The title compound is prepared as described in EXAMPLE 438 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one (EXAMPLE 80) and 5-chloro-thiophene-2-carbonyl azide (EXAMPLE 38). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 10.01 (s, 1H), 9.73 (bs, 2H), 8.83 (s, 1H), 8.39 (d, 1H), 7.65 (d, 1H), 7.58 (s, 1H), 6.79 (d, 1H), 6.44 (d, 1H), 4.85 (d, 1H), 4.71 (m, 1H), 4.69 (d, 1H), 4.17 (d, 1H), 3.50 (m, 3H), 1.45 (d, 3H). ESI MS, [M+H]$^+$=431,433 (Cl pattern). Anal. ($C_{19}H_{19}ClN_6O_2S$·TFA·1.9H_2O) C, H, N.

EXAMPLE 638. 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide.

The title compound is prepared as described in EXAMPLE 439 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one (EXAMPLE 75) and 5-chloro-thiophene-2-carbonyl azide (EXAMPLE 38). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 10.00 (s, 1H), 9.73 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.65 (d, 1H), 7.60 (s, 1H), 6.80 (d, 1H), 6.42 (d, 1H), 4.86 (d, 1H), 4.80 (m, 1H), 4.70 (d, 1H), 4.18 (d, 1H), 3.96 (dd, 1H), 3.60 (m, 4H), 3.30 (s, 3H). ESI MS, [M+H]$^+$=461,463 (Cl pattern). Anal. ($C_{20}H_{21}ClN_6O_3S$·TFA·1.1H_2O) C, H, N.

The following compounds are prepared using the methods described above.

Example	Name	m/z [M+H]
639	4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469
640	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	467, 469 Cl pattern
641	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide	505, 507
642	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-3-yl)-amide	461, 463
643	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	461
644	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	453, 455 Cl pattern
645	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-bromo-phenyl)-amide	499

646	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	459, 461
647	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-2-methoxy-phenyl)-amide	483, 485 Cl pattern
648	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-2-chloro-phenyl)-amide	533, 535
649	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-trifluoromethoxy-phenyl)-amide	505
650	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide	439
651	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-dichloro-phenyl)-amide	489, 491
652	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-difluoro-phenyl)-amide	457
653	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide	455
654	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide	459, 460 Cl pattern
655	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (6-chloro-pyridin-3-yl)-amide	426, 428
656	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	499, 501
657	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	486, 488
658	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-5-(R,S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469, 471
659	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	483, 485
660	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	425, 427
661	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	439, 441
662	4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-4-methoxy-thiophen-2-yl)-	491, 493 Cl pattern

	amide	

EXAMPLE 663. (3S, 5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one.

(3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (260 mg, 0.56 mmol), EXAMPLE 88, is dissolved in 5 mL of DMF. Potassium carbonate (193.4 mg, 1.4 mmol) is added followed by the addition of 2-bromomethyl-6-chloro-benzo[b]thiophene (218 mg, 0.84 mmol), EXAMPLE 5. Reaction is left to stir overnight. The crude mixture is purified by reverse phase HPLC (10 -70% ACN/H_2O) to afford the product (27 mg, 6%) as a clear wax with a melting point of 130-131 °C . $C_{24}H_{24}ClN_5OS$ MS m/z: 466, 468.

EXAMPLE 664. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one. and

EXAMPLE 665. (3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one.

(3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (60 mg, 0.13 mmol) is dissolved in 1 mL of DMF. Potassium carbonate (53 mg, 0.39 mmol) is added followed by the addition of 3-bromoallyl-5-chloro-thiophene (75 mg, 0.32 mmol). Reaction is left to stir overnight. The two epimers are separated by reverse phase HPLC (10 -70% ACN) in 43% yield.

The major epimer is assigned as (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5 -dimethyl-piperazin-2-one trifluoroacetic acid salt (30.8 mg) and is isolated as a yellow solid with a melting point of 69-72 °C . $C_{22}H_{24}ClN_5OS$ MS m/z: 442, 444.

The minor epimer is assigned as (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one trifluoroacetic acid salt (13.1 mg) with a melting point of 67-70 °C . $C_{22}H_{24}ClN_5OS$ MS m/z: 442, 444. 1H NMR (CD_3OD) δ: 8.67 (s, 1H); 8.31 (d, 1H, J = 8.56 Hz); 7.83 (s, 1H); 7.74 (d, 2H, J = 8.56 Hz); 7.14 (d, 1H, J = 15.6 Hz); 6.92 (d, 1H, J = 3.74 Hz); 6.10-6.03 (m, 1H); 5.0-4.74 (m, 2H); 4.25-3.63 (m, 6 H); 1.78 (d, 3H, J = 7.03 Hz); 1.50 (d, 3H, J = 6.47 Hz).

EXAMPLE 666. (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one.

(3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (43 mg, 0.123 mmol), minor epimer fromEXAMPLE 88, Part D, is taken up in methylene chloride to this is added triethylamine (0.034 ml, 0.25 mmol) followed by 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride (40 mg, 0.16 mmol), EXAMPLE 3. The reaction is stirred overnight, and

the crude material is purified by preparative thin layer chromatography (15 % methanol/CH_2Cl_2). The product (1.4 mg, 2.3%) is isolated as a yellow wax. $C_{21}H_{22}ClN_5O_3S_2$ MS m/z: 492, 494. 1H NMR (CD_3OD) δ 8.36 (s, 1H); 8.03 (d, 1H, J = 7.5 Hz); 7.61 (s, 1H); 7.49-7.44 (m, 2H); 7.19 (d, 1H, J = 3.83 Hz); 6.98 (d, 1H, J = 3.75 Hz); 6.76 (d, 1H, J = 15.1 Hz); 4.86-4.71 (m, 2H); 4.45-4.39 (m, 1H); 4.13-4.09 (m, 1H); 3.64-3.7 (m, 2H); 1.63 (d, 3H, J = 7.09 Hz); 1.33 (d, 3H, J = 6.80 Hz).

EXAMPLE 667. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one.

The product (7 mg, 9.4 %) is isolated as a yellow solid with a melting point of 218-221 °C . $C_{21}H_{22}ClN_5O_3S_2$ MS m/z: 492, 494. 1H NMR (CD_3OD) δ 8.37 (s, 1H); 8.10 (d, 1H, J = 8.57 Hz); 7.61- 7.45 (m, 3H); 7.24 (d, 1H, J = 3.94 Hz); 6.98 (d, 1H, J = 3.85 Hz); 6.71 (d, 1H, J = 15.1 Hz); 4.76 (s, 2H); 4.32 (m, 1H); 3.71 (m, 1H); 3.36 (m, 2H); 1.62 (d, 3H, J = 7.06 Hz); 1.20 (d, 3H, J = 6.63 Hz).

EXAMPLE 668. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-sulfonyl)-3,5-dimethyl-piperazin-2-one.

The desired product (5.4 mg, 8.5 %) is isolated as yellow solid with a melting point of 224-226°C. $C_{23}H_{22}ClN_5O_3S_2$ MS m/z: 516, 518.

EXAMPLE 669. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-piperazin-2-one.

To a solution of (3S,5S)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (42 mg, 0.147 mmol), major epimer from EXAMPLE 88, Part D, in 2 mL of DMF is added TBTU (52 mg, 0.162 mmol), triethylamine (0.02 mL, 0.162 mmol) and 3-(5-chloro-thiophen-2-yl)-acrylic acid (28 mg, 0.15 mmol), EXAMPLE 25. After stirring for two hours, the reaction mixture is directly purified by reverse phase HPLC (10-70 % ACN/H_2O). The product (35.5 mg, 36%) is isolated as a yellow solid with a melting point of 116-120°C. $C_{22}H_{22}ClN_5O_2S$: MS m/z: 456, 458. Anal. calcd. for $C_{22}H_{22}ClN_5O_2S \bullet C_2HF_3O_2$: C, 50.57; H, 4.07; N, 12.29. Found: C, 46.48; H, 3.64; N, 11.04.

EXAMPLE 670. (3S, 5R)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide.

4-Bromo-phenyl isocyanate (20.8 mg, 0.105 mmol) is added to solution of (3S,5R)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (30 mg, 0.105 mmol), minor epimer

from EXAMPLE 88, Part D, in 1 mL of DMF. The reaction is stirred for two hours at room temperature. The product (21.4 mg, 33%) is isolated from reverse phase HPLC (10 -70% ACN/H_2O) as white solid. The melting of the compound is 142-144 °C . $C_{22}H_{23}BrN_6O_2$ MS m/z: 483, 485. Anal. cald.for $C_{22}H_{23}BrN_6O_2 \bullet 2C_2HF_3O_2$: C, 43.90; H, 3.54; N, 11.81. Found: C, 44.52; H, 3.86; N, 12.44.

EXAMPLE 671. (3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide.

The desired product (35 mg, 47%) is isolated as a white solid with a melting point of 142-144°C . $C_{22}H_{23}BrN_6O_2$ MS m/z: 483, 485. Anal. cald.for $C_{22}H_{23}BrN_6O_2 \bullet 2C_2HF_3O_2$: C, 43.90; H, 3.54; N, 11.81. Found: C, 44.73; H, 3.59; N, 12.38.

EXAMPLE 672. (3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

The product (24.7 mg, 50%) is obtained as a white solid with a melting point of 123-125 °C . $C_{22}H_{23}ClN_6O_2$ MS m/z: 439, 441. Anal. cald.for $C_{22}H_{23}ClN_6O_2 \bullet 2C_2HF_3O_2$: C, 46.82; H, 3.78; N, 12.60. Found: C, 47.69; H, 4.33; N, 13.32.

EXAMPLE 673. 1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.

A. 1-(4-Chloroquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.

1-(4-chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one hydrochloride (0.49 g, 1.4 mmol), EXAMPLE 89, is treated with acetonitrile (20 mL), triethyl amine (1.2 ml, 8.4 mmol) and a solution of 6-chlorobenzo[b]thiophen-2-sulfonyl chloride (0.41 g, 1.54 mmol), EXAMPLE 1, in acetonitrile (10 mL) at 0°C. After 2 h the solution is poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried over sodium sulfate and concentrated to yielded the title compound (0.45 g, 0.95 mmol). MS m/z: 506, $[M+1]^+$; ^1H NMR (CD_3OD, 300 MHz) δ 8.8 (d, 1H), 8.15 (d, 1H), 7.9 (d, 2H), 7.85 (s, 1H), 7.4-7.5 (m, 2H), 6.8 (s, 1H), 4.8 (s, 2H), 4.0 (s, 2H), 3.4-3.45 (m, 4H).

B. 1-(4-Azidoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one

1-(4-Chloroquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one (0.52 g, 1.03 mmol) is dissolved in DMF (15 mL), treated with sodium azide (0.52 g, 8.0 mmol), tetrabutyl ammonium chloride (0.1 g, 0.36 mmol) and heated to 65 °C overnight. The reaction

mixture is cooled, poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried (sodium sulfate) and concentrated to give the title compound (0.5 g, 1.04 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 9.0 (d, 1H), 8.2 (d, 1H),8.0 (s, 1H), 7.9 (d, 2H), 7.8 (d,1H), 7.6 (d,1H), 7.5 (d,1H),6.9 (s, 1H), 4.85 (s, 2H), 4.0 (s, 2H), 3.5-3.7 (m, 4H).

C. 1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.

A suspension of 1-(4-azidoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one (0.50 g, 1.04 mmol) in 100 mL of acetic acid/methanol (~ 1:10) is treated with 10% Pd/C (0.15 g) and stirred under hydrogen for 1.5 hours. The resulting solution is filtered through Celite and the filtrate is evaporated in vacuo. The organic layer is concentrated and the residue is purified by reverse phase HPLC (gradient elution of 30 % of 0.1 % aqueous TFA/acetonitrile to 100 % acetonitrile) and lyopholized to give the title compound (0.39 g, 0.86 mmol). MS (ISP) m/z 487, 489, (M+H), Cl pattern.

The following compounds are prepared from the compound of Example 89 or 91 using the methods described above.

Example	Name	m/z [M+H]
674	1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethene-sulfonyl]-piperazin-2-one	463, 465
675	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-methyl-piperazin-2-one	501, 503
676	(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one	491, 493
677	(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one	491, 493
678	(S,R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid	531, 533
679	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide	544
680	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	558
681	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	558

682	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	600

EXAMPLE 683. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

A. (S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

(S)-1-(4-chloroquinolin-7-ylmethyl)-3-methylpiperazin-2-one hydrochloride (0.25 g, 1.0 mmol), EXAMPLE 91, is treated with 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene (0.35 g 1.2 mmol), EXAMPLE 17, and potassium carbonate (0.5 g, 3 mmol). The resulting suspension is sonicated for 10 minutes then stirred vigorously for 16 h at ambient temperature. The reaction mixture is poured into water and extracted with ethyl acetate (2 X 150 mL). The organic layer is washed with water (4 X 200 mL), dried over sodium sulfate and concentrated. The residue is chromatographed (3 % methanol/methylene chloride) to give the title compound (0.31 g, 0.73 mmol).

B. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

(S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one (0.35 g, 0.82 mmol) is treated with phenol (2 g) and ammonium acetate (0.7 g, 9.1 mmol) and heated to 120 °C in a sealed vessel for 1 hour. Upon cooling, the solution is partitioned between 2 N NaOH and ethyl acetate. The organic layer is separated and washed with fresh 2 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC to give the title compound as a white solid (0.15 g, 0.35 mmol). MS (ISP) m/z 427, 429, (M+H), Cl pattern.

The following compounds are prepared from starting materials prepared as described in Examples 61-64, 89 or 91 using the methods described above.

Example	Name	m/z [M+H]
684	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	413, 415
685	(3S, 5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one	465, 467
686	(3S, 5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-	464

	benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one	
687	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-methyl-piperazin-2-one	446,448
688	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-methyl-piperazin-2-one	444
689	(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one	441, 443
690	(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one	441, 443
691	1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	420, 422
692	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-ethyl-piperazin-2-one	458
693	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one	470
694	1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-(S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one	489
695	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one	464, 466
696	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-methyl-piperazin-2-one	434, 436
697	4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(2-hydroxy-ethylamino)-quinolin-7-ylmethyl]-piperazin-2-one	464
698	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one	462
699	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one	492
700	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one	448
701	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-1-(4-methylamino-quinolin-7-ylmethyl)-piperazin-2-one	478
702	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-4-oxy-piperazin-2-one	443

EXAMPLE 703. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one.

A. (S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl piperazin-2-one.

(S)-1-(4-chloroquinolin-7-ylmethyl)-3-methylpiperazin-2-one hydrochloride (0.35 g, 1.4 mmol), EXAMPLE 91, is treated with DMF (20 mL), 3-(4-bromothiophen-2-yl)-(E)-acrylic acid (0.32 g, 1.4 mmol), prepared according to EXAMPLE 26, using 4-bromothiophene-2-carboxaldehyde, triethyl amine (0.21 ml, 1.4 mmol) and 2-(1H-benzotriazol-1-yl)1,1,3,3-tertamethyluronium tetrafluoroborate (0.45 g, 1.4 mmol) and heated to 50 °C for 5 minutes. The reaction mixture is stirred at ambient temperature for 16 h then partitioned between ethyl acetate and water. The organic layer is concentrated and the residue is chromatographed (5% methanol/methylene chloride) to give crude title compound (0.5 g , 0.9 mmol). MS m/z: $[M+H]^+$ = 504. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.9 (d, 1H), 8.2-8.3(m, 2H), 8.0 (s, 1H), 7.7-7.8 (m, 1H), 7.4 (s, 1H), 7.3-7.4 (m, 1H), 6.7-6.8 (m, 1H), 6.6 (d, 1H), 5.1-5.2 (m, 1H), 4.6-4.7 (m, 2H), 3.4-3.6 (m, 2H), 3.0-3.3 (m, 2H), 1.5 (d, 3H).

B. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one.

(S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl piperazin-2-one (0.50 g, 0.9 mmol) is treated with phenol (~ 2 g) and ammonium acetate (0.5 g, 6.4 mmol) and heated to 120 °C in a sealed vessel for 1 hour. Upon cooling, the solution is partitioned between 2 N NaOH and ethyl acetate. The organic layer is separated and washed with fresh 2 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC (gradient elution of 10 % of 0.1 % aqueous TFA/acetonitrile to 100 % acetonitrile) to give the title compound (0.22 g, 0.56 mmol). MS m/z: $[M+H]^+$ = 485, 487, Cl pattern. ^1H NMR (CD_3OD, 300 MHz) δ 8.2-8.4 (m, 2H), 7.7-7.8 (m, 2H), 7.6 (d, 1H), 7.5 (s, 1H), 7.3 (s, 1H), 6.9-7.0 (m, 1H), 6.7 (d, 1H), 5.0-5.1 (m, 1H), 4.9 (q, 2H), 4.3-4.4 (m, 1H), 3.5-3.7 (m, 2H), 3.3-3.4 (m, 2H), 1.5 (d, 3H).

The following compounds are prepared from starting materials prepared as described in Examples 75-87 using the methods described above.

Example	Name	m/z [M+H]

704	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	469 Cl pattern
705	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-(S)-3-ethyl-1-(4-hydroxyamino-quinolin-7-ylmethyl)-piperazin-2-one	471, 473
706	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	427, 429
707	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	454
708	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one	441, 443
709	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one	471, 473
710	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-piperazin-2-one	470
711	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	498
712	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-ethyl-piperazin-2-one	458
713	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-6-methyl-piperazin-2-one	488
714	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-3-(1-(R)-methoxy-ethyl)-piperazin-2-one	484
715	1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)-acryloyl]-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate	528
716	1-(4-Aminoquinolin-7-ylmethyl)-4-[(5-chlorothiophen-2-yloxy-acetyl]-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate	488
717	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	454

EXAMPLE 718. 1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one.

A. 1-(4-Chlorocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one

1-(4-chlorocinnolin-7-ylmethyl)-piperazin-2-one hydrochloride (0.14 g, 0.4 mmol), EXAMPLE 90, is treated with acetonitrile (20 mL), triethylamine (2 mL, 14 mmol) and 2-(5-chlorothiophen-2-yl)ethene-sulfonyl chloride (0.097 g, 0.4 mmol), EXAMPLE 3, at 0°C. The

solution is warmed to ambient temperature over 1.5 h and diluted with ethyl acetate. The solution is washed with 10 % sodium bicarbonate solution and water, dried (sodium sulfate) and concentrated to yield the title compound (0.17 g, 0.35 mmol). MS m/z: $[M+H]^+$ = 483; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.4 (s, 1H), 8.4 (s, 1H), 8.3 (d, 1H) 7.85 (d, 1H), 7.7 (d, 1H), 7.1 (d, 1H), 6.95 (d, 1H), 6.35 (d, 1H), 4.9 (s, 2H), 4.0 (s, 2H), 3.4-3.5 (m, 4H).

B. 1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one

1-(4-Chlorocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one (0.06 g, 0.12 mmol) is treated with phenol (0.20 g) and ammonium acetate (0.2 g, 2.6 mmol) and heated to 120 °C for 45 minutes. The reaction mixture is cooled, diluted with ethyl acetate and washed with 1 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC (20 % aqueous TFA (0.1 %)/acetonitrile to 100 % acetonitrile). Fractions containing the desired product are lyophilized to obtain the title compound (0.02 g, 0.043 mmol). MS m/z: $[M+H]^+$ = 464; ^1H NMR (CD_3OD, 300 MHz) δ 8.6 (s, 1H), 8.4 (d, 1H), 7.75 (d, 1H), 7.65 (d, 1H), 7.35 (d, 1H), 7.1 (d,1H), 6.8 (d, 1H), 4.9 (s, 2H), 4.05 (s, 2H), 3.6 (m, 4H).

EXAMPLE 719. 4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one.

1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one (0.20 mmol), EXAMPLE 90, is dissolved in MeCN (5 mL) and treated with 4-methylmorphorline (0.055 ml, 0.50 mmol). 6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl chloride (54 mg, 0.20 mmol) in MeCN (2 mL) is added dropwise. The reaction mixture is stirred at r.t. for 1.5 h, then subjected to HPLC purification, to give the title compound as white solid (0.021 g, 0.037 mmol). MS m/z 452, 454 (M+1); ^1H NMR (CD_3OD, 300 MHz) δ 8.37 (d, 1H), 8.30 (b, 1H), 8.12 (d, 1H), 8.02 (s, 1H), 7.97 (d, 1H), 7.57 (d. 1H), 6.98 (d, 1H), 6.88 (d, 2H), 3.73 (s, 2H), 3.60-3.48 (m, 8H).

EXAMPLE 720. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(methyl-pyridin-4-yl-amino)-ethyl]-piperazin-2-one.

A portion (~50%) of the crude 1-[2-{(Methyl)-(pyridin-4-yl)-amino}-ethyl]-piperazin-2-one, EXAMPLE 93 is reacted with 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (54 mg, 0.20 mmol), EXAMPLE 1, using same procedure as described in EXAMPLE 719. The residue obtained after HPLC purification is subjected to silica gel chromatography using $NH_4OH/MeOH/CH_2Cl_2$ (1:4:95) as eluant to give title compound (30 mg, 0.064 mmol) as a white solid. MS m/z 465, 457 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, 2H), 7.88 (s, 1H), 7.85 (d,

1H), 7.79 (s, 1H), 7.47 (d, 1H), 6.47 (d. 2H), 3.80 (s, 2H), 3.50 (m, 4H), 3.43 (d, 2H), 3.30 (d, 2H), 2.98 (s, 3H).

EXAMPLE 721. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one.

1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one (38 mg, 0.16 mmol), EXAMPLE 94, is reacted with 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride (40 mg, 0.16 mmol), EXAMPLE 3, using the same procedure as described in EXAMPLE 719. Reverse phase HPLC purification gives the title compound (29 mg, 0.052 mmol) as a white solid. MS m/z 441, 443 (M+H); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.08 (d, 1H), 7.98 (s, 1H), 7.56 (d, 1H), 7.30 (d, 1H), 7.02 (s, 1H), 7.00 (d. 1H), 6.78 (d, 1H), 3.87 (s, 2H), 3.70-3.50 (m, 8H), 2.15 (s, 3H).

The following compounds are prepared from starting materials obtained as described in Examples 92-97 using the methods described above.

Example	Name	m/z [M+H]
722	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	520 (M+)
723	1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	417
724	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	483,485
725	1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one	418
726	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	427,429
727	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(methylpyridin-4-ylamino)-ethyl]-piperazin-2-one	441
728	4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	443
729	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one	465, 467
730	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-yl-ethyl)-piperazin-2-one	450, 452

731	1-[2-(2-Amino-3-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	476, 478
732	1-[2-(2-Amino-5-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	476, 478
733	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(2,3,5,6-tetrachloro-pyridin-4-ylamino)-ethyl]-piperazin-2-one	563, 565, 567, 569
734	1-[2-(2-Amino-3,5,6-trichloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	544, 546, 548
735	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	391, 393

EXAMPLE 736. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridazin-4-yl-amino)-ethyl]-piperazin-2-one.

1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one hydrochloride (0.5 g, 1.7 mmol), EXAMPLE 95, is reacted with 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.40 g, 1.5 mmol), EXAMPLE 1, using essentially the same procedure as described in EXAMPLE 719. Reverse phase HPLC purification gives the title compound (0.34 g, 0.75 mmol) as a white solid. MS m/z (M+H= 452); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.6 (d, 1H), 8.4 (d, 1H), 8.05 (s, 1H), 8.05 (s, 1H), 7.9 (d, 1H), 7.5 (d, 1H), 7.2 (d, 1H), 3.8 (s,2H), 3.4-3.7 (m, 8H).

EXAMPLE 737. 1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one.

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester from EXAMPLE 96, Part B (45 mg, 0.10 mmol) is dissolved in 20% TFA/ CH_2Cl_2 and stirred at r.t. for 2 hours. The solution is concentrated to residue. The residue is dissolved in MeCN (2.5 ml) and treated with 4-methylmorphorline (0.027 ml, 0.25 mmol). 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride (24 mg, 0.10 mmol), EXAMPLE 3, in MeCN (1 mL) is then added dropwise. The reaction mixture is stirred at r.t. for 1 h, then subjected to reverse phase HPLC purification, to give the title compound as white solid (0.040 g, 0.037 mmol). MS m/z 439, 441 (M+H); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.20 (br, 1H), 8.10 (s, 1H), 8.08 (d, 1H), 7.60 (d, 1H), 7.53 (d. 1H), 7.35 (d, 1H), 7.21 (d, 1H), 7.07 (d,1H), 6.82 (d, 1H), 5.27 (m, 1H), 3.88 (s, 2H), 3.60-3.50 (m, 4H), 3.30 (d, 2H).

The following compounds are prepared from starting materials obtained as described in Examples 92-97 using the methods described above.

Example	Name	m/z [M+H]
738	1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	463, 465
739	1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	463, 465
740	1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	439, 441
741	1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	465, 467
742	1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	441, 443

EXAMPLE 743. 4-[2-(5-Chlorothiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one.

4-(Benzyloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one (0.028 g, 0.074 mmol), EXAMPLE 98, is treated with 4 % HCO_2H/MeOH (5 mL) and a catalytic amount of Pd black for 5 minutes. The reaction mixture is filtered washed with methanol and the filtrate is concentrated to a residue. The residue is treated with acetonitrile (3 mL) excess N-methylmorpholine (0.04 mL) and 2-(5-chlorothiophen-2-yl)ethene-sulfonyl chloride (0.018 g, 0.074 mmol), EXAMPLE 3, and processed as usual (EXAMPLE 719). Further chromatographic purification (NH_4OH/MeOH/CH_2Cl_2:1/4/95) yields the title compound: MS m/z 451, 453 (M+H); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.93 (bs, 1H), 8.24 (bs, 1H), 7.41 (d, 1H), 7.23 (d, 1H), 7.14 (m, 2H), 6.94 (d, 1H), 6.68 (d. 1H), 6.18 (d, 1H), 4.43 (t, 2H), 3.67 (t, 2H), 2.88 (t, 2H), 2.66 (t, 2H).

EXAMPLE 744. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (4.3 g, 13.0 mmol), EXAMPLE 69, in CH_3CN (250 mL) is cooled to 0°C. Potassium carbonate (1.98 g, 14.3 mmol) is added to the reaction mixture followed by propargyl bromide (1.55g, 13.0 mmol). The mixture is slowly warmed to ambient temperature and

maintained until complete consumption of starting material is observed by TLC (approx. 8 h). The mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted twice with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to provide 3.38 g (70%) of the title compound as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 9H), 2.34 (t, J = 2.4 Hz, 1H), 2.89 (m, 2H), 3.42 (s, 2H), 3.45 (d, J = 2.4 Hz, 2H), 3.52 (m, 2H), 4.95 (d, J = 1.4 Hz, 2H), 6.42 (br s, 1H), 7.88 (dd, J = 5.8, 0.8 Hz, 1H), 8.41 (d, J = 5.8 Hz, 1H), 8.78 (d, J = 0.8 Hz, 1H) ppm; MS (EI): m/z 368 (M+).

B. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.3 g, 3.53 mmol) in CH_2Cl_2 (100 mL) is added TFA (20 mL) at 0 °C. After 6 h, the reaction mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (500 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide 616 mg (65%) of the title compound as a pale yellow solid.
^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (app t, J = 2.4 Hz, 1H), 2.76 (m, 2H), 3.33 (s, 2H), 3.83 (d, J = 2.4 Hz, 2H), 3.45 (m, 2H), 4.57 (s, 2H), 6.47 (s, 1H), 7.23 (d, J = 5.7 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H), 8.85 (d, J = 0.9 Hz, 1H), 9.34 (br s, 1H) ppm; MS (EI): m/z 268 (M+).

EXAMPLE 745. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-[4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (100 mg, 0.27 mmol), EXAMPLE 743, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (87 mg, 0.27 mmol), EXAMPLE 69, Part B, Et_3N (110 mg, 1.08 mmol), $(Ph_3P)_4PdCl_2$ (10 mg, 0.013 mmol), and CuI (1 mg, 0.008 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine,

dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 77 mg (51%) of the title compound as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$, ~2:1mixture of rotamers) major rotamer: δ 1.53 (s, 9H), 1.69 (s, 9H), 2.98 (m, 2H), 3.49 (s, 2H), 3.56 (m, 2H), 3.78 (s, 2H), 4.98 (s, 2H), 6.43 (s, 1H), 7.89 (m, 1H), 8.09 (m, 2H), 8.34 (m, 1H), 8.41 (m, 1H), 8.75 (m, 1H) ppm; MS (ISP loop): m/z 561 (M+H).

B. 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

1,8-Diazabicyclo[5.4.0]undec-7-ene (42 mg, 0.27 mmol) is added to a suspension containing 2-{4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (77 mg, 0.14 mmol) in anhydrous CH_3CN (10 mL) and the mixture is warmed to 50 °C. After 4 h, the reaction mixture is concentrated to dryness and the residue is partitioned between CH_2Cl_2 (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with CH_2Cl_2 (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 85 mg of the title compound as a crude solid which is used directly without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 9H), 1.70 (s, 9H), 2.91 (m, 2H), 3.41 (s, 2H), 3.49 (m, 2H), 4.26 (s, 2H), 4.95 (d, J = 1.1 Hz, 2H), 6.39 (d, J = 0.7 Hz, 1H), 6.68 (d, J = 0.7 Hz, 1H), 7.86 (m, 1H), 8.41 (m, 1H), 8.76 (br s, 1H), 8.82 (br s, 1H) ppm; MS (EI): m/z 561 (M+H).

C. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (85 mg, 0.14mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at 0°C and the solution is allowed to slowly warm to ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 35 mg (36%, two steps) of the title compound as a pale yellow, lyophilized solid.
^1H NMR (300 MHz, d_6-DMSO) δ 2.80 (m, 2H), 3.25 (s, 2H), 3.37 (m, 2H), 3.93 (s, 2H), 4.76 (s, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.85 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 6.6 Hz, 1H), 8.37 (d, J = 6.7 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 9.17 (s, 1H), 9.19 (s, 1H), 12.80 (s, 1H), 12.96 (s, 1H), 14.91 (br s, 2H) ppm; MS (ion spray): m/z 361 (M+H). $C_{23}H_{25}ClN_4OS$ MS m/z: 441,443.

The following compounds are prepared from starting materials obtained as described in Examples 69-71 using the methods described above.

Example	Name	m/z [M+H]
746	4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	395, 397
747	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	443, 445
748	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	386, 388
749	4-(5-Chloro-1H-indol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	394, 396
750	4-(6-Chloro-naphthalen-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	405, 407
751	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	406, 408
752	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	501, 503
753	1-(5-Chloro-1H-indol-2-ylmethyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	452, 454
754	1-[(5-Chloro-thiophen-2-yloxy)-acetyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	463, 465
755	1-(6-Chloro-benzo[b]thiophene-2-carbonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	483, 485
756	1-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	554, 556
757	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one	361
758	4-(3-Phenyl-prop-2-ynyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	345
759	4-[3-(5-Chloro-thiophen-2-yl)-prop-2-ynyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	384

The following compounds are prepared from 3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one using the procedures described above.

Example	Name	m/z [M+H]
760	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	431, 433
761	4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	438, 440
762	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	487, 489
763	4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	469, 471
764	4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	540, 542
765	4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	439, 441
766	(S)-2-Methoxymethyl-3-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	428, 430
767	(S)-4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	445, 447

EXAMPLE 768. 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-[4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-2-oxopiperazin-1-ylmethyl]-(pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 123 using 6-chloro-benzo[b]thiophene-2-carboxylic acid, EXAMPLE 1 and 2-(2-oxopiperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester EXAMPLE 69. The mixture is stirred overnight, then concentrated to dryness. The residue is diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound as a solid. The crude material can be used in the subsequent step without further purification.

B. 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

Trifluoroacetic acid (0.5 mL) is added dropwise to a solution of 2-[4-(6-chloro-benzo[b]thiophene-2-carbonyl)-2-oxopiperazin-1-ylmethyl]-(pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (0.14 g, 0.27 mmol) in 6 mL CH_2Cl_2 at 0°C. After 1 h, the ice bath is removed and the solution stirred at room temperature for 2 hours. The reaction mixture is concentrated in vacuo. The crude residue is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are combined and lyophilized to provide the title compound (0.07 g, 0.13 mmol) as a white solid. ESI MS, $[M+H]^+$=425, 427 (Cl pattern).

The following compounds are prepared using starting materials obtained as described in Example 69 using the methods described above.

Example	Name	m/z [M+H]
769	4-[3-(6-Chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	451, 453
770	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	405, 407
771	4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	497, 499
772	4-(5'-Chloro-[2,2']bithiophenyl-5-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	457, 459
773	4-(5-Chloro-1H-indole-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	364, 366
774	4-[4-(6-Methoxy-pyridin-3-yl)-benzoyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	442
775	4-(4-Pyridin-3-yl-benzoyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	412
776	4-[3-(4-Bromo-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	446
777	4-[3-(5-Chloro-thiophen-2-yl)-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	403, 405
778	4-[(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	453, 455
779	4-[2-(4-Chloro-phenyl)-2-methyl-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	411, 413

780	4-[3-(3,4-Dichloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	431, 433
781	4-[(4-Chloro-phenyl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	383, 385
782	4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	395, 397
783	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	400, 402

EXAMPLE 784. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.

To a solution containing (S)-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester (0.43 g, 1.77 mmol), EXAMPLE 56, and 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (0.66 g, 1.77 mmol), EXAMPLE 13, in anhydrous DMF (5 mL) at 0°C is added 60% NaH (78 mg, 1.95 mmol). After 30 min, the reaction mixture is warmed to ambient temperature and maintained for 6 hours. The reaction mixture is carefully quenched with water and then diluted with water and diethyl ether. The layers are separated and the organic phase is washed twice with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (2:1 hexane/ethyl acetate to 1:1 hexane/ethyl acetate) to provide 0.37 g (39%) of the title compound as a glassy solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01-3.22 (m, 2H), 3.58 (m, 2H), 3.73 (s, 3H), 3.86-3.92 (m, 1H), 4.42-4.58 (m, 4H), 5.25 (m, 2H), 5.93 (m, 1H), 6.57 (br s, 1H), 6.85 (d, J = 8.2 Hz, 1 H), 7.17-7.51 (m, 9H), 7.76 (m, 2H) ppm; MS (ion spray): m/z 537 (M+H).

B. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

Tetrakis(triphenylphosphine)palladium(0) (237 mg, 0.2 mmol) is added to a solution containing (±)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester (1.10 g, 2.05 mmol) and morpholine (894 mg, 10.2 mmol) in CH_2Cl_2 (30 mL). After ~5 min, the reaction mixture is absorbed onto silica gel and chromatographed (CH_2Cl_2 to 10% MeOH/ CH_2Cl_2) to provide 900 mg (97%) of the title compound as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (br s, 1H), 2.95 (dd, J = 13.5, 4.3 Hz, 1H), 3.27 (br

d, J = 13.5 Hz, 1H), 3.46-3.72 (m, 4H), 3.73 (s, 3H), 5.40 (d, J = 15.3 Hz, 1H), 6.57 (br s, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 7.17-7.50 (m, 9H), 7.75-7.77 (m, 2H) ppm; MS (ion spray): m/z 453 (M+H).

C. (±)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester.

To a mixture of (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (630 mg, 1.39 mmol) and K_2CO_3 (380 mg, 2.78 mmol) in anhydrous CH_3CN (5 mL) at 0 °C is added 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester (720 mg, 2.09 mmol), EXAMPLE 21, in CH_3CN (4 mL). The reaction mixture is allowed to warm to ambient temperature then maintained for 16 hours. The reaction mixture is diluted with diethyl ether/water and the layers are separated. The organic phase is washed twice with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica (CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to provide 550 mg (55%) of the title compound which is used directly in the next reaction without further characterization.

D. (±)-2-[4-(3-Amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

Partially-purified (±)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester (550 mg, 0.76 mmol) is suspended in reagent grade MeOH (20 mL). To the heterogeneous mixture is added 12M HCl (5 drops) and the reaction mixture is maintained at ambient temperature until homogeneous (~30 min). The reaction mixture is partitioned between diethyl ether and water containing excess $NaHCO_3$ (500 mL). The layers are separated and the organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to provide 400 mg (94%) of the title compound which is used directly in the next reaction. MS (ISP loop): 532 (M+H).

E. (±)-2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A solution containing (±)-2-[4-(3-amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (100 mg, 0.18 mmol), 1,3,5-triazine (146 mg, 1.81 mmol), and glacial HOAc (99 mg, 1.81 mmol) in absolute EtOH (10 mL) is maintained at reflux for 16 hours. A second portion of 1,3,5-triazine (146 mg, 1.81 mmol) and glacial HOAc (99 mg, 1.81 mmol) is added and the reaction mixture is maintained at reflux

for an additional 16 hours. The reaction mixture is concentrated in vacuo and the crude product is diluted with water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 26 mg (20%) of the title compound as a white solid which is used directly in the next reaction without further characterization.

F. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

To a solution containing (±)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (26 mg, 0.03 mmol) in CH_2Cl_2 (4 mL) is added trifluoroacetic acid (1mL) at ambient temperature. After 4 h, the reaction mixture is concentrated in vacuo and then dissolved in water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 10 mg (47%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 2.62 (m, 1H), 3.05-3.51 (m, 4H), 3.59 (s, 3H), 3.81 (d, J = 14.0 Hz, 1H), 4.26 (m, 1H), 4.69 (ABq, Δ_{AB} = 310 Hz, J_{AB} = 16.4 Hz, 2H), 6.26 (s, 1H), 7.02 (dd, J = 8.6, 2.0 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.47 (s, 1H), 8.77 (s, 1H), 9.69 (br s, 2H), 11.17 (s, 1H) ppm; MS (ion spray): m/z 479 (M+H).

EXAMPLE 785. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

A. (±)-1-(3-Amino-4-cyano-benzyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

LiOH monohydrate (380 mg, 9.06 mmol) is added at ambient temperature to a solution containing (±)-2-[4-(3-amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (1.0 g, 1.81 mmol), EXAMPLE 784, Part E, in 1:1:1 THF/MeOH/water (30 mL). After 16 h, HOAc (0.5 mL) is added and the reaction mixture is concentrated in vacuo. The residue is dissolved in CH_3CN/water and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 378 mg (48%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.03 (m, 1H), 3.48 (m, 1H), 3.51 (ABq, Δ_{AB} = 69.2 Hz, J_{AB} = 16.4 Hz, 2H), 3.78 (d, J = 15.9 Hz, 1H), 4.05-4.09 (m, 2H), 5.04 (d, J = 15.9 Hz, 1H), 6.41 (m, 2H), 6.58

(s, 1H), 7.04 (dd, J = 8.6, 2.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.51, d, J = 2.0 Hz, 1H) ppm; MS (ISP loop): m/z 438 (M+H).

B. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (200 mg, 0.30 mmol), 1,3,5-triazine (244 mg, 3.00 mmol), and glacial HOAc (180 mg, 3.00 mmol) in absolute EtOH (20 mL) is maintained at reflux for 16 hours. The reaction mixture is cooled to ambient temperature and the solid is collected on a Buchner funnel and washed with EtOH followed by diethyl ether. Oven-drying in vacuo provided 13 mg (76%) of the title compound as an off-white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 2.63 (m, 1H), 3.06 (d, J = 16.4 Hz, 1H), 3.24-3.42 (m, 4H), 3.68 (ABq, Δ_{AB} = 34.5 Hz, J_{AB} = 14.1 Hz, 2H), 3.96 (m, 1H), 4.63 (ABq, Δ_{AB} = 400 Hz, J_{AB} = 15.8 Hz, 2H), 6.27 (s, 1H), 6.99 (dd, J = 8.6, 2.0 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.40 (s, 1H), 7.46 (s, 1H), 7.69 (br s, 2H), 8.10 (d, J = 8.5 Hz, 1H), 8.32 (s, 1H), 11.20 (s, 1H) ppm; MS (ion spray): m/z 465 (M+H).

EXAMPLE 786. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylamide

To a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (25 mg, 0.03 mmol), EXAMPLE 785, and N-methylmorpholine (36 mg, 0.36 mmol) in anhydrous DMF (1 mL) is added methylamine hydrochloride (10 mg, 0.14 mmol) followed by HATU (40 mg, 0.10 mmol) at ambient temperature. After 3 h, the solvent is removed under high vacuum and the residue is dissolved in CH_3CN/water and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 22 mg (88%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 2.57 (d, J = 4.4 Hz, 3H), 2.70 (m, 1H), 3.0 (m, 1H), 3.66 (d, J = 14.2 Hz, 1H), 3.77 (d, J = 14.2 Hz, 1H), 3.85 (m, 1H), 4.03 (d, J = 16.3 Hz, 1H), 5.18 (d, J = 16.3 Hz, 1H), 6.28 (s, 1H), 7.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.51 (s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.97 (m, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.79 (s, 1H), 9.72 (br s, 2H), 11.18 (s, 1H) ppm; MS (ISP loop): m/z 478 (M+H).

Table 1: Amide Analogs Derived From C-6 Carboxylic Acid.

Example	Name	m/z

		[M+H]
787	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	492
788	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	492
789	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid benzylamide	554
790	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-amide	508
791	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid bis-(2-hydroxy-ethyl)-amide	552
792	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	534
793	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylcarbamoylmethyl-amide	535

The following compounds are prepared using the procedures described above.

Example	Name	m/z [M+H]
794	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid	458
795	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid methyl ester	472
796	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid amide	457
797	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid ethylamide	458
798	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-(4-methyl-piperazine-1-carbonyl)-piperazin-2-one	540

EXAMPLE 799. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (42 mg, 0.08 mmol), EXAMPLE 99, 1,3,5-triazine (40 mg, 0.48 mmol), and glacial HOAc (30 mg, 0.48 mmol) in absolute EtOH (1 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated and then dissolved in water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA;

Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 17 mg (32%) of the title compound as a white solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 3.47 (m, 1H), 3.67 (s, 3H), 3.71 (d, J = 16.1 Hz, 1H), 4.00 (d, J = 16.5 Hz, 1H), 4.05 (m, 1H), 4.52 (m, 1H), 4.72 (ABq, Δ_{AB} = 248 Hz, J_{AB} = 16.5 Hz, 2H), 7.57 (m, 2H), 8.05 (d, J = 8.6 Hz, 1H), 8.20 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H), 8.49 (s, 1H), 8.72 (s, 1H), 9.57 (br s, 2H) ppm; MS (ion spray): m/z 546 (M+H).

EXAMPLE 800. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Water (1 mL) is added to a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (20 mg, 0.03 mmol), EXAMPLE 799, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature, LiOH monohydrate (15 mg, 0.35 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 12 mg (63%) of the title compound as a white solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 3.69 (d, J = 16.0 Hz, 1H), 3.97 (d, J = 16.0 Hz, 1H), 4.08 (d, J = 11.7 Hz, 1H), 4.18 (d, J =16.2 Hz, 1H), 4.31 (d, J = 2.7 Hz, 1H), 5.20 (d, J =16.2 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.52 (s, 1H), 7.58 (dd, J = 8.6, 1.9 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.54 (s, 1H), 8.77 (br s, 1H) ppm; MS (ion spray): m/z 532 (M+H).

EXAMPLE 801. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide

To a mixture containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (45 mg, 0.08 mmol), EXAMPLE 800, N-methylmorpholine (18 mg, 0.18 mmol), and HATU (35 mg, 0.09 mmol) in anhydrous DMF (1 mL) is added NH_3 (7N in MeOH, 2 drops, approx. 0.5 mmol). The heterogeneous mixture is stirred 16 h at ambient temprature and then concentrated to dryness. The residue is dissolved in water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 25 mg (46%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.63 (d, J = 16.0 Hz, 1H), 4.01 (m, 4H), 5.17 (d, J = 16.6 Hz, 1H), 7.58 (m, 3H), 8.08 (d, J = 8.6 Hz, 1H), 8.17 (s, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.74 (s, 1H), 9.63 (br s, 2H) ppm; MS (ISP loop): m/z 531 (M+H).

The following compounds are prepared using the procedures described above.

Example	Name	m/z [M+H]
802	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester	560
803	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid	531
804	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide	544
805	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	558
806	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	558
807	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	600

EXAMPLE 808. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

To a solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (1.17 g, 2.6 mmol), EXAMPLE 784, Part B, 5-chlorothiophen-2-yloxyacetic acid (0.5 g, 2.6 mmol), EXAMPLE 24,and N-methylmorpholine (0.58 g, 5.72 mmol) in anhydrous DMF (10 mL) is added HATU (1.09 g, 2.86 mmol) at ambient temperature. After 1.5 h, the reaction mixture is diluted with CH_2Cl_2 (100 mL) and aqueous $NaHCO_3$ (100 mL) and the layers are separated. The aqueous phase is washed four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed once with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude amide is purified by flash silica gel chromatography (hexane/EtOAc, 4:1 to 1:2) to afford 1.5 g of the title compound which is used directly in the next reaction. ^1H NMR (300 MHz, $CDCl_3$, ~2:1 mixture of rotomers) major rotomer: δ 3.55 (d, J = 15.2 Hz, 1H), 3.60 (m, 1H), 3.69 (m, 5H), 4.37 (d, J = 17.7 Hz, 1H), 4.62 (m, 2H), 4.79 (d, J = 13.3 Hz, 1H), 5.35 (d, J = 15.2 Hz, 1H), 6.05 (d, J = 3.9 Hz, 1H), 6.52 (m. 2H), 6.84 (d, J = 8.1 Hz, 1H), 7.18-7.49 (m, 11H), 7.76 (m, 1H) ppm; MS (ISP loop): m/z 627 (M+H).

B. (±)-1-(3-Amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

Concentrated HCl (12M, 0.5 mL) is added at 0 °C to a solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (1.5 g, 2.39 mmol) in 4:1 MeOH/THF (25 mL). After 1.5 h, the reaction mixture is concentrated to dryness and then partitioned between a 1:1 mixture of EtOAc/aqueous $NaHCO_3$ (200 mL) and the layers are separated. The aqueous phase is extracted with EtOAc and then the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (hexane/EtOAc, 4:1 to 1:2) to provide 934 mg (84%, two steps) of the title compound. ^1H NMR (300 MHz, $CDCl_3$, ~2:1 mixture of rotomers) selected peaks: δ 3.16 (app. dd, J 14.0, 3.8 Hz, 1H), 3.68 (s, 3H), 3.96 (app. dd, J = 3.8, 2.0 Hz, 1H), 4.17 (d, J = 17.7 Hz, 1H), 4.45 (br s, 2H), 4.62 (m, 2H), 4.87 (d, J = 14.1 Hz, 1H), 5.21 (d, J = 15.1 Hz, 1H), 6.07 (m, 1H), 6.51 (d, J = 3.8 Hz, 1H), 6.57 (d, J = 7.9 Hz, 1H), 6.62 (br s, 1H), 7.35 (d, J = 7.9 Hz, 1H) ppm; MS (ISP loop): m/z 463 (M+H).

C. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (110 mg, 0.25 mmol), 1,3,5-triazine (207 mg, 2.55 mmol), and glacial HOAc (157 mg, 2.55 mmol) in absolute EtOH (5 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated to dryness and then purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 50 mg (32%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.34-3.89 (m, 2H), 3.60 (s, 3H), 4.14-4.54 (m, 3H), 4.64 (br d, J = 14.4 Hz, 1H), 4.78-5.11 (m, 3H), 6.19 (d, J = 4.1 Hz, 1H), 6.73 (d, J = 4.1 Hz, 1H), 7.64 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.79 (s, 1H), 9.71 (br s, 2H) ppm; MS (ion spray): m/z 490 (M+H).

EXAMPLE 809. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methylamide.

Water (1 mL) is added to a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (20 mg, 0.03 mmol), EXAMPLE 808, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature,

LiOH monohydrate (3 mg, 0.07 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 25 mg (>100 %) of the associated acid as a white solid after lyophilization which is used directly in the next reaction.

To a mixture containing (+/-)-1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid (12 mg, 0.02 mmol), N-methylmorpholine (19 mg, 0.19 mmol), and HATU (22 mg, 0.05 mmol) in anhydrous DMF (1 mL) is added $MeNH_2$ hydrochloride (5 mg, 0.19 mmol). The reaction mixture is stirred 1 h at ambient temperature and then concentrated to dryness. The residue is dissolved in water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 7 mg (58%) of the title compound as a white solid.

^{1}H NMR (300 MHz, d_6-DMSO) mixture of rotamers: δ 2.51 (m, 3H), 4.07-4.54 (m, 6H), 4.87 (m, 2H), 5.10 (m, 1H), 6.18 (m, 1H), 6.74 (m, 1H), 7.62 (m, 2H), 8.06 (br s, 1H), 8.32 (br d, J = 8.8 Hz, 1H), 8.78 (s, 1H), 9.61 (br s, 2H) ppm; MS (ISP loop): 489 (M+H).

The following compound is prepared using the procedures described above.

Example	Name	m/z [M+H]
810	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethylamide	503

EXAMPLE 811. (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid.

Water (0.5 mL) is added to a solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (35 mg, 0.08 mmol), EXAMPLE 808, Part B, in a 1:1 mixture of THF/MeOH (1 mL). At ambient temperature, LiOH monohydrate (4 mg, 0.10 mmol) is then added. After 16 h, an additional portion of LiOH monohydrate (4 mg, 0.10 mmol) is added and the reaction mixture is stirred for another 2 h then diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 40 mg (95%) of the associated acid as a white solid after lyophilization which is used directly in the next reaction. MS (ISP loop): m/z 449 (M+H).

A solution containing (+/-)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid (20 mg, 0.03 mmol), 1,3,5-triazine (28 mg, 0.34 mmol), and glacial HOAc (20 mg, 0.34 mmol) in absolute EtOH (6 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated to dryness and then purified by reverse-

phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 15 mg (75%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.75-4.38 (m, 5H), 4.67 (d, J = 14.8 Hz, 1H), 4.79 (d, J = 15.3 Hz, 1H), 4.95 (m, 1H), 5.09 (br d, J = 16.0 Hz, 1H), 6.18 (m, 1H), 6.71 (m, 1H), 7.64 (m, 2H), 8.31 (d, J = 8.5 Hz, 1H), 8.75 (s, 1H), 9.64 (br s, 2H) ppm; MS (ISP loop): m/z 476 (M+H).

EXAMPLE 812. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (4.3 g, 13.0 mmol), EXAMPLE 69, in CH_3CN (250 mL) is cooled to 0°C. Potassium carbonate (1.98 g, 14.3 mmol) is added to the reaction mixture followed by propargyl bromide (1.55g, 13.0 mmol). The mixture is slowly warmed to ambient temperature and maintained until complete consumption of starting material is observed by TLC (approx. 8 h). The mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted twice with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to provide 3.38 g (70%) of the title compound as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 9H), 2.34 (t, J = 2.4 Hz, 1H), 2.89 (m, 2H), 3.42 (s, 2H), 3.45 (d, J = 2.4 Hz, 2H), 3.52 (m, 2H), 4.95 (d, J = 1.4 Hz, 2H), 6.42 (br s, 1H), 7.88 (dd, J = 5.8, 0.8 Hz, 1H), 8.41 (d, J = 5.8 Hz, 1H), 8.78 (d, J = 0.8 Hz, 1H) ppm; MS (EI): m/z 368 (M+).

B. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.3 g, 3.53 mmol) in CH_2Cl_2 (100 mL) is added TFA (20 mL) at 0 °C. After 6 h, the reaction mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (500 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide 616 mg (65%) of the title compound as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (app t, J = 2.4 Hz, 1H), 2.76 (m, 2H), 3.33 (s, 2H), 3.83 (d, J = 2.4 Hz, 2H), 3.45 (m, 2H), 4.57 (s, 2H), 6.47 (s, 1H), 7.23 (d, J = 5.7 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H), 8.85 (d, J = 0.9 Hz, 1H), 9.34 (br s, 1H) ppm; MS (EI): m/z 268 (M+).

EXAMPLE 813. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-{4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (100 mg, 0.27 mmol), EXAMPLE 812, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (87 mg, 0.27 mmol), EXAMPLE 69, Part B, Et_3N (110 mg, 1.08 mmol), $(Ph_3P)_4PdCl_2$ (10 mg, 0.013 mmol), and CuI (1 mg, 0.008 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 77 mg (51%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ~2:1mixture of rotamers) major rotamer: δ 1.53 (s, 9H), 1.69 (s, 9H), 2.98 (m, 2H), 3.49 (s, 2H), 3.56 (m, 2H), 3.78 (s, 2H), 4.98 (s, 2H), 6.43 (s, 1H), 7.89 (m, 1H), 8.09 (m, 2H), 8.34 (m, 1H), 8.41 (m, 1H), 8.75 (m, 1H) ppm; MS (ISP loop): m/z 561 (M+H).

B. 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

1,8-Diazabicyclo[5.4.0]undec-7-ene (42 mg, 0.27 mmol) is added to a suspension containing 2-{4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (77 mg, 0.14 mmol) in anhydrous CH_3CN (10 mL) and the mixture is warmed to 50 °C. After 4 h, the reaction mixture is concentrated to dryness and the residue is partitioned between CH_2Cl_2 (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with CH_2Cl_2 (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 85 mg of the title compound as a crude solid which is used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 9H), 1.70 (s, 9H), 2.91 (m, 2H), 3.41 (s, 2H), 3.49 (m, 2H), 4.26 (s, 2H), 4.95 (d, J = 1.1 Hz, 2H), 6.39 (d, J = 0.7 Hz,

1H), 6.68 (d, J = 0.7 Hz, 1H), 7.86 (m, 1H), 8.41 (m, 1H), 8.76 (br s, 1H), 8.82 (br s, 1H) ppm; MS (EI): m/z 561 (M+H).

C. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (85 mg, 0.14mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at 0 °C and the solution is allowed to slowly warm to ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 35 mg (36%, two steps) of the title compound as a pale yellow, lyophilized solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 2.80 (m, 2H), 3.25 (s, 2H), 3.37 (m, 2H), 3.93 (s, 2H), 4.76 (s, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.85 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 6.6 Hz, 1H), 8.37 (d, J = 6.7 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 9.17 (s, 1H), 9.19 (s, 1H), 12.80 (s, 1H), 12.96 (s, 1H), 14.91 (br s, 2H) ppm; MS (ion spray): m/z 361 (M+H). $C_{23}H_{25}ClN_4OS$ MS m/z: 441,443.

EXAMPLE 814. 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile.

A. {1-[3-Benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester:

Sodium hydride (140 mg, 3.51 mmol) is added to a cooled solution of (2-oxo-piperidin-4-yl)-acetic acid ethyl ester (500 mg, 2.70 mmol) in 10 mL of THF. After stirring for forty five minutes, 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (1.43 g, 3.82 mmol), EXAMPLE 13, is added, and the reaction is left to stir overnight. THF is removed, and the residue is taken up in 250 mL of ethyl acetate. Excess sodium hydride is quenched with 5 mL of water, and normal aqueous work-up followed. The crude product is chromatographed on silica gel (50% EtOAc/Hexane) to give{1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester (732 mg, 57%)as a light yellow solid. $C_{30}H_{29}N_3O_3$ MS m/z: 480, 482. Anal cald. for $C_{30}H_{29}N_3O_3$: C,75.13; H, 6.09; N, 8.76. Found C, 73.01; H, 6.02; N, 8.46.

B. {1-[3-Benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid.

To a solution of {1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester (732 mg, 1.53 mmol) in 5 mL of THF is added 1N sodium hydroxide (1.53 ml, 1.53 mmol). After stirring for four hours, the THF is removed and EtOAc (500 mL) is added.

The reaction mixture is acidified to a pH of 6 and normal aqueous work-up followed. The desired carboxylic acid (571 mg, 83% yield) is isolated as a white solid.

C. N-(2-Amino-5-chloro-phenyl)-2-{1-[3-(benzhydrylidene-amino)-4-cyano-benyl]-2-oxo-piperidin-4-yl}-acetamide.

To a slurry of the {1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid (190 mg, 0.422 mmol) in THF (5 mL) and methylene chloride (3 mL) is added triethylamine (0.09 ml, 0.633 mmol). The solution is cooled to 0 °C , and 1M isopropyl chloroformate in toluene (0.422 mL, 0.422 mmol) is added. The homogenous mixture is allowed to warm to room temperature, and 4-chloro-1,2-phenylene-diamine (150 mg, 1.06 mmol) is added. The reaction is stirred at room temperature overnight. The volatile solvents are removed, and the resulting residue is chromatographed (SiO_2, 5%MeOH/EtOAc) to give N-(2-amino-5-chloro-phenyl)-2-{1-[3-(benzhydrylidene-amino)-4-cyano-benyl]-2-oxo-piperidin-4-yl}-acetamide (200 mg, 82% yield). $C_{34}H_{30}ClN_5O_2$ MS m/z: 576, 578.

D. 2-(Benzhydrylidene-amino)-4-[4-(6-cloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl}-benzonitrile.

The acetamide (200 mg, 0.35 mmol) is dissolved in 2 mL of acetic acid and refluxed for three hours. The acetic acid is removed, and the residue taken up in ethyl acetate and washed with saturated sodium bicarbonate. Concentration of the solvent afforded 2-(benzhydrylidene-amino)-4-[4-(6-cloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl}-benzonitrile (200 mg, 100% yield) which is used without further purification. $C_{34}H_{28}ClN_5O_5$ MS m/z:+ 558, 560.

E. 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt

The above benzonitrile (220 mg, 0.36 mmol) is dissolved in 5 ml of methanol. Hydrochloric acid is bubbled into the ice-cooled methanol solution followed by three drops of water. After stirring at room temperature for one hour, the MeOH is removed. The resulting white solid is titurated with EtOAc. After drying under high vacuum, 2-amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (145.6 mg, 87% yield) is obtained as a white solid. $C_{21}H_{20}ClN_5O$: MS m/z: 394,396.

EXAMPLE 815. 4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzamidine

Hydrochloric acid is bubbled into an ice cooled solution of 4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile (127 mg, 0.336 mmol) in 10 mL of methanol. The solution also contained 3Å molecular sieves. The reaction is stored at -30 for forty-eight hours. The methanol is condensed on the rotovap. Fresh methanol (15 mL) is added followed by a stream of ammonia gas. The reaction is heated to reflux for two and half hours. The reaction mixture is filtered at room temperature. Methanol is removed from the mother liquor. The resulting residue is purified by reverse phase HPLC (0-50 % ACN/H_2O). The product is isolated as a white solid with a melting point of 105-110 °C . $C_{21}H_{22}ClN_5O$ MS m/z: 396,398. Anal. cald. for $C_{21}H_{22}ClN_5O \cdot 2C_2HF_3O_2$: C, 48.13; H, 3.88; N,11.22. Found: C, 45.05; H, 3.52; N, 9.89.

EXAMPLE 816. 1-(4-Amino-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one.

To a solution of 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (143 mg, 0.308 mmol), EXAMPLE 814, Part E, in 2 mL of ethanol is added triethylamine (0.05 mL, 0.366 mmol), glacial acetic acid (0.02mL, 0.366 mmol) and triazine (15 mg, 0.183 mmol). The resulting mixture is refluxed overnight. The volatile solvents are removed on the rotovap, and the residue is purified by reverse phase HPLC (0 - 50% Acetonitrile/H_2O). The desired product (110 mg, 55% yield) is isolated as a white powder with a melting point of 128-132 °C . $C_{22}H_{21}ClN_6O$ MS m/z: 421, 423. Anal. calcd. for $C_{22}H_{21}ClN_6O$: C, 48.12; H, 3.57; N, 12.95. Found: C, 45.79; H, 3.68; N, 11.94. H NMR (CD_3OD) δ: 8.67 (s, 1H); 8.31 (d, 1H, J = 4.0 Hz); 7.83-7.55 (m, 5H); 4.93-4.73 (m, 2H); 3.48-3.42 (m, 2H); 3.31-3.21 (m, 2H); 2.71-2.58 (m, 2H); 2.43-2.33 (m, 1H); 2.07- 2.01 (m, 1H); 1.82 - 1.69 (m, 1H).

EXAMPLE 817. 4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(2,4-diamino-quinazolin-7-ylmethyl)-piperidin-2-one

2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (70 mg, 0.15 mmol), EXAMPLE 814, Part E, pyridine (1.0 mL) and freshly made chloroformamide hydrochloride (150 mg, 1.33 mmol) are placed in a sealed tube and heated to 200 °C . The resulting mixture is heated for twenty four hours. The crude reaction mixture is directly purified by reverse phase HPLC (0-50% ACN/H_2O). The product (53 mg, 45% yield) is isolated as a tanish solid. $C_{22}H_{22}ClN_7O$ MS m/z: 436,438. Anal. calcd. for $C_{22}H_{22}ClN_7O$: C, 43.23; H, 3.24; N, 12.60. Found: C, 43.16; H, 3.44; N, 13.40.

EXAMPLE 818. 1-(4-Amino-2-methyl-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one.

A stream of hydrogen chloride gas is bubbled intermittently through an ice-cold mixture of 2-amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (57 mg, 0.123 mmol), EXAMPLE 814, Part E, and acetonitrile (0.03 mL, 0.93 mmol) in 1.5 mL of dioxane for six hours. The dioxane is removed; the residue is purified by reverse phase HPLC (0-40 % ACN/H_2O). The desired product (9.5 mg, 12% yield) is isolated as a clear wax. $C_{23}H_{23}ClN_6O$ MS m/z : 435, 437.

The following compounds are prepared using the methods described above.

Example	Name	m/z [M+H]
819	(3S, 5R)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443
820	(3S,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443
821	4-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl}-benzamidine	431, 433
822	(3R,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443

EXAMPLE 823. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide.

A. 4-tert-Butoxycarbonylmethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid benzyl ester (4.68g, 20mmol) in 20 mL of DMF at) 0°C is added sodium hydride (60%, 880 mg, 22 mmol). The suspension is stirred at ambient temperature for one t-butyl bromoacetate (4.68 g, 24 mmol) is added. The resulting mixture is stirred at ambient temperature overnight. After dilution with ethyl acetate (200 mL), the mixture is washed with brine (3 x 50 mL). The crude residue obtained from concentration of the organic phase is chromatographied on silica gel (30% ethyl acetate/Hexane) to give 5.57 g (80%) of 4-tert-butoxycarbonylmethyl-3-oxopiperazine-1-carboxylic acid benzyl ester as a white solid.

B. (2-Oxo-piperazin-1-yl)acetic acid tert-butyl ester.

4-tert-Butoxycarbonylmethyl-3-oxopiperazine-1-carboxylic acid benzyl ester (2.0g, 5.75 mmol) is dissolved in 20 mL of methanol and 2 mL of acetic acid. Palladium (5%) on carbon (100 mg) is added, and the reaction mixture is stirred in an atmosphere of hydrogen overnight. The mixture is filtered and concentrated. Ethyl acetate is added, and the mixture is neutralized to pH 7 using 1N NaOH. The organic layer is concentrated to give (2-oxo-piperazin-1-yl)acetic acid tert-butyl ester (1.22g).

C. [4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester.

To a solution of (2-oxo-piperazin-1-yl)acetic acid tert-butyl ester (1.22 g, 5.7 mmol) in 10 ml of methylene chloride is added triethylamine (1.2 mL, 8.55 mmol) and 6-chlorobenzothiophenesulfonyl chloride (1.52 g, 5.7 mmol). The reaction mixture is stirred overnight at ambient temperature. Flash column chromatography (50 % ethyl acetate / hexane) affords 2.3 g (92%) of [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester.

D. [4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]-acetic acid.

[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester (500 mg, 1.13 mmol) is dissolved in 1 mL of trifluoroacetic acid and 3 mL of CH_2Cl_2. The solvents are azeotropically removed with toluene. [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid (438 mg) is isolated as a white solid.\

E. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide.

To a slurry of [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid (47 mg, 0.12 mmol) in 2 mL of tetrahydrofuran is added Et_3N (0.025 mL, 0.18 mmol). The mixture is cooled to 0°C, and 1M solution of isopropyl chloroformate in toluene (0.12 mL, 0.12mmol) is added. The mixture is stirred for fifteen minutes and histamine (13.3 mg, 0.12 mmol) is added. The mixture is stirred overnight at room temperature. Reverse phase HPLC ($AcCN/H_2O$/TFA) affords 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide trifluoroacetic acid salt (17 mg, 25%) as a solid. mp 77-82°C; MS m/z 482 (M+H).

The followin compounds are prepared from the appropriate starting materials using the method of EXAMPLE 823.

Example	Name	m/z [M+H]
824	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-4-yl-acetamide	465, 467
825	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-3-ylmethyl-acetamide	479, 481
826	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-piperidin-4-yl-acetamide	471, 473
827	N-(1-Carbamimidoyl-piperidin-4-yl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	513, 515
828	5-(2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetylamino}-ethyl)-imidazole-1-carboxylic acid ethyl ester	554, 556
829	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyrimidin-4-yl-acetamide	466, 468
830	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-phenyl-acetamide	464, 466
831	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(9H-purin-6-yl)-acetamide	506, 508
832	N-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	509, 511
833	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-imidazol-1-yl-propyl)-acetamide	496, 498
834	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-imidazol-4-yl)-ethyl]-acetamide	496, 498
835	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-4-yl-ethyl)-acetamide	493, 495
836	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(3-methyl-3H-imidazol-4-yl)-ethyl]-acetamide	496, 498
837	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-2-yl-ethyl)-acetamide	493, 495
838	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-3-yl-ethyl)-acetamide	493, 495
839	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-imidazol-1-yl-ethyl)-acetamide	482, 484
840	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-	495, 497

	N-[2-(1-methyl-1H-pyrrol-2-yl)-ethyl]-acetamide	
841	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(5-methyl-1H-imidazol-4-yl)-ethyl]-acetamide	496, 498
842	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(4-dimethylamino-[1,3,5]triazin-2-yl)-acetamide	510, 512
843	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-pyridin-4-yl-acetamide	479, 481
844	N-[2-(2-Amino-pyridin-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	508, 510
845	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(4-methyl-thiazol-5-yl)-ethyl]-acetamide	513, 515
846	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-thiazol-4-yl-ethyl)-acetamide	499, 501
847	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-guanidino-propyl)-acetamide trifluoroacetic acid salt	487, 489
848	N-(3-Amino-propyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	445, 447
849	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-mercapto-1H-imidazol-4-yl)-ethyl]-acetamide	514, 516
850	N-[2-(2-Amino-thiazol-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	514, 516
851	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-(2-pyridin-4-yl-ethyl)-acetamide	507, 509
852	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-methylsulfanyl-1H-imidazol-4-yl)-ethyl]-acetamide	528, 530

EXAMPLE 853. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one.

A. 3-Oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester.

3-Oxo-piperazin-1-carboxylic acid benzyl ester (702 mg, 3.0 mmol) is dissolved in dimethylformamide (10 mL) and cooled to 0°C . Sodium hydride (60%, 148 mg, 3.7 mmol) is added, followed by the addition of 5-(3-chloro-propenyl)-1-trityl-1H-imidazole (473 mg, 1.2 mmol). The resulting mixture is left to stir at room temperature overnight. Most of the dimethylformamide is removed on the high vacuum. The reaction mixture is diluted with ethyl

acetate (250 mL) and quenched with water. The two layers are separated and ethyl acetate (2x 100 mL) is used to extract and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (50% EtOAc/hexane) to give 3-oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester (360 mg) as the desired product.

B. 4-[3-(3-tert-Butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

3-Oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester (360 mg, 0.62 mmol) is stirred vigorously in a 30% solution of trifluoroacetic acid and methylene chloride (10 mL). After stirring for three hours, the trityl group is removed. The volatile solvents are removed in vacuo, and the crude product is taken-up in methylene chloride (10 mL). Pyridine (0.5 ml) and Di-tert-butyl dicarbonate (176 mg, 0.81 mmol) is added to the solution, and the resulting mixture is left to stir overnight. The reaction mixture is condensed and purified by flash column (SiO_2, 20% EtOAc/Hexane) to give 4-[3-(3-tert-butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester (100 mg).

C. 5-{3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester.

Palladium on carbon (10 %, 15 mg) is added to a solution of 4-[3-(3-tert-butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester (50 mg, 0.114 mmol) in 5 mL of methanol. The reaction mixture is left to stir in an atmosphere of hydrogen overnight. The palladium is filtered off, and the volatile solvents are removed on the rotovap. The crude product (50 mg, 0.114 mmol) is redissolved in methylene chloride (5 mL). Triethylamine (0.06 ml, 0.43 mmol) 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (39 mg, 0.15 mmol) is added, and the resulting mixture is stirred overnight. The crude product is directly purified by flash column (SiO_2, 30% EtOAc/Hexane) to afford 5-{3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester (30 mg).

D. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one:

5-{3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester (30 mg, 0.055 mmol) is stirred vigorously in a 30 % solution of trifluoroacetic acid and methylene chloride (2 mL). The reaction is complete after stirring for three hours. The volatile solvents are removed on the rotovap, and the gummy solid is titurated

with ether several times to afford 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one trifluoroacetic acid salt (30 mg) as a yellow solid. $C_{18}H_{19}ClN_4O_3S_2$ (m/z)+: 439, 441. Anal cald. for $C_{18}H_{19}ClN_4O_3S_2 \cdot C_2HF_3O_2$: C, 43.44; H, 3.65; N, 10.13. Found C, 42.03; H, 3.55; N, 8.26.

The following compounds are prepared using the methods described above.

Example	Name	m/z [M+H]
854	4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxamidine	470, 472 Cl pattern
855	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperazin-1-yl-propyl)-piperazin-2-one	457, 459 Cl pattern
856	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-pyridin-4-yl-propyl)-piperazin-2-one	450, 452 Cl pattern
857	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-piperidin-4-yl-butyl)-piperazin-2-one	470, 472 Cl pattern
858	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-piperidin-4-yl-ethyl)-piperazin-2-one	442
859	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperidin-4-yl-propyl)-piperazin-2-one	456

EXAMPLE 860. 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one.

A. 3-Methoxymethyl-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared by the method in EXAMPLE 66, Part A, substituting 5-(4-bromomethyl-phenyl)-2-methoxy-pyridine for 4-bromomethyl tolynitrile and 2-methoxymethyl-3-oxopiperazin-1-carboxylic acid benzyl ester for 3-oxopiperazin-1-carboxylic acid benzyl ester. MS (ISP) m/z 476, (M+H).

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one

The title compound is prepared by deprotecting 3-methoxymethyl-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester as described in EXAMPLE 75, Part C. The crude amine is then coupled as described in EXAMPLE 123 with 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid, EXAMPLE 25. MS (ISP) m/z 516, 518, (M+H), Cl pattern.

The following compounds are prepared according to the method of Example 860.

Example	Name	m/z [M+H]
861	4'-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile	522, 524 Cl pattern
862	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-3-hydroxy-benzyl)-piperazin-2-one	471, 473 Cl pattern
863	1-Benzyl-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	421,423 Cl pattern
864	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-benzyl)-piperazin-2-one	455, 457 Cl pattern
865	4-[(4-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516, 518 Cl pattern
866	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	502, 504 Cl pattern
867	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516, 518 Cl pattern
868	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	502, 504 Cl pattern
869	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	482
870	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	468
871	1-Biphenyl-4-ylmethyl-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	
872	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	498, 500 Cl pattern
873	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	512, 514 Cl pattern

EXAMPLE 874. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one.

A. 2-Amino-4-(2-oxo-piperazin-1-ylmethyl)-benzonitrile.

To a solution of 4-(3-Amino-4-cyano-benzyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester hydrochloride (4.0 g, 10.0mmol) in CH_3OH (45 ml) and CH_2Cl_2 (10 ml) is added 10% Pd

on carbon (0.6 g). The mixture is stirred under an atmosphere of H_2 for 2 hours then is filtered through a pad of celite. The filtrate is concentrated and the residue purified by column chromatography eluting with 10% 7M NH_3 in CH_3OH / CH_2Cl_2 to yield the title compound (1.62 g, 7.0 mmol). ^1H NMR (DMSO,300MHz) δ 7.34 (d, 1H), 6.64 (s, 1H), 6.46 (d, 1H), 6.04 (bs, 2H), 4.40 (s, 2H), 3.28 (s, 2H), 3.14 (m, 2H), 2.87 (m, 2H), 2.77 (bs, 1H). MS (ion spray): m/z 231 $(M+H)^+$.

B. 2-Amino-4-[4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile.

To a cooled solution (0° C) of 2-Amino-4-(2-oxo-piperazin-1-ylmethyl)-benzonitrile (0.345 g, 1.5 mmol) in DMF (2 ml) is added finely powdered anhydrous K_2CO_3 (0.311 g, 2.25 mmol) and allowed to stir for 20 minutes. To this mixture is added a solution of 2-bromomethyl-benzo[b]thiophene (0.392 g, 1.5 mmol) in DMF (3 ml), the cold bath removed and allowed to stir for 2 hours. The reaction mixture is concentrated under high vacuum and the residue purified by column chromatography eluting with 55% EtOAc/ 5% CH_3OH/ hexane to yield the title compound (0.477 g, 1.16 mmol) as a white solid. ^1H NMR (DMSO,300MHz) δ 8.06 (d, 1H), 7.78 (d, 1H), 7.37 (m, 3H), 6.64 (s, 1H), 6.44 (d, 1H), 6.09 (bs, 2H), 4.42 (s, 2H), 3.88 (s, 2H), 3.21 (m, 4H), 2.72 (m, 2H). MS (ion spray): m/z 411, 413 $(M+H)^+$, Cl pattern.

C. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one.

To a cooled solution (0° C) of 2-Amino-4-[4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile (0.365 g, 0.89 mmol) in concentrated HCl (2.1 ml) is added dropwise a solution of sodium nitrite (0.068 g, 0.98 mmol) in H_2O (0.2 ml). The reaction mixture is added to a cooled solution (0° C) of tin (II) chloride dihydrate (1.61 g, 7.12 mmol) in concentrated HCl (0.62 ml) and H_2O (3 ml). The precipitate is collected by vacuum filtration and dried under high vacuum. The crude solid is purified by column chromatography eluting with 10% 7M NH_3 in CH_3OH / CH_2Cl_2 to yield the title compound (0.144 g, 0.34 mmol) as a yellow solid. ^1H NMR (DMSO,300MHz) δ 11.35 (bs, 1H), 8.05 (d, 1H), 7.78 (d, 1H), 7.64 (d, 1H), 7.37 (m, 2H), 7.08 (s, 1H), 6.78 (d, 1H), 5.75 (s, 1H), 5.40 (bs, 1H), 4.58 (s, 2H), 3.88 (s, 2H), 3.20 (m, 4H), 2.70 (bt, 2H). MS (ion spray): m/z 426 $(M+H)^+$. Anal. cald. for $C_{21}H_{20}N_5OSCl;(H_2O)_{0.25}$: C, 58.6; H, 4.8; N, 16.3. Found C, 58.6; H, 4.7; N, 15.9. M.P.= 246-248°C.

EXAMPLE 875. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one.

A. 2-Amino-4-{4-[3-(5-chloro-thiophen-2-yl)-allyl]-2-oxo-piperazin-1-ylmethyl}-benzonitrile.

Using essentially the same procedure as in EXAMPLE 874, Part B using 2-(3-bromo-propenyl)-5-chloro-thiophene is obtained the title compound. MS (EI): m/z 386, 388 (M^+), Cl pattern.

B. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one.

Using essentially the same procedure as in EXAMPLE 874, Part C there is obtained the title compound. ^{1}H NMR (DMSO, 300MHz) δ 11.32 (bs, 1H), 7.62 (d, 1H), 7.06 (s, 1H), 7.02 (d, 1H), 6.96 (d, 1H), 6.78 (d, 1H), 6.67 (d, 1H), 5.96 (m, 1H), 5.32 (bs, 2H), 4.57 (s, 2H), 3.19 (bt, 2H), 3.12 (m, 4H), 2.64 (bt, 2H). MS (EI): m/z 401, 403 (M^+), Cl pattern. Anal. cald. for $C_{19}H_{20}ClN_5OS$: C, 56.8; H, 5.0; N, 17.4. Found C, 56.6; H, 4.8; N, 17.2. M.P.= 167-169°C

EXAMPLE 876. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

A. 2-Amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperzin-1-ylmethyl]-benzonitrile.

Using essentially the same procedure as in EXAMPLE 874, Part B except using 6-chloro-benzo[b]thiophene-2-sulfonyl chloride, EXAMPLE 1, is obtained the title compound. MS (ion spray): m/z 461, 463 $(M+H)^+$, Cl pattern.

B. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

Using essentially the same procedure as in EXAMPLE 874, Part C there is obtained the title compound. ^{1}H NMR (DMSO, 300MHz) δ 11.29 (s, 1H), 8.35 (s, 1H), 8.18 (s, 1H), 8.08 (d, 1H), 7.58 (m, 2H), 7.05 (s, 1H), 6.70 (d, 1H), 5.30 (bs, 2H), 4.56 (s, 2H), 3.84 (s, 2H), 3.40 (m, 2H), 3.30 (m, 2H). MS (ion spray): m/z 476, 478 $(M+H)^+$, Cl pattern. Anal. cald. for $C_{20}H_{18}ClN_5O_3S_2$: C, 50.5; H, 3.8; N, 14.7. Found C, 50.3; H, 3.6; N, 14.5. M.P.=274-276°C.

The following compounds are prepared using the procedures described above.

Example	Name	m/z
877	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(S)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamidine	441, 443 Cl pattern
878	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(R)-methyl-3,6-dioxo-	441, 443

	piperazin-1-ylmethyl]-benzamidine	Cl pattern
879	3-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine	427, 429 Cl pattern
880	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine	427, 429 Cl pattern

Example 881: 5-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester.

A. 5-Chloro-indole-1-carboxylic acid tert-butyl ester:

To a suspension of NaH (60%, 1.0 g, 25.2 mmol) in anhydrous THF (50 mL) at 0 °C is added 5-chloro-indole (2.73 g, 18.0 mmol). After 20 min, di-*t*-butyl dicarbonate (4.71 g, 21.6 mmol) is added and the reaction mixture is maintained at 0 °C for 4 h. The reaction mixture is partitioned between diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL) and the layers are separated. The aqueous phase is extracted twice with diethyl ether (2 x 50 mL) and then the combined organic extracts are washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 30:1 to 20:1) to provide 4.0 g (89%) of 5-chloro-indole-1-carboxylic acid tert-butyl ester as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, 9H), 6.50 (d, J = 3.5 Hz, 1H), 7.27 (m, 1H), 7.52 (s, 1H), 7.60 (d, J = 3.3 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H) ppm.

B. 5-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester.

To a solution containing 5-chloro-indole-1-carboxylic acid tert-butyl ester (4.0 g, 15.9 mmol) in anhydrous THF (60 mL) at -78 °C is added 1.7 M *t*-BuLi in pentane (11.2 mL, 19.0 mmol) dropwise from a syringe. After 1 h at -78 °C, SO_2 gas is introduced into the reaction mixture for 5-10 min. The reaction mixture is warmed to ambient temperature and then concentrated to dryness *in vacuo*. The resulting solid is then suspended in hexane (80 mL), cooled to -60 °C, and SO_2Cl_2 (2.6 g, 19.0 mmol) is added dropwise.

After 16 h, the reaction mixture is concentrated to dryness and the residue is partitioned between EtOAc (100 mL) and aqueous $NaHCO_3$ (100 mL). The layers are separated and the organic phase is washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 100:1 to 30:1) to afford 3.35 g (60%) of 5-chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester as a off-white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 9H), 7.52 (dd, J = 9.1, 2.0 Hz, 1H), 7.60 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 9.1 Hz, 1H) ppm.

Example 882: 6-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester

A. 6-Chloro-indole-1-carboxylic acid tert-butyl ester.

To a suspension of NaH (60%, 0.41 g, 10.3 mmol) in anhydrous THF (20 mL) at 0 °C is added 6-chloro-indole (1.2 g, 7.4 mmol). After 10 min, di-*t*-butyl dicarbonate (1.93 g, 8.88 mmol) is added and the reaction mixture is slowly warmed to ambient temperature overnight. The reaction mixture is concentrated to dryness and the residue is partitioned between diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL) and the layers are separated. The aqueous phase is extracted twice with diethyl ether (2 x 50 mL) and then the combined orgaic extracts are washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 10:1) to provide 6.0 g (82%) of 6-chloro-indole-1-carboxylic acid tert-butyl ester as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, 9H), 6.52 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 8.3, 1.8 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 3.6 Hz, 1H), 8.18 (s, 1H) ppm.

B. 6-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester.

To a solution containing 6-chloro-indole-1-carboxylic acid tert-butyl ester (2.1 g, 8.34 mmol) in anhydrous THF (30 mL) at -78 °C is added 1.7 M *t*-BuLi in pentane (6 mL, 10.2 mmol) dropwise from a syringe. After 1 h at -78 °C, SO_2 gas is introduced into the reaction mixture for 5-10 min. The reaction mixture is warmed to ambient temperature and then concentrated to dryness *in vacuo*. The resulting solid is then suspended in hexane (80 mL), cooled to -60 °C, and SO_2Cl_2 (0.81 g, 10.0 mmol) is added dropwise. After 16 h, the reaction mixture is concentrated to dryness and the residue is partitioned between diethyl ether (100 mL) and aqueous $NaHCO_3$ (100 mL). The layers are separated and the organic phase is washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 100:1 to 30:1) to afford 5.34 g (64%) of 6-chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester as a off-white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 9H), 7.35 (dd, J = 8.5, 1.8 Hz, 1H), 7.63 (m, 2H), 8.31 (m, 1H) ppm.

EXAMPLE 883. 3-(5-Chloro-thiophen-2-yl)-3-oxo-propionic acid tert-butyl ester.

A 0.25M THF solution of tert-butyl acetate (2.90 g, 25 mmol) is added dropwise to a cold (-78°C) solution of potassium bis(trimethylsilyl)amide (100 ml of a 0.5M toluene solution) and ethyl 5-chlorothiophene-2-carboxylate (Lancaster)(4.77 g, 25 mmol) in 50 ml of THF. The reaction is allowed to warm to 0°C over one hour. After stirring an additional hour at 0°C, the reaction is poured into 100 ml of a 1M HCl solution. The organic layer is extracted with brine

and evaporated *in vacuo*. The crude residue is purified by flash column chromatography eluting with 5% ethyl acetate/hexane to provide the product (4.54 g, 17 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7,53 (d, 1H), 6.98 (d, 1H), 3.78 (3, 2H), 1.50 (s, 9H).

EXAMPLE 884 Methyl06-Chloro-benzofurancarboxylate.

A. 4-Chloro-2-hydroxy-benzylalcohol.

To 7 g of $LiAlH_4$ in 200 ml of THF is added portionwise 15 g of 4-chlorosalicylic acid. The resulting mixture is heated under reflux for one hour, cooled and stirred at room temperature for 21 hours. Water (7 ml) in THF (50 ml) is added dropwise, followed by 1N hydrochloric acid (250 ml), concentrated hydrochloric acid (50 ml) and ethyl acetate (200 ml). After filtration on a pad of celite the two layers are separated, the organic layer washed with brine, dried over magnesium sulfate, concentrated. The brown oil is dissolved in iso-propyl ether and filtered on a short column of silica gel. After concentration the solid is crystallized in cyclohexane, filtered, washed and dried to give 4-chloro-2-hydroxy-benzylalcohol as a white solid (9.7 g, 70% yield)

$C_7H_7ClO_2$ MS (M^+) m/z: 158, 160, Cl pattern.

B. Ethyl-(2-hydroxymethyl-5-chloro-phenoxy)-acetate.

To a solution of 4-chloro-2-hydroxy-benzylalcohol (9.7 g, 61.3 mmol) in 100 ml of DMF is added potassium carbonate (17 g, 123.1 mmol), and the resulting suspension is stirred for 15 minutes at room temperature. Ethyle bromoacetate (7.96 ml, 67 mmol) is added and the mixture is stirred at room temperature for two days. The mixture is poured in 500 ml of water, extracted with ethyl acetate (500 ml). The ethyl acetate layer is separated, washed with water (500 ml), brine (500ml) and dried over magnesium sulfate. After concentration ethyl-(2-hydroxymethyl-5-chloro-phenoxy)-acetate is obtained as a white solid (13.7 g, 91 % yield)

$C_{11}H_{13}ClO_4$, MS (M^+) m/z: 244, 246, Cl pattern.

C. Ethyl-(2-formyl-5-chloro-phenoxy)-acetate.

Ethyl-(2-hydroxymethyl-5-chloro-phenoxy)-acetate (2.44 g, 10 mmol) is dissolved in 40 ml of chloroform. Activated manganese (IV) oxyde (8.7 g ,100 mmol) is added in two portions and the resulting suspension is stirred at room temperature for 5 hours. After fitration on a pad of celite and concentration ethyl-(2-formyl-5-chloro-phenoxy)-acetate (2.18 g , 90% yield) is obtained as a pale yellow oil.

$C_{11}H_{11}ClO_4$, MS $(M+H)^+$: 243, Cl pattern.

D. Methyl-6-chloro-benzofurancarboxylate

Magnesium (1.2 g, 50 mmol) is dissolved in 40 ml of methanol. A solution of ethyl-(2-formyl-5-chloro-phenoxy)-acetate (2.1 g , 8.65 mmol) in 15 ml of methanol is added and the resulting mixture is heated under reflux for one hour, cooled , poured in 1N hydrochloric acid (150ml). After stirring at room temperature the yellow solid is filtered, washed thoroughly with water and dried. Methyl-6-chloro-benzofurancarboxylate is obtained as a yellow solid (0.835 g , 46 % yield).

$C_{10}H_7ClO_3$, MS ($M^{+\cdot}$) : 210, Cl pattern

EXAMPLE 885. 2-Cyclopentyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, sustitituting CBZ-1-amino-cyclopentyl-1-caboxylic acid for Cbz-O-methyl-serine. ^1H NMR (CD_3OD, 300MHz) δ 7.32 (m, 5H), 5.12 (s, 2H), 3.71 (m, 2H), 3.28 (m, 2H), 2.17 (m, 4H), 1.8 (m, 4H). MS (ion spray) m/z 289, (M+H).

EXAMPLE 886 (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

A. (+/-)-cis-decahydroquinoxalin-2-one.

cis-1,2-Diaminocyclohexane (4.1 g, 36 mmol) is dissolved in 150 ml of H_2O. Chloroacetic acid (3.4 g, 36 mmol) in 50 ml of H_2O is added dropwise at 10° C in 5 minutes, then potassium carbonate (7.9 g , 57 mmol) in 30 ml of H_2O is added dropwise at 10 C. The reaction mixture is allowed to warm slowly to room temperature and stirred 24 hours. The solution is heated at 90°C for 2 hours, concentrated. The resulting solid is taken-up in boiling toluene (100 ml), filtered while hot, concentrated to give (+/-)-cis-decahydroquinoxalin-2-one (0.8 g, 14% yield) as a white solid.

$C_8H_{14}N_2O$, MS (M+H)+ : 155

B. (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

(+/-)-cis-decahydroquinoxalin-2-one (0.8 g, 5.19 mmol) is suspended in 25 ml of H_2O. $NaHCO_3$ (0.87 g, 10.35 mmol) is added and the reaction mixture is cooled to 10° C. Benzylchloroformate (1 ml, 6.68 mmol) is added dropwise to the vigorously stirred mixture. After 20 hours at room temperature the solid is filtered, washed thoroughly with H_2O, air-dried. The title compound (1.46g, 98 % yield) is obtained as a white solid.

$C_{16}H_{20}N_2O_3$, MS $(M+H)^+$: 289

EXAMPLE 887 5-Methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester.

A. [1-(Methoxy-methoxyl-methyl-carbamoyl]-carbamic acid benzyl ester.

To a solution of N-Cbz-L-alanine (12.9 g, 66.7 mmol) and N,O-dimethyl hydroxyl amine hydrochloride (7.2 g, 73.8 mmol) in CH_2Cl_2 (200mL) is added TBTU (21.43 g, 66.7 mmol) and diisopropyl ethyl amine (25.9 g, 231.5 mmol). After 6 h, the solution is diluted with CH_2Cl_2 (200mL) and is washed with 1N HCl, H_2O, and sat. NaCl. The organic layer is dried over MgSO4, filtered and concentrated to give the title compound as an oil. MS (EI) m/z 266, (M+).

B. [1-Methyl-2-oxo-ethyl]-carbamic acid benzyl ester.

To a solution of [1-(methoxy-methoxyl-methyl-carbamoyl]-carbamic acid benzyl ester (66.7 mmol) in THF (160mL) is added a 1.0M solution of lithium aluminum hydride in THF (81.1 mmol, 81.1mL) dropwise at 0°C. After 20 min., 1N $KHSO_4$ is added drpwise. The solution is diluted with H_2O (200mL) and the pH is adjusted to 3 with 1N $KHSO_4$. The resulting solution is extracted with Et_2O. The Et2O extracts are wshed with H2O and sat. NaCl. The organic layer is dried over MgSO4, filtered and concentrated to give the title compound (12g, 66 mmol) of the title compound. MS (EI) m/z 177, (M+).

C. 2-[2-Benzyloxycarbonylamino-propylamino]-pentanoic acid methyl ester.

To a solution of [1-methyl-2-oxo-ethyl]-carbamic acid benzyl ester (12.3 g, 69 mmol) and norvaline methylester hydrochloride (11.6 g, 69mmol) in MeOH (300mL) is added diisopropyl ethyl amine (9.4 g, 73 mmol) and 2 drops of acetic acid. After 10 min., $ZnCl_2$ (9.46 g, 69mmol) and sodium cyanoborohydride (8.72g, 14 mmol) is added. The solution is stirred at ambient for 16 h. The solution is then concentrated. The residue is dissolved in EtOAc and 1N $KHSO_4$. The oraganic layer is washed with 1N $KHSO_4$, H_2O, and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentated. The crude product is purified by column chromatograghy eluting with a gradient of 20% EtOAc/hexane to 40% EtOAc/hexanes. The title compound (8.6 gm, 26.6 mmol) isobtained as a foam. MS (ion spray) m/z 323, (M+H).

D. 5-Methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester.

A solution of 2-[2-benzyloxycarbonylamino-propylamino]-pentanoic acid methyl ester (6.6g, 20.5 mmol) in MeOH (100mL) is added 4 drops of AcOH and 0.65g of 10% Pd/C. The atmosphere above the reaction is replaced by hydrogen. The reaction is stirred overnight. The solution is then filtered to give a clear solution. The solution is concentrated and the residue is

dissolved in EtOH. The solution is heated to reflux for 2 h. After this time the ethanolic solution is concentrated. The residue is dissolved in CH_2Cl_2 (60 mL) and BOC_2O (3.3 g, 15.1 mmol) followed by DMAP (0.16 g, 1.3 mmol) are added. After 16 h, the reaction is diluted with CH_2Cl_2 (150mL)and washed with 1N KHSO4, H2O and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the title compound (3.1 g, 12.1 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.78 (s, 1H), 4.36 (m, 1H), 4.02 (m, 1H), 3.48 (m, 2H), 2.49 (m, 1H), 1.77 (m, 1H), 1.55 (m, 1H), 1.39 (s, 9H), 1.02 (d, 3H), 0.8 (m, 3H). MS (ion spray) m/z 257, (M+H).

EXAMPLE 888 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine

A. 3-[3-Amino-4-cyanobenzyl]-2-propyl-5-methyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

To a solution of 5-methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester (3.07 g, 12 mmol), prepared as described in EXAMPLE 887, .in THF (150 mL) is added t-BuOK (1.3 g, 11 mmol). The solution is stirred at ambient temperatures for 25 min. After this time, the reaction mixture is cooled to 0°C and 2-amino-4-bromomethyl-benzonitrile (2.9 g, 11.3 mmol) and 18-C-6 (15 mgs) are added. The solution is allowed to warm to ambient temperatures and is stirred for 16 h. After this time, 0.5 mL of a saturated NH_4Cl solution is added. The solution is concentrated. The residue is purified by column chromatograghy eluting with 20% EtOAc/CH_2Cl_2 to give the title compound as a white solid.
MS (ion spray) m/z 387, (M+H).

B. 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl-ester.

To a solution of 3-[3-amino-4-cyanobenzyl]-2-propyl-5-methyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.16 g, 3.0 mmol) in ethanol (30 mL) is added acetic acid (0.55 g, 9.0 mmol) and triazine (0.73 g, 9.0 mmol). The solution is refluxed overnight. After this time, the solution is concentrated. The residue is purified by column chromatography eluting with 5% MeOH/ CH_2Cl_2 to give the title compound (0.91 g) as a white solid.
MS (ion spray) m/z 414, (M+H).

C. 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine.

To a solution of 4-[4-amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl-ester (0.91 g, 2.2 mmol) in EtOAc (40 mL) is bubbbled HCl (gas) for

5 min. at 0°C. After this time, the solution is stirred at ambient temperatures for 15 min. The solution is concentrated. The residue is purified by column chromatograpghy eluting with 1:5:100 $NH_4OH/MeOH/CH_2Cl_2$. The title compound (0.5 g) is obtained as a white solid. ^1H NMR (300 MHz, CDOD) δ 8.40 (s, 1H), 8.04 (d, 1H), 7.52 (s, 1H), 7.36 (m, 1H), 5.10 (d, 1H), 4.45 (d, 1H), 3.55 (m, 2H), 3.10 (m, 1H), 2.81 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.44 (m, 2H), 1.29 (d, 3H), 0.96 (m, 3H).

MS (ion spray) m/z 314, (M+H).

Example 889: (*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester

A. (*S*)-2-Benzyloxycarbonylamino-3-methoxy-propionic acid methyl ester.

A solution containing Z-L-serine (30 g, 0.126 mol) in anhydrous DMF (500 mL) is cooled to 0 °C. Sodium hydride (60%, 11.05 g, 0.28 mol) is added portionwise over ~20 min and the mixture is left to stir for 1 h. Methyl iodide (23.5 mL, 0.38 mol) is added and the mixture is stirred for 30 min at 0 °C and then at room temperature for 2.5 h after which time TLC indicated complete consumption of starting material. Water (1200 mL) is added and the mixture is extracted with diethyl ether (4 x 200 mL). The combined organic extracts are washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4 and concentrated to afford 30 g of crude (*S*)-2-benzyloxycarbonylamino-3-methoxy-propionic acid methyl ester as a pale yellow oil.

B. (*R*)-(1-Hydroxymethyl-2-methoxy-ethyl)-carbamic acid benzyl ester.

Calcium chloride (16.63 g, 149.8 mmol) is added to a stirring suspension of sodium borohydride (11.33 g, 299.6 mmol) in ethanol (300 mL) at -40 °C. The heterogeneous mixture is warmed to -20 °C and stirred for 1 h. (*S*)-2-Benzyloxycarbonylamino-3-methoxy-propionic acid methyl ester (20 g, 74.9 mmol) in abs EtOH (250 mL) is then added via cannula transfer. The heterogeneous mixture is stirred at -20 °C for 3 h. The reaction is quenched with water (400 mL) and carefully acidified with 1. 0 M HCl. The aqueous layer is extracted with CH_2Cl_2 (4 x 200 mL) and the combined organic phases are washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to afford a colorless oil. The mixture is absorbed onto the silica gel and chromatographed on silica gel (hexane:EtOAc, 4:1 > 2:1 > 1:1 > 1:2) to afford 11.5 g (64%) of (*R*)-(1-hydroxymethyl-2-methoxy-ethyl)-carbamic acid benzyl ester as a colorless oil.

C. (*S*)-(1-Formyl-2-methoxy-ethyl)-carbamic acid benzyl ester.

To a solution of DMSO (3.56 mL, 50.21 mmol) in anhydrous CH_2Cl_2 (50 mL) at -78 °C is added 2.0 M oxalyl chloride in CH_2Cl_2 (12.55 mL, 25.1 mmol) via syringe. The mixture is stirred at -78 °C for 10 min, then a solution of (*R*)-(1-hydroxymethyl-2-methoxy-ethyl)-carbamic acid benzyl ester (5 g, 20.92 mmol) in anhydrous CH_2Cl_2 (100 mL) is added via cannula transfer. The mixture is stirred at -78 °C for 30 min. Triethylamine (14.6 mL, 104.6 mmol) is added and the mixture is placed in a 0 °C bath. The reaction is complete in 10 min.
The mixture is quenched with saturated $NaHSO_4$ (200 mL) and the product is extracted with CH_2Cl_2 (4 x 100 mL). The combined organic extracts are washed with brine (100 mL), dried over Na_2SO_4, and concentrated to afford (*S*)-(1-formyl-2-methoxy-ethyl)-carbamic acid benzyl ester as a yellow oil which is used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.63 (dd, J = 9.6, 4.5 Hz, 1H), 3.93 (dd, J = 9.6, 3.3 Hz, 1H), 4.36 (m ,1H), 5.13 (s, 2H), 5.68 (br d, 1H), 7.29-7.37 (m, 5H), 9.60 (s, 1H) ppm.

D. (*R*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid methyl ester.

To a solution of glycine methyl ester HCl (10.51 g, 83.68 mmol) in anhydrous MeOH (100 mL) at 0 °C is added a solution of (*S*)-(1-formyl-2-methoxy-ethyl)-carbamic acid benzyl ester (20.92 mmol) in anhydrous MeOH (20 mL). The solution is stirred at 0 °C for 10 minutes, then 1.0 M $NaBH_3CN$ in THF (31.38 mL, 31.38 mmol) is added and the now heterogeneous mixture is allowed to warm to room temperature and stir overnight. The mixture is concentrated to dryness, then partitioned between $NaHCO_3$ (200 mL) and EtOAc (200 mL). The layers are separated and the aqueous layer is extracted twice with EtOAc (100 mL) and the combined organic phases are washed with brine (100 mL), dried over Na_2SO_4, and concentrated to afford a yellow oil which is absorbed onto silica gel and chromatographed (CH_2Cl_2 => 1% MeOH/CH_2Cl_2 => 2% MeOH/CH_2Cl_2) to afford 3.9 g (60%) of *R*-(2-benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid methyl ester as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (br s, 1H), 2.71 (dd, J = 12.1, 5.7 Hz, 1H), 2.84 (dd, J = 12.2, 5.7 Hz, 1H), 3.32 (s, 3H), 3.39 (d, J = 8.6 Hz, 2H), 3.40-3.52 (m, 2H), 3.70 (s, 3H), 3.82 (m, 1H), 5.09 (s, 2H), 5.35 (br d, 1H), 7.25-7.35 (m, 5H) ppm. Mass spectrum (ion spray): *m/z* 331 (M+H).

E. (*R*)-6-methoxymethyl-piperazin-2-one.

(*R*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid methyl ester (3.9 g, 12.58 mmol) is dissolved in MeOH (~200 mL) and warmed in the presence of decolorizing charcoal for 1 h. The mixture is filtered through celite and the clear filtrate is concentrated. The residue is redissolved in MeOH (160 mL) and placed in a Parr bottle. Palladium-on-carbon (10%, 800 mg) is added and the mixture is hydrogenated for 5 h at 45 PSI. An additional

portion of Pd-on-C (250 mg) is added and the mixture left is reacted for 16 h at 45 PSI. The mixture is filtered through celite and concentrated to afford 1.5 g (83%) of (*R*)-6-methoxymethyl-piperazin-2-one as a yellow solid which is used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1,77 (br s, 1H), 2.70 (dd, J = 13.1, 7.2 Hz, 1H), 3.07 (dd, J = 13.1, 4.5 Hz, 1H), 3.26 (dd, J = 9.1, 7.7 Hz, 1H), 3.33 (s, 3H), 3.37-3.45 (m, 3H), 3.61 (m , 1H), 6.51 (br s, 1H) ppm.

F. (*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester.

(*R*)-6-methoxymethyl-piperazin-2-one (2.3 g, 16.0 mmol) is dissolved in anhydrous CH_2Cl_2 (60 mL) and cooled to 0 °C. Triethylamine (3.4 mL, 24.0 mmol) is added, followed, after 5 minutes, by allyl chloroformate (2.0 mL, 19.2 mmol). The mixture is allowed to warm to room temperature over 2 h when TLC analysis indicated that the reaction is complete.
The mixture is partitioned between water (100 mL) and CH_2Cl_2 (100 mL) and the layers are separated. The aqueous phase is extracted twice with CH_2Cl_2 (2 x 75 mL) and the combined organic phases are washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated to afford the crude product which is purified by flash silica gel chromatography (CH_2Cl_2 to 1%, 2%, 4% MeOH/CH_2Cl_2) to afford 3.41 g (93%) of (*R*)-3-methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (dd, J = 9.3, 7.4 Hz, 1H), 3.31 (s, 3H), 3.36 (m, 1H), 3.63 (m, 1H), 3.76 (m, 1H), 4.07 (ABq, Δ_{AB} = 39.9 Hz, J_{AB} = 18.5 Hz, 2H), 4.58 (d, J = 5.59 Hz, 2H), 5.21 (m, 2H), 5.88 (m, 1H), 7.05 (br, 1H) ppm.

Example 890: 6-Isopropyl-piperazin-2-one.

A. (*R*)-2-Benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester.

To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-butyric acid (5.0 g, 20.0 mmol) in anhydrous CH_2Cl_2 (20 mL) is added DMAP (258 mg, 2.0 mmol) followed by chilled EtSH (1.6 mL, 22.0 mmol). Dicyclohexylcarbodiimide (4.5 g, 22.0 mmol) is added in one portion and the reaction is complete after 30 min. The solid material is removed by vacuum filtration and the filtrate is concentrated. The crude product is purified by flash silica gel chromatography (hexane to 8:1 hexane/EtOAc) to provide (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.21 g, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H), 2.27 (m, 1H), 2.88 (q, J = 7.5 Hz, 2H), 4.35 (dd, J = 9.5, 4.6 Hz, 1H), 5.13 (s, 2H), 5.25 (br d, J = 9.5 Hz, 1H), 7.30-7.36 (m, 5H) ppm.

B. (*R*)-(1-Formyl-2-methyl-propyl)-carbamic acid benzyl ester.

To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.2 g, 17.6 mmol) in acetone (100 mL) is added Pd-on-C (10%, 233 mg). The heterogeneous mixture is cooled to 0 °C and Et_3SiH (8.4 mL, 53 mmol) is quickly added. After 30 min, the reaction mixture is filtered through a pad of celite and the clear filtrate is concentrated to a residue which is partitioned between hexane (200 mL) and acetonitrile (300 mL). The layers are separated and the ACN phase is washed once with hexane (100 mL) and then concentrated to afford crude (*R*)-(1-Formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g) which is used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (m, 1H), 4.31 (m, 1H), 5.09 (s, 2H), 5.45 (br, 1H), 7.30-7.45 (m, 5H), 9.65 (s, 1H) ppm.

C. (*R*)-(2-Benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester.

To a solution containing crude (*R*)-(1-formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g, 17.6 mmol) in anhydrous MeOH (100 mL) at 0 °C is added glycine ethyl ester hydrochloride (9.5 g, 70.4 mmol). After 10 min, 1.0 M $NaCNBH_3$ in THF (27 mL, 27 mmol) is added and the heterogeneous reaction mixture is allowed to warm to ambient temperature overnight.

The reaction mixture is concentrated and the residue is partitioned between diethyl ether (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The layers are separated and the aqueous layer is extracted twice with diethyl ether (2 x 200 mL). The combined organic extracts are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product which is purified by flash silica gel chromatography (hexane/EtOAc, 2:1 to 1:1) which provided 4.2 g (74%) of (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.25 (t, J = 8.4 Hz, 3H), 1.62 (br s, 1H), 1.80 (m, 1H), 2.65-2.70 (m, 2H), 3.37 (ABq, Δ_{AB} = 32.3 Hz, J_{AB} = 17.4 Hz, 2H), 4.16 (q, J = 8.4 Hz, 2H), 5.14 (s, 2H), 7.28-7.36 (m, 5H) ppm. Mass spectrum (ion spray): *m/z* 323 (M+H).

D. (*R*)-6-Isopropyl-piperazin-2-one.

To a Parr vessel charged with (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester (4.2 g, 13.0 mmol) in MeOH (130 mL) is added Pd-on-C (10%, 396 mmol). The reaction vessel is pressurized with 40 PSI hydrogen pressure and shaken for 4 h at ambient temperature. The reaction mixture is then filtered through celite and the filtrate is concentrated to provide 1.77 g (95%) of (*R*)-6-isopropyl-piperazin-2-one as an off-white solid which is used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.8 Hz, 3H),

0.97 (d, J = 6.8 Hz, 3H), 1.68 (sept, J = 6.7 Hz, 1H), 2.67 (dd, J = 12.8, 8.9 Hz, 1H), 3.09-3.22 (m, 2H), 3.46 (ABq, Δ_{AB} = 34.3 Hz, J_{AB} = 17.5 Hz, 2H), 5.97 (br s, 1H) ppm.

EXAMPLE 891 9-(4-Aminoquinazolin-7-ylmethyl)-6,9-diaza-spiro[4,5]decan-10-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-cyclopentyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 885, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.38 (s, 1H), 8.09 (d, 1H), 7.56 (s, 1H), 7.39 (d, 1H), 4.72 (s, 2H), 3.38 (m, 2H), 3.07 (m, 2H), 2.21 (m, 2H), 1.72 (m, 6H).

EXAMPLE 892 (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

A. (+/-)-cis-decahydroquinoxalin-2-one.

cis-1,2-Diaminocyclohexane (4.1 g, 36 mmol) is dissolved in 150 ml of H_2O. Chloroacetic acid (3.4 g, 36 mmol) in 50 ml of H_2O is added dropwise at 10° C in 5 minutes, then potassium carbonate (7.9 g , 57 mmol) in 30 ml of H_2O is added dropwise at 10 C. The reaction mixture is allowed to warm slowly to room temperature and stirred 24 hours. The solution is heated at 90°C for 2 hours, concentrated. The resulting solid is taken-up in boiling toluene (100 ml), filtered while hot, concentrated to give (+/-)-cis-decahydroquinoxalin-2-one (0.8 g, 14% yield) as a white solid.

$C_8H_{14}N_2O$, MS (M+H)+ : 155

B. (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

(+/-)-cis-Decahydroquinoxalin-2-one (0.8 g, 5.19 mmol) is suspended in 25 ml of H_2O. $NaHCO_3$ (0.87 g, 10.35 mmol) is added and the reaction mixture is cooled to 10° C. Benzylchloroformate (1 ml, 6.68 mmol) is added dropwise to the vigorously stirred mixture. After 20 hours at room temperature the solid is filtered, washed thoroughly with H_2O, air-dried. The title compound (1.46g, 98 % yield) is obtained as a white solid.

$C_{16}H_{20}N_2O_3$, MS $(M+H)^+$: 289

EXAMPLE 893 (+/-)-cis-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one.

The title compound is prepared as described in EXAMPLE 75, subsituting (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one EXAMPLE 892 for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. $C_{17}H_{21}N_5O$, MS $(M+H)^+$: 312

EXAMPLE 894 (+/-)-trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one

A. (+/-)-trans-decahydroquinoxalin-2-one.

(+/-)-trans-1,2-Diaminocyclohexane (22.84 g, 200 mmol) is dissolved in 600 ml of H_2O. Chloroacetic acid (18.8 g, 200 mmol) in 200 ml of H_2O is added dropwise at 10° C in 30 minutes, then potassium carbonate (44 g , 320 mmol) in 120 ml of H_2O is added dropwise at 10 C. The reaction mixture is allowed to warm slowly to room temperature and stirred 24 hours. The solution is heated at 90° C for 2 hours, concentrated. The resulting solid is taken-up in boiling EtOH (800 ml), filtered while hot, concentrated. The off-white solid is recrystallized in boiling toluene (1000 ml), dried to give(1) (9.72 g, 31% yield) as a white solid.

$C_8H_{14}N_2O$, MS (M+H)+ : 155

B. (+/-)-trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

(+/-)-trans-4-Benzyloxycarbonyl-decahydroquinoxalin-2-one (0.8 g, 5.19 mmol) is suspended in 25 ml of H_2O. $NaHCO_3$ (0.87 g, 10.35 mmol) is added and the reaction mixture is cooled to 10° C. Benzylchloroformate (1 ml, 6.68 mmol) is added dropwise to the vigorously stirred mixture. After 5 hours at room temperature the solid is filtered, washed thoroughly with H_2O, air-dried. The title compound (1.33 g, 89 % yield) is obtained as a white solid.

EXAMPLE 895 (+/-)-trans-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one.

The title compound is prepared as described in EXAMPLE 75, subsituting trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one (EXAMPLE 894) for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

$C_{17}H_{21}N_5O$, MS $(M+H)^+$: 312

EXAMPLE 896 4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

A. [1-(2,2-Dimethoxy-ethylcarbamoyl)-3-(S)-methylsulfanyl-propyl]-carbamic acid benzyl ester

To a solution of (L)-N-Benzyloxycarbonyl-methionine (25g, 88.2 mmol) in 400 ml of CH_2Cl_2 is added TBTU (28.3 g, 88.2 mmol), followed by NEt_3 (36.6 ml, 264 mmol) and aminoacetaldehyde dimethylacetal (10.6 ml, 69.7 mmol). The solution is stirred for 16 hours, washed with H_2O, 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over magnesium sulfate and concentrated. The resulting crude product is purified by column chromatography eluting with a gradient of 1%MeOH:CH_2Cl_2 to 5%MeOH:CH_2Cl_2. The title compound (23.3 g, 71% yield) is obtained as a white solid.

$C_{17}H_{26}N_2O_5S$ MS $(M+H)^+$: 371

B. 4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-3,4-dihydro-1H-pyrazine-2-one

To a solution of [1-(2,2-dimethoxy-ethylcarbamoyl)-3-(S)-methylsulfanyl-propyl]-carbamic acid benzyl ester (23.3 g, 63 mmol) in toluene (300 ml) is added p-toluenesulfonic acid monohydrate (1.14 g , 6.3 mmol). The resulting solution is stirred at 70°C for 4 hours, cooled, washed with H_2O, brine, dried over magnesium sulfate and concentrated. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH:CH_2Cl_2 to 5%MeOH:CH_2Cl_2. The title compound (17.9 g, 93% yield) is obtained as an oil.

$C_{15}H_{18}N_2O_3S$ MS $(M+H)^+$: 307

C. 4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-3,4-dihydro-1H-pyrazine-2-one (0.3 g, 1 mmol) in CH_2Cl_2 is added Et_3SiH (1.57 ml, 10 mmol). The resulting solution is cooled to 0° C and CF_3CO_2H (2.2 ml, 30 mmol) is added dropwise. The mixture is stirred 16 hours at room temperature, washed with a saturated aqueous $NaHCO_3$ solution, brine. The solution is dried over $MgSO_4$, concentrated. The resulting crude product is purified by column chromatography on silica gel eluting with a gradient of 50% AcOEt:Hexane to 100 % AcOEt. The title compound (0.138 g, 46 % yield) is obtained as an oil.

$C_{15}H_{20}N_2O_3S$ MS $(M+H)^+$: 309

EXAMPLE 897 1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

A. 4-Benzyloxycarbonyl-1- [3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (1.15 g, 3.74 mmol) in 10 ml of DMF is added at 0°C sodium hydride (164 mg at 60% in oil, 4.12 mmol). The solution is stirred 10 minutes then 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (2.6 g at 52%, 3.74 mmol) in 25 ml of DMF is added dropwise. The resulting mixture is stirred for 20 hours at room temperature, diluted with ethyle acetate, washed with water, with a saturated aqueous $NaHCO_3$ solution, brine. The solution is dried over $MgSO_4$, concentrated. The resulting crude product is purified by column chromatography on silica gel eluting with 2%MeOH:CH_2Cl_2. The title compound (1.8 g, 80 % yield) is obtained as a viscous oil.

$C_{36}H_{34}N_4O_3S$ MS $(M+H)^+$: 603

B. 4-Benzyloxycarbonyl-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-1- [3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (1.8 g, 3 mmol) in 20 ml of ethyle acetate is added concentrated hydrochloric acid (10 drops) and H_2O (10 drops). The resulting mixture is stirred for 1 hour, the ethyle acetate solution is decanted, washed with a saturated aqueous $NaHCO_3$ solution, with water, brine. The solution is dried over $MgSO_4$, concentrated. The resulting crude product is purified by column chromatography on silica gel eluting with 1%MeOH:CH_2Cl_2. The title compound (1.17 g, 89% yield) is obtained as a yellow foam.

$C_{23}H_{26}N_4O_3S$ MS $(M+H)^+$: 439

C. 1-(4-Amino-quinazolin-7-ylmethyl)-4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (1.17 g, 2.67 mmol) in 15 ml of ethanol is added 1,3,5-triazine and glacial acetic acid (3.1 ml, 53.4 mmol). The resulting solution is refluxed for 20 hours, concentrated under vacuum. The residue is dissolved in ethyle acetate, washed with 1N hydrochloric acid, a saturated aqueous $NaHCO_3$ solution, water, brine. The solution is dried over $MgSO_4$, concentrated . The resulting crude product is purified by column chromatography eluting with a gradient of 5%MeOH:CH_2Cl_2 to 10%MeOH:CH_2Cl_2. The title compound (489 mg, 39% yield) is obtained as a yellow solid.

$C_{24}H_{27}N_5O_3S$ MS $(M+H)^+$: 466.

D. 1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

1-(4-Amino-quinazolin-7-ylmethyl)-4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (100 mg, 0.215 mmol) is dissolved in 5 ml of 30% hydrogen bromide in acetic acid. The mixture is stirred for 1 hour, diluted with ethyle ether. The ether is decanted and the resulting solid is washed thoroughly with ethyle ether. The resulting crude product is purified by column chromatography eluting with a 4/2/1 mixture of CH_2Cl_2 /MeOH/ NH_4OH (30% in H_2O). with a gradient of 5%MeOH:CH_2Cl_2 to 10%MeOH:CH_2Cl_2. The resulting product is purified by another column chromatography eluting with a gradient of 20%MeOH:CH_2Cl_2 to 50%MeOH:CH_2Cl_2. The title compound (30 mg, 42 % yield) is obtained as an off-white solid.

$C_{16}H_{25}N_5OS$ MS $(M+H)^+$: 332.

The following compounds are prepared from the templates described above, coupled with an amino-quinazoline group, and the appropriate sulfonyl choride using the method of Example 101.

Example	Name	m/z (M+H)
898	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one	513
899	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one	530
900	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one	514
901	(R/S)1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester	544
902	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	515
903	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one	514
904	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one	513
905	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-octahydro-quinoxalin-2-one	542
906	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	515, 517 Cl pattern
907	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-piperazin-2-one	471
908	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-piperazin-2-one	471
909	[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid	546
910	[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid tert-butyl ester	602
911	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	516
912	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-	628

	benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide	
913	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester	629
914	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	532
915	(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	532
916	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-sulfonic acid (4-chloro-phenyl)-amide	491

The following compounds can be prepared from the templates described above, coupled with an amino-quinazoline group, and the appropriate sulfonyl choride using the method of Example 101.

Example	Name
917	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-imidazol-1-yl-ethyl ester
918	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-morpholin-4-yl-ethyl ester
919	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid pyrrolidin-2-ylmethyl ester
920	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-methylamino-ethyl ester
921	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one
922	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one
923	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one
924	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one
925	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one
926	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-

	6-methyl-piperazin-2-one
927	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one
928	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
929	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
930	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one
931	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one
932	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
933	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
934	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one
935	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one
936	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one
937	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one

The following compounds are prepared from the templates described above, coupled with an amino-quinazoline group, and the appropriate alkylating reagent using the method of Example 268.

Example	Name	m/z (M+H)
938	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-imidazo[1,2-a]pyridin-7-ylmethyl)-piperazin-2-one	422
939	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one	495
940	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	470, 472 Cl pattern
941	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-	481, 483

	ylmethyl)-(S)-3-propyl-piperazin-2-one	CI pattern
942	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo(S)--2-propyl-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester	563, 565 CI pattern
943	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-(S)-3-propyl-piperazin-2-one	463, 465 CI pattern
944	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-ylmethyl)-3(S)-propyl-piperazin-2-one	464
945	9-(4-Amino-quinazolin-7-ylmethyl)-6-[3-(5-chloro-thiophen-2-yl)-allyl]-6,9-diaza-spiro[4.5]decan-10-one	468
946	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one	468,470 CI pattern
947	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one	475, 477 CI pattern
948	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-isobutyl-piperazin-2-one	477, 479 CI pattern
949	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3(S)-isobutyl-piperazin-2-one	489, 491 CI pattern
950	3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-benzamidine	434
951	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one	475, 477 CI pattern
952	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one	468, 470 CI pattern
953	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-octahydro-quinoxalin-2-one	487, 489 CI pattern
954	2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-N-methyl-acetamide	504, 506 CI pattern
955	2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-acetamide	490, 492 CI pattern
956	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	471, 473 CI pattern
957	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl)-N-methyl-acetamide	485, 487 CI pattern
958	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-	470, 472

	3(S)-isobutyl-piperazin-2-one	CI pattern
959	(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methoxymethyl-piperazin-2-one	458, 460 CI pattern
960	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one	465
961	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-(4-pyrimidin-4-yl-benzyl)-piperazin-2-one	470
962	4-[4-(2-Amino-pyrimidin-4-yl)-benzyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	485
963	3-Amino-5-[4-(4-amino-quinazolin-7-ylmethyl)-2(S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-thiophene-2-carbonitrile	438
964	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one	472

EXAMPLE 965. 3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzonitrile.

To a solution of 1-(4-amino-quinazoline-7-ylmethyl)-3-(S)-methoxymethyl-piperazine-2-one, EXAMPLE 75, (50 mg, 0.16 mmol) and 3-cyanocinnamic acid (29 mg, 0.17 mmol, prepared from 3-cyanobenzaldehyde) in 1 mL of DMF is added N,N-diisopropylethylamine (0.07 mL, 0.38 mmol), followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (59 mg, 0.18 mmol). The resulting mixture is stirred at room temperature for 16 h and the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) over 30 min and the appropriate product fractions are combined and lyopholized to provide the title compound (73 mg, 0.13 mmol) as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.72 (bs, 2H), 8.78 (s, 1H), 8.40 (s, 1H), 8.35 (d, 1H), 8.04 (m, 1H), 7.83 (d, 1H), 7.60 (m, 4H), 7.46 (d, 1H), 5.25-4.44 (m, 4H, rotamers), 4.02 (m, 1H), 3.66 (m, 1H), 3.51-3.40 (m, 3H), 3.27 (s, 3H). ISP MS, $[M+H]^+$=457.

EXAMPLE 966. 3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzamidine.

3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzonitrile (68 mg, 0.12 mmol) is dissolved in 9 mL of 2:1 ethanol/CH_2Cl_2. The solution is cooled to 0°C and HCl gas is bubbled through the solution for 5 min. The ice bath is removed and the reaction mixture is stirred at room temperature overnight. After this time, the

solution is concentrated. The residue is dissolved in 10 mL of methanol. The solution is cooled to 0°C and NH_3 gas is bubbled through the solution for 5 min. The reaction mixture is heated at reflux for 2 h. After this time, the solution is concentrated. The residue is purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) over 30 min. The appropriate fractions are lyophilized to give the title compound (55 mg, 0.08 mmol) as a solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.75 (bs, 2H), 9.36 (bs, 4H), 8.80 (s, 1H), 8.42 (s, 1H), 8.13 (m, 1H), 8.10 (m, 1H), 7.79 (d, 1H), 7.62 (m, 4H), 7.42 (m, 1H), 5.20-4.46 (m, 4H, rotamers), 4.03 (m, 1H), 3.86 (m, 1H), 3.56-3.34 (m, 3H), 3.28 (s, 3H). ISP MS, $[M+H]^+$=474.

EXAMPLE 967. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 4-hydroxy-cinnamic acid and 1-(4-amino-quinazoline-7-ylmethyl)-3-(S)-methoxymethyl-piperazine-2-one (EXAMPLE 75).

^1H NMR (d_6-DMSO, 300 MHz) δ 9.88 (s, 1H), 9.68 (bs, 2H), 8.80 (s, 1H), 8.36 (d, 1H), 7.58 (m, 4H), 7.48 (d, 1H), 7.07 (d, 1H), 6.76 (d, 2H), 5.06-4.41 (m, 3H, rotamers), 3.62-3.25 (m, 4H), 1.87 (m, 2H), 1.32 (m, 2H), 0.89 (t, 3H). ISP MS, $[M+H]^+$=446.

EXAMPLE 968. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 3-chloro-cinnamic acid and 1-(4-amino-quinazoline-7-ylmethyl)-3-(S)-methoxymethyl-piperazine-2-one (EXAMPLE 75). ^1H NMR (d_6-DMSO, 300 MHz) δ 9.64 (bs, 2H), 8.78 (s, 1H), 8.36 (d, 1H), 7.96 (m, 1H, rotamers), 7.66 (m, 2H), 7.53 (m, 2H), 7.40 (m, 3H), 5.10-4.42 (m, 3H, rotamers), 3.65 (m, 1H), 3.52-3.22 (m, 3H), 1.90 (m, 2H), 1.33 (m, 2H), 0.90 (t, 3H). ISP MS, $[M+H]^+$=464.

EXAMPLE 969. 1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione.

The titled compound is prepared by a modification of a procedure published by Witzeman and Nottingham. (J. Org. Chem. 1991, *56*, 1713.). 1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one (0.299 g, 1mmol) and 3-(5-chloro-thiophen-2-yl)-3-oxo-propionic acid tert-butyl ester (0.287 g, 1.1 mmol) are dissolved in 10 ml of pyridine. The flask containing the resulting solution is placed in an oil bath preheated to 125°C. The reaction is heated with stirring under a stream of nitrogen gas for one hour until most of the pyridine had evaporated.

The remaining pyridine is evaporated *in vacuo*. The residue is purified by flash column chromatography eluting with a gradient of 5% CH_3OH/H_2CCl_2 to 10% CH_3OH/H_2CCl_2 to provide the product (0.48 g, 0.98 mmol). The product could be recrystallized from CH_2Cl_2/hexane to yield a yellow solid. M.P. 120-5°C (dec). MS (ion spray) m/z 486, (M+H).

EXAMPLE 970. 1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-2-fluoro-propane-1,3,dione.

Prepared by a procedure of Differding and Ofner. (*Synlett* 1991, 187.). A solution of 1-[4-(4-aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione (0.486 g, 1 mmol) in 40 ml of THF is added dropwise to an ice cold suspension of NaH (0.16 g of 60% NaH, 4 mmol) and 5 ml of THF. After the mixture had stirred one hour at 0°C, a solution of N-fluorobenzenesulfonimide (Aldrich) (0.378 g, 1.2 mmol) in 10 ml of THF is added dropwise. The reaction is stirred overnight at room temperature before quenching with glacial acetic acid (0.23 ml, 0.240 g, 4 mmol). The volatiles are evaporated in vacuo and the residue purified by flash column chromatography eluting with a gradient of 5% CH_3OH/H_2CCl_2 to 10% CH_3OH/H_2CCl_2 to provide the product as a white solid. The product could be recrystallized from THF/hexane. M.P. 194-6°C. MS (ion spray) m/z 504, (M+H).

EXAMPLE 971. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (100 mg, 0.3 mmol) in 2 ml of DMF is added DIPEA (158 ml, 0.9 mmol) ,TBTU (107 mg, 0.33 mmol) and 5-chlorothiophen-2-yloxyacetic acid (61 mg, 0.32 mmol). The solution is stirred for 20 hours at room temperature, concentrated under vacuum. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (63 mg, 33 % yield).

$C_{22}H_{24}N_5O_3S_2Cl.CF_3CO_2H$ $(M+H)^+$: 506

EXAMPLE 972. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfinyl-ethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (29 mg, 0.057 mmol) in 1 ml of CH_2Cl_2 is added at 0°C 3-chloroperbenzoic acid (14 mg at 71 %, 0.057 mmol). The resulting mixture is stirred at room temperature for 2 hours, concentrated. The product is purified by RP-HPLC eluting in a gradient

of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (10 mg, 27 % yield).
$C_{22}H_{24}N_5O_4S_2Cl.CF_3CO_2H$ $(M+H)^+$: 522

EXAMPLE 973 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfonyl-ethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (29 mg, 0.057 mmol) in 1 ml of CH_2Cl_2 is added at 0°C 3-chloroperbenzoic acid (28 mg at 71 %, 0.114 mmol). The resulting mixture is stirred at room temperature for 2 hours, concentrated. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (25 mg, 67 % yield).
$C_{22}H_{24}N_5O_5S_2Cl.CF_3CO_2H$ $(M+H)^+$: 538

Using the methods and templates described above, coupled to an amino-quinazoline group, and methods described in EXAMPLE 123, the following compounds are prepared.

Example	Name	m/z (M+H)
974	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-dimethylaminomethyl-piperazin-2-one	449, 451 Cl pattern
975	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo-[b]thiophene-2-carbonyl)-(3S)-methoxymethyl-piperazin-2-one	496
976	1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	488, 490 Cl pattern
977	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	492, 494 Cl pattern
978	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one	510, 512 Cl pattern
979	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chlorobenzo[b]-thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one	494, 496 Cl pattern
980	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	508, 510 Cl pattern
981	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	508, 510 Cl pattern

982	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
983	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
984	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
985	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
986	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one	478, 480 Cl pattern
987	3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidine	462
988	3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidine	418
989	4-[3-(4-Amino-cyclohexyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one	451
990	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one	494, 496 Cl pattern
991	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one trifluoroacetate	478, 480 Cl pattern
992	1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(3-chloro-phenyl)-propane-1,3-dione	480
993	4-[(5-Amino-pyridin-2-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-(S)-3-methoxymethyl-piperazin-2-one	452
994	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(R)-methoxymethyl-piperazin-2-one	476, 478 Cl pattern
995	3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine	432
996	3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine	476
997	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-imidazol-1-yl-benzoyl)-3(S)-propyl-piperazin-2-one	470
998	(6-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-yl)-carbamic acid tert-butyl	552

	ester	
999	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one	486, 488 Cl pattern
1000	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one	486, 488 Cl pattern
1001	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-octahydro-quinoxalin-2-one	482, 484 Cl pattern
1002	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-6-oxo-1,6-dihydro-pyridin-3-yl)-acryloyl]-(S)-3-propyl-piperazin-2-one	481, 483 Cl pattern
1003	1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(4-hydroxy-phenyl)-propane-1,3-dione	462
1004	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	485, 487 Cl pattern
1005	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	485, 487 Cl pattern
1006	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	489, 491 Cl pattern
1007	{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetic acid methyl ester	504, 506 Cl pattern
1008	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide	499, 501 Cl pattern
1009	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide	503, 505 Cl pattern
1010	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide	499, 501 Cl pattern
1011	4-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzenesulfonamide	511
1012	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-pyridin-2-yl)-acetamide	492
1013	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-propyl-piperazin-2-one	473
1014	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one	475
1015	3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-	448

	piperazine-1-carbonyl]-benzamidine	
1016	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(piperidin-3-yloxy)-acetyl]-piperazin-2-one	399
1017	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-4-hydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one	482
1018	(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-hydroxy-naphthalene-2-carbonyl)-3-propyl-piperazin-2-one	470
1019	(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-hydroxy-1H-indole-2-carbonyl)-3-propyl-piperazin-2-one	459
1020	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one	452
1021	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	460
1022	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-(S)-propyl-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide	488
1023	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
1024	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	482, 484 Cl pattern
1025	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one	
1026	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	478, 480 Cl pattern
1027	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
1028	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	478
1029	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide	487, 489 Cl pattern
1030	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide	445, 447 Cl pattern
1031	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 490 Cl pattern
1032	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-	484, 490

	acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	Cl pattern
1033	2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide	489, 491 Cl pattern
1034	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one	476
1035	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,4-dihydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one	464
1036	4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	450
1037	4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one	448
1038	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one	458, 460 Cl pattern
1039	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-6-methyl-pyridin-2-yl)-acetamide	516
1040	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide	502
1041	4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-butyl-piperazin-2-one	474
1042	1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione	444
1043	4-[3-(3-Amino-4-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	481
1044	4-[3-(3-Amino-5-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	481
1045	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
1046	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
1047	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-benzenesulfinyl)-acetyl]-(3-S)-propyl-piperazin-2-one	500
1048	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one	452
1049	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-	442

	acetyl]-piperazin-2-one	
1050	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfinyl)-acetyl]-(3S)-methoxymethyl-piperazin-2-one	502
1051	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	448
1052	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	448
1053	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-hydroxymethyl-piperazin-2-one	462, 464 Cl pattern
1054	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one	458, 460 Cl pattern
1055	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one	521
1056	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one	476
1057	4-[(6-Amino-pyrimidin-4-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one	453
1058	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfonyl)-acetyl]-piperazin-2-one	474
1059	1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(4-chloro-phenyl)-propane-1,3-dione	438
1060	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylsulfanyl)-acetyl]-piperazin-2-one	442
1061	4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one	460
1062	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-3-hydroxy-acryloyl]-piperazin-2-one	438
1063	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-dimethylamino-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one	473
1064	3-(S)-6-(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-hydroxymethyl-3-methoxymethyl-piperazin-2-one	506
1065	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-isobutyl-piperazin-2-one	460
1066	4-[3-(2-Amino-pyrimidin-5-yl)-acryloyl]-1-(4-amino-quinazolin-7-	447

	ylmethyl)-3(S)-propyl-piperazin-2-one	
1067	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one	446
1068	4-[3-(3-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	447
1069	4-[3-(4-Amino-3-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	481
1070	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
1071	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one	470, 472 Cl pattern
1072	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-piperazin-2-one	484, 486 Cl pattern
1073	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-piperazin-2-one	488, 490 Cl pattern
1074	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-amino-thiazol-4-yl)-acetyl]-(S)-3-propyl-piperazin-2-one	440
1075	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethyl ester	504, 506 Cl pattern
1076	4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one	445
1077	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one	508, 510, 512 Cl_2 pattern
1078	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one	510, 512, 514 Cl_2 pattern
1079	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-(2-methoxy-ethyl)-piperazin-2-one	462
1080	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one	486, 488 Cl pattern
1081	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one	486, 488 Cl pattern

EXAMPLE 1082. 4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

To a solution of 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine (12 mg, 0.04 mmol, EXAMPLE 888) in 2 mL of DMF is added 4-chlorophenyl isocyanate (9 mg, 0.06 mmol). After stirring at 100 °C for 1h , the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (16 mg, 0.03 mmol) as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.77 (m, 2H), 8.35 (m, 1H), 7.56 (m, 2H), 7.46 (d, 2H), 7.21 (d, 2H), 5.00-4.38 (m, 3H, rotamers), 4.20 (m, 1H, rotamers), 3.58 (m, 1H, rotamers), 3.10 (m, 1H), 1.86 (m, 2H), 1.33 (m, 2H), 1.08 (m, 3H, rotamers), 0.90 (t, 3H). ISP MS, $[M+H]^+$=467, 469 (Cl pattern).

EXAMPLE 1083. 4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide.

A mixture of 5-chloro-thiophene-2-carbonyl azide (28 mg, 0.15 mmol, EXAMPLE 38) and 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine, EXAMPLE 888, (26 mg, 0.08 mmol) in 3 mL of dry DMF is heated at 100 °C for 1 h. The resulting mixture is concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (18 mg, 0.03 mmol) as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.96 (bs, 1H), 9.70 (bs, 2H), 8.72 (s, 1H), 8.22 (d, 1H), 7.55 (d, 1H), 7.50 (s, 1H), 6.68 (d, 1H), 6.37 (d, 1H), 4.99-4.38 (m, 3H, rotamers), 4.15 (m, 1H, rotamers), 3.58 (m, 1H, rotamers), 3.10 (m, 1H), 1.85 (m, 2H), 1.32 (m, 2H), 1.07 (m, 3H, rotamers), 0.88 (t, 3H). ISP MS, $[M+H]^+$=473, 475 (Cl pattern).

Using the above procedures and templates described above, coupled with an amino-quinazoline, the following EXAMPLES are prepared;

Example	Name	m/z (M+H)
1084	4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-isobutyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	466
1085	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-hydroxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	440
1086	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide	504

1087	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide	462
1088	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide	460
1089	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-hydroxy-phenyl)-amide	437
1090	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methylcarbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	481
1091	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-carbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	467
1092	(4aRS,8aRS)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-octahydro-quinoxaline-1-carboxylic acid (4-chloro-phenyl)-amide	465
1093	4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methylsulfanyl-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	485, 487 Cl pattern
1094	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-furan-2-yl)-amide	445
1095	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide	506
1096	N-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carbonyl]-4-chloro-benzenesulfonamide	517, 519 Cl pattern

Using the templates described above with and amino-quinoline or an amino-cinnoline and the methods described in EXAMPLES 718-721;

Example	Name	m/z (M+H)
1097	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	452
1098	1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-propyl-piperazin-2-one,	455
1099	1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-4-oxy-3-propyl-piperazin-2-one	471
1100	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methoxymethyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	425
1101	(S)-4-(4-Aminoquinolin-7-ylmethyl)-2-methoxylmethyl-3-oxo-2-piperazine-1-carboxylic acid (5-chlorothiophen-2-yl)-amide	460
1102	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-	390

	1-carboxylic acid phenylamide	
1103	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	454
1104	1-(S)-4-(4-Amino-cinnolin-7-ylmethyl)-2-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,	425
1105	1-(S)-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one,	442
1106	1-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-piperazin-2-one	428

The following compounds are prepared using the methods described above using the appropriate ketopiperazine and sulfonyl chloride. The racemates are separated on a CHIRALPAK AD 10 □m column.

Example	Name	m/z (M+H)
1107	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid methyl ester	598, 600, Cl pattern
1108	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid methyl ester	598, 600, Cl pattern
1109	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid amide	504, 506, Cl pattern
1110	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid amide	504, 506, Cl pattern
1111	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483, Cl pattern
1112	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	505, 507, Cl pattern
1113	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483 Cl pattern
1114	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	505, 507 Cl pattern
1115	4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	444
1116	4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-	488, 490

	pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	CI pattern
1117	4-(7-Methoxy-naphthalene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	451
1118	4-(Benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	427

Representative Syntheses of Alkyl Azaindoles:

Example 1119 4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

A. 4-(5-Chloro-thiophen-2-yl)-benzaldehyde

4-Formylphenylboronic acid (1.37 g, 9.15 mmol), 2-bromo-5-chlorothiophene (1 mL, 9.15 mmol), 2M Na_2CO_3 (9 mL, 18.3 mmol) and $Pd(PPh_3)_4$ (0.53 mg, 0.46 mmol) in DME (30 mL) are heated to reflux for 4 h after which time the reaction mixture is concentrated in vacuo and taken up in EtOAc. The organic solution is washed with water (x2) then brine and dried over $MgSO_4$, filtered and concentrated to dryness. The crude residue is purified by chromatography using 5% EtOAc/hexanes as the eluent to yield a yellow solid (1.8 g, 8.1 mmol) as the title compound. EI MS $[M^{\cdot}]$+= 222, 224, Cl pattern.

B. 2-{4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester

To a solution of 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (0.10 g, 0.30 mmol) in acetonitrile (5 mL) is added 4-(5-chloro-thiophen-2-yl)-benzaldehyde (0.067 g, 0.30 mmol) followed by triacetoxyborohydride (0.13 g, 0.60 mmol) and glacial acetic acid (1 drop). The resulting mixture is stirred at room temperature overnight then poured into EtOAc and washed with water (x2) and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness then purified by column chromatography using EtOAc as the eluent to yield the title compound (0.90 g, 0.17 mmol). ESI MS [M+H]+= 537.

C. 4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

2-{4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (0.90 g, 0.17 mmol) is stirred in 30% TFA/CH_2Cl_2 (8 mL) for 1 h then concentratated to dryness and purified by RP-HPLC using 10-100% acetonitrile/0.1% TFA water as the eluent. The appropriate fractions are collected and lypholized to yield the title product as an amorphous white solid (0.44 mg, 0.08 mmol).

Example	Name	m/z (M+H)
1120	4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	479

1121	4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	437
1122	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	438
1123	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	480
1124	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	482
1125	4-[2-(4-Chloro-phenyl)-1H-indol-3-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	512
1126	4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	482
1127	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481
1128	4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	438
1129	4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	443
1130	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	487
1131	4-[2,2']Bithiophenyl-5-ylmethyl-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	453
1132	4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	485
1133	4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	480
1134	4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	455
1135	4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	421
1136	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	437
1137	4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	497

1138	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	479
1139	4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	463
1140	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	429,431 Cl pattern
1141	4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	436
1142	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	485, 487 Cl pattern
1143	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481
1144	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	482

The following compounds are prepared using the templates described above coupled with an amino-methyl-quinazoline, a quinazolinone, hydroxy-quinoline, an oxo-1,6-dihydro-pyridin-benzyl, a 6-methoxy-pyridin-3-yl)-benzyl or 3-imidazol-1-yl-benzyl group using the methods described in EXAMPLE 860 and the sulfonylation, alkylation or amide coupling reactions described above.

Example	Name	m/z (M+H)
1145	1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	487
1146	7-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one	471, 473 Cl pattern
1147	7-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one	475, 477 Cl pattern
1148	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
1149	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-(S)-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one	442, 444, Cl pattern
1150	7-{4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-2H-isoquinolin-1-one	457
1151	7-[4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-2-oxo-	477, 479

	piperazin-1-ylmethyl]-2H-isoquinolin-1-one	CI pattern
1152	4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	489, 491 CI pattern
1153	4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	561, 563 CI pattern
1154	6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3-methyl-3H-quinazolin-4-one	491, 493 CI pattern
1155	6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3H-quinazolin-4-one	477, 479 CI pattern
1156	4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	473, 475 CI pattern
1157	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	459, 461 CI pattern
1158	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	487, 489 CI pattern
1159	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	501, 503 CI pattern
1160	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	473, 475 CI pattern
1161	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	515, 517 CI pattern
1162	4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	503
1163	4-[3-(6-Amino-pyridin-3-yl)-propionyl]-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	476
1164	(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516
1165	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	510
1166	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(3-imidazol-1-yl-benzyl)-3-(S)-methoxymethyl-piperazin-2-one	475, 477 CI pattern
1167	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	514
1168	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-	486

	dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	
1169	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	472
1170	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	500, 502 Cl pattern
1171	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	500, 502 Cl pattern
1172	4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	496, 498 Cl pattern
1173	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	496, 498 Cl pattern
1174	4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	510, 512 Cl pattern
1175	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	514, 516 Cl pattern
1176	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	510, 512 Cl pattern
1177	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	514, 516 Cl pattern

EXAMPLE 1178 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one.

A: 4-Cyanomethyl-piperazine-1-carboxylic acid tert-butyl ester

To a partially dissolved solution of piperazine-1-carboxylic acid tert-butyl ester (2.0 g, 10 mmol) in THF (30 mL) is added 60% NaH (0.44 g, 11 mmol). The resulting solution is stirred for 5 min before the addition of bromoacetonitrile (0.9 mL, 13 mmol). The reaction is stirred for 4 h. MeOH (1 mL) is added and the solution is concentrated and the residue is diluted with EtOAc, washed with 1 N HCl, H_2O, $NaHCO_3$ and the solution is dried over $MgSO_4$. The filtrate is concentrated and the crude product is chromatographed using a silica column (50% EtOAc/PE - EtOAc) to yield 4-cyanomethyl-piperazine-1-carboxylic acid tert-butyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 4.41 (s, 2H), 4.16 (s, 2H), 3.75 (t, 2H), 3.51 (t, 2H), 1.47 (s, 9H).

B: Piperazin-1-yl-acetonitrile

To a solution of 30% TFA/CH_2Cl_2 (10 mL) is added 4-cyanomethyl-piperazine-1-carboxylic acid tert-butyl ester (1.7 g, 6.8 mmol) and the reaction is stirred for 14 h. The reaction is concentrated and chromatoghraphed using silica gel (%1 NH_4OH/7% MeOH/ CH_2Cl_2) to isolate

piperazin-1-yl-acetonitrile as the free base. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (s, 2H), 3.54 (s, 2H), 3.45 (t, 2H), 3.13 (t, 2H).

C: [4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-acetonitrile

To a solution of piperazin-1-yl-acetonitrile (0.32 g, 2.3 mmol) and Et_3N (350 mg, 3.4 mmol) is added 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (615 mg, 2.3 mmol) at 0 °C. The reaction is warmed to room temperature and stirred 4 h. The reaction is diluted with CH_2Cl_2, washed with 1 N HCl, $NaHCO_3$ and dried over $MgSO_4$. The solution is concentrated and the residue is triturated with PE, triturated with Et_2O, and pumped to yield [4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-acetonitrile which can be used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.84 (m, 3H), 7.48 (dd, 1H), 4.36 (s, 2H), 3.92 (s, 2H), 3.64-3.61 (m, 2H), 3.57-3.54 (m, 2H); MS (Ion Spray) 444 $(M+H)^+$.

D: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide

A suspension of [4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-acetonitrile (1.2 g, 3.2 mmol) is heated with diisopropylethylamine (0.65 g, 5.0 mmol) in a solution of ethanol saturated with hydrogen sulfide gas for 4 hours. The reaction is cooled, filtered and washed with cold ethanol to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (bs, 1H), 9.01 (bs, 1H), 8.35 (d, 1H), 8.21 (s, 1H), 8.08 (d, 1H), 7.59 (dd, 1H), 4.15 (s, 2H), 3.73 (s, 2H), 3.43 (s, 4H).

E: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one

To a solution of toluene/t-butanol (1:1) is added 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide (180 mg, 0.45 mmol) and 3-bromo-cyclohexane-1,2-dione (135 mg, 0.80 mmol). The reaction is heated at 90 °C for 4 h and is then concentrated and crude product is dissolved in CH_2Cl_2 and washed with $NaHCO_3$. The solution is concentrated and purified using 1% MeOH/EtOAc to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.47 (dd, 1H), 4.80 (s, 2H), 3.91 (s, 2H), 3.61 (t, 2H), 3.43 (t, 2H), 3.05 (t, 2H), 2.65 (t, 2H), 2.24 (dt, 2H); MS (Ion Spray) 496 $(M+H)^+$.

Using the corresponding α-haloketones, the following products can be produced:

EXAMPLE 1179 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methylamide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 5.69 (br, 1H), 4.74 (s, 2H), 3.91 (s, 2H), 3.63-3.59 (m, 2H), 3.49-3.43 (m, 2H), 2.94 (d, 3H), 2.61 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

EXAMPLE 1180 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 3H), 7.46 (dd, 1H), 4.76 (s, 2H), 3.90 (s, 2H), 3.62-3.59 (m, 2H), 3.46-3.42 (m, 2H), 3.03 (br, 6H), 2.37 (s, 3H); MS (Ion Spray) 513 $(M+H)^+$.

EXAMPLE 1181 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-4-yl-thiazol-2-ylmethyl)-piperazin-2-one hydrobromide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br, 2H), 7.83-7.80 (m, 3H), 7.77 (br, 2H), 7.66 (s, 1H), 7.44 (dd, 1H), 4.87 (s, 2H), 3.96 (s, 2H), 3.70-3.66 (m, 2H), 3.52-3.49 (m, 2H); MS (Ion Spray) 505 $(M+H)^+$.

EXAMPLE 1182 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.84 (br, 1H), 5.60 (br, 1H), 4.85 (d, 1H), 4.66 (d, 1H), 3.91 (s, 2H), 3.64-3.52 (m, 3H), 3.47-3.44 (m, 2H), 2.76-2.62 (m, 2H), 2.41-2.33 (m, 1H), 1.93-2.81 (m, 3H); MS (Ion Spray) 525 $(M+H)^+$.

EXAMPLE 1183 {2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid methyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 7.11 (s, 1H), 4.80 (s, 2H), 3.93 (s, 2H), 3.78 (s, 2H), 3.73 (s, 3H), 3.61-3.57 (m, 2H), 3.47-3.44 (m, 2H); MS (Ion Spray) 500 $(M+H)^+$.

EXAMPLE 1184 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.86-7.81 (m, 3H), 7.46 (dd, 1H), 4.86 (s, 2H), 4.41 (q, 2H), 3.93 (s, 2H), 3.63-3.59 (m, 2H), 3.48-3.44 (m, 2H), 1.39 (t, 3H); MS (Ion Spray) 500 $(M+H)^+$.

EXAMPLE 1185 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.83 (m, 3H), 7.47 (dd, 1H), 4.76 (s, 2H), 3.93 (s, 2H), 3.84 (s, 3H), 3.64-3.60 (m, 2H), 3.49-3.45 (m, 2H) 2.66 (s, 3H); MS (Ion Spray) 500 $(M+H)^+$.

EXAMPLE 1186 1-(4-tert-Butyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.79 (s, 1H), 4.81 (s, 2H), 3.93 (s, 2H), 3.61-3.58 (m, 2H), 3.48-3.44 (m, 2H), 1.29 (s, 9H); MS (Ion Spray) 484 $(M+H)^+$.

EXAMPLE 1187 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(5-chloro-thiophen-2-yl)-thiazol-2-ylmethyl]-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.81 (m, 3H), 7.45 (dd, 1H), 7.18 (s, 1H), 7.13 (d, 1H), 6.86 (d, 1H), 4.81 (s, 2H), 3.95 (s, 2H), 3.67-3.64 (m, 2H), 3.52-3.48 (m, 2H); MS (Ion Spray) 544 $(M+H)^+$.

EXAMPLE 1188 1-[4-(4-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 3H), 7.70 (ddd, 2H), 7.53 (ddd, 2H), 7.45 (dd, 1H), 7.38 (s, 1H), 4.86 (s, 2H), 3.96 (s, 2H), 3.68-3.65 (m, 2H), 3.51-3.48 (m, 2H); MS (Ion Spray) 582 $(M+H)^+$.

EXAMPLE 1188 1-[4-(3-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, 1H), 7.83-7.80 (m, 3H), 7.73 (dd, 1H), 7.48-7.40 (m, 3H), 7.28 (dd, 1H), 4.86 (s, 2H), 3.96 (s, 2H), 3.69-3.65 (m, 2H), 3.52-3.48 (m, 2H); MS (Ion Spray) 582 $(M+H)^+$.

EXAMPLE 1189 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-methyl-thiazol-2-ylmethyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.80 (m, 3H), 7.45 (dd, 1H), 6.79 (s, 1H), 4.78 (s, 2H), 3.92 (s, 2H), 3.59-3.56 (m, 2H), 3.47-3.43 (m, 2H) 2.38 (s, 3H); MS (Ion Spray) 442 $(M+H)^+$.

EXAMPLE 1190 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (dd, 1H), 8.58 (dd, 1H), 8.11 (ddd, 1H), 7.83-7.79 (m, 3H), 7.43 (dd, 1H), 7.33 (dd, 1H), 4.86 (s, 2H), 3.95 (s, 2H), 3.67-3.64 (m, 2H), 3.51-3.47 (m, 2H); MS (Ion Spray) 505 $(M+H)^+$.

EXAMPLE 1191 1-(5-Acetyl-4-methyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.45 (dd, 1H), 4.75 (s, 2H), 3.92 (s, 2H), 3.65-3.61 (m, 2H), 3.48-3.45 (m, 2H), 2.65 (s, 3H), 2.61 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

EXAMPLE 1192 3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.85 (s, 1H), 4.80 (s, 2H), 3.98 (q, 2H), 3.92 (s, 2H), 3.60-3.57 (m, 2H), 3.46-3.43 (m, 2H), 2.66 (s, 2H), 1.40 (s, 6H), 1.12 (t, 3H); MS (Ion Spray) 556 $(M+H)^+$.

EXAMPLE 1193 1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 6.74 (s, 1H), 4.81 (s, 2H), 3.93 (s, 2H), 3.60-3.57 (m, 2H), 3.48-3.44 (m, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80-1.71 (m, 6H); MS (Ion Spray) 562 $(M+H)^+$.

EXAMPLE 1194 1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 6.74 (s, 1H), 4.81 (s, 2H), 3.93 (s, 2H), 3.60-3.57 (m, 2H), 3.48-3.44 (m, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80-1.71 (m, 6H); MS (Ion Spray) 562 $(M+H)^+$.

EXAMPLE 1195 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-phenyl-thiazol-2-ylmethyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.79 (m, 5H), 7.45-7.31 (m, 5H), 4.87 (s, 2H), 3.95 (s, 2H), 3.69-3.65 (m, 2H), 3.51-3.47 (m, 2H); MS (Ion Spray) 504 $(M+H)^+$.

EXAMPLE 1195 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.80-7.78 (m, 3H), 7.63 (ddd, 2H), 7.41 (dd, 1H), 7.17 (s, 1H), 6.83 (ddd, 1H), 4.81 (s, 2H), 3.92 (s, 2H), 3.68-3.61 (m, 2H), 3.48-3.44 (m, 2H); MS (Ion Spray) 520 $(M+H)^+$.

EXAMPLE 1196 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.79 (m, 3H), 7.43 (dd, 1H), 7.36-7.34 (md, 3H), 7.25 (m, 1H), 6.83 (dd, 1H), 6.10 (br, 1H), 4.86 (s, 2H), 3.95 (s, 2H), 3.68-3.64 (m, 2H), 3.50-3.47 (m, 2H); MS (Ion Spray) 520 $(M+H)^+$.

EXAMPLE 1197 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 4.80 (s, 2H), 3.91 (s, 2H), 3.61-3.58 (m, 2H), 3.46-3.43 (m, 2H), 2.72 (bm, 4H), 1.83 (bs, 4H); MS (Ion Spray) 482 $(M+H)^+$.

EXAMPLE 1198 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.47 (dd, 1H), 4.83 (s, 2H), 3.92 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 3.18 (s, 3H), 3.10 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

EXAMPLE 1199 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.46 (dd, 1H), 4.81 (s, 2H), 4.17 (q, 2H), 3.91 (s, 1H), 3.89 (s, 1H), 3.80 (t, 0.5), 3.60-2.52 (m, 2.5H), 3.45-3.36 (m, 2H), 2.78-2.68 (m, 2H), 2.16-1.77 (m, 4H), 1.25 (t, 3H); MS (Ion Spray) 554 $(M+H)^+$.

EXAMPLE 1200 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzoic acid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 1H), 7.80-7.76 (m, 3H), 7.55-7.35 (m, 5H), (s, 2H), 3.94 (s, 2H), 3.55 (m, 2H), 3.43 (m, 2H); MS (ion spray) 548 $(M+H)^+$.

EXAMPLE 1201 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(2-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.82-7.79 (m, 3H), 7.55 (dd, 1H), 7.45-7.40 (m, 2H), 7.24 (d, 1H), 6.97-6.89 (m, 2H), 4.87 (s, 2H), 3.95 (s, 2H), 3.61 (m, 2H), 3.50 (m, 2H); MS (ion spray) 520 $(M+H)^+$.

EXAMPLE 1202 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-2-yl-thiazol-2-ylmethyl)-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.99 (d, 1H), 7.96 (s, 1H), 7.83-7.74 (m, 4H), 7.43 (dd, 1H), 7.23-7.19 (m, 1H), 4.88 (s, 2H), 3.94 (s, 2H), 3.65 (m, 2H), 3.48 (m, 2H); MS (ion spray) 505 $(M+H)^+$.

EXAMPLE 1203 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzamide

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.84-7.79 (m, 2H), 7.61-7.55 (m, 2H), 7.48-7.37 (m, 4 H), 5.86 (d (broad), 2H), 4.83 (s, 2H), 3.92 (s, 2H), 3.65 (m, 2H), 3.47 (m, 2H)
MS (ion spray) 547 $(M+H)^+$.
Using procedures described above the following compounds can be made;

EXAMPLE 1204 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1205 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1206 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1207 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1208 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[4,5-c]pyridin-6-one

The following compounds are prepared according to the methods described above;

Example	Name	MS (m/z) (M+H)

1209	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide	569
1210	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one	526
1211	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl ester	544/546
1212	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide	557
1213	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one	549
1214	(R)-3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester	600
1215	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid	516
1216	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide	543
1217	(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide	513
1218	(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid ethyl ester	488
1219	(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid dimethylamide	487
1220	(S)-(2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazol-4-yl)-acetic acid methyl ester	488
1221	(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one	470

EXAMPLE 1222 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one

To a suspension of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one (7 mg, 0.01 mmol) in EtOH (1 mL) is added sodium borohydride (3 mg, 0.08 mmol). After 15 min the reaction is diluted with EtOAc and washed

with 1N HCl, $NaHCO_3$ and brine. The solution is dried (MgSO4) and concentrated to provide 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 3H), 7.46 (dd, 1H), 4.83-4.81 (m, 1H), 4.76 (s, 1H), 4.75 (s, 1H), 3.92 (s, 1H), 3.91 (s,1H), 3.62-3.55 (m, 2H), 3.47-3.41 (m, 2H), 2.76-2.62 (m, 2H), 2.05-1.78 (m, 4H); MS (Ion Spray) 498 $(M+H)^+$.

EXAMPLE 1223 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one (24 mg, 0.05 mmol), hydroxylamine hydrochloride (20 mg, 0.3mmol), sodium acetate (20 mg, 0.3 mmol) and EtOH (2 mL) are combined and stirred 3.5 h. The reaction is diluted with CH_2Cl_2 and washed with NH_4Cl, $NaHCO_3$ and concentrated to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.34 (d, 1H), 8.20 (s, 1H), 8.07 (d, 1H), 7.59 (dd, 1H), 4.70 (s, 2H), 3.87 (s, 2H), 3.49 (s, 4H), 2.74 (t, 2H), 2.61 (t, 2H), 1.81 (dt, 2H); MS (Ion Spray) 511 $(M+H)^+$.

EXAMPLE 1224a 1-(4-Amino-benzothiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one and

EXAMPLE 1224b 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one (60 mg, 0.12 mmol) is dissolved in $CHCl_3$ (4 mL) and sulfuric acid (0.5 mL) is added with vigorous stirring. Sodium azide (25 mg 0.4 mmol) is added and the reaction is stirred 1 ¾ h. The reaction is then added dropwise to a rapidly stirring mixture of $K_2CO_3/H_20/CH_2Cl_2$. The organic phase is separated and washed with water, dried ($MgSO_4$) and concentrated. The residue is purified by column chromatography (silica, 2% to 6% $MeOH/CH_2Cl_2$) to provide a mixture of two products.

The faster eluting product is the Semler-Wolff aromatization product, 1-(4-amino-benzothiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, 1H), 8.21 (s, 1H), 8.07 (d, 1H), 7.59 (dd, 1H), 7.08 (t, 1H), 6.98 (d, 1H), 6.13 (d, 1H), 5.59 (s, 2H), 4.84 (s, 2H), 3.93 (s, 2H), 3.54 (s, 4H); MS (Ion Spray) 493 $(M+H)^+$.

The slower eluting product is the ring expanded lactam, 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.47 (dd, 1H), 6.47 (bs, 1H), 4.80 (m, 2H), 3.91 (s,2H),

3.65-3.61 (m, 2H), 3.46-3.42 (m, 2H), 3.37-3.32 (m, 2H), 3.07 (t, 2H) 2.17-2.10 (m, 2H); MS (Ion Spray) 511 $(M+H)^+$.

EXAMPLE 1225 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide

A: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid

A solution of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid ethyl ester (75 mg, 0.15 mmol) is dissolved in THF/MeOH -3:1 (2 mL) and a solution of 1N NaOH is added (0.5 mL). The reaction is stirred for 2h and then diluted with EtOAc and washed with 2N HCl. The organic phase is dried (MgSO4) and concentrated to yield 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 8.04 (d, 1H), 7.57 (dd, 1H), 4.74 (s, 2H), 3.87 (s, 2H), 3.49 (s, 4H); MS (Ion Spray) 471 $(M)^+$.

B: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide

To a solution of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid (14 mg, 0.03 mmol) in N-methyl-pyrolidinone (0.3 mL) is added TBTU (0.05 mmol) and diisopropylethylamine (0.06 mmol) and dimethylamine hydrochloride (0.06). The reaction is stirred 3h and an additional aliquot of TBTU, DIEA and amine are added. The reaction is stirred 1h and the reaction is concentrated and purified by column chromatography (silica, 2% MeOH/EtOAc) to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.47 (dd, 1H), 4.83 (s, 2H), 3.92 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 3.18 (s, 3H), 3.10 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

When alternative amines are used in the above reaction the following products are isolated:

EXAMPLE 1226 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.87-7.81 (m, 3H), 7.47 (d, 1H), 4.81 (s, 2H), 3.92 (s, 2H), 3.82 (m, 2H), 3.72-3.61 (m, 4H), 3.46 (m, 2H), 1.97-1.87 (m, 4H); MS (ion spray) 525 $(M+H)^+$.

EXAMPLE 1227 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(morpholine-4-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 4H), 7.46 (dd, 1H), 4.82 (s, 2H), 3.93 (s, 2H), 3.88-3.67 (m, 8H), 3.61 (m, 2H), 3.46 (m, 2H); MS (ion spray) 541 $(M+H)^+$.

EXAMPLE 1228 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(piperazine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

As the TFA salt: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.9 (s (broad), 1H), 7.99 (s, 1H), 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 4.80 (s, 2H), 4.39-3.96 (m (broad), 4H), 3.90 (s, 2H), 3.59 (m, 2H), 3.47 (m, 2H), 3.28 (s (broad), 4H); MS (ion spray) 540 $(M+H)^+$.

EXAMPLE 1229 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid N',N'-dimethyl-hydrazine

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.86-7.80 (m, 3H), 7.46-7.43 (m, 1H), 4.77 (s, 2H), 3.92 (s, 2H), 3.83 (m, 2H), 3.52 (m, 2H), 3.21 (s, 6H); MS (ion spray) 514 $(M+H)^+$.

EXAMPLE 1230 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid (2-hydroxy-ethyl)-methyl-amide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.46 (dd, 1H), 4.81 (s, 2H), 4.68 (t, 1H), 3.94 (s, 2H), 3.72 (m, 2H), 3.64-3.54 (m, 4H), 3.49 (m, 2H), 3.08 (s, 3H); MS (ion spray) 529 $(M+H)^+$.

EXAMPLE 1231 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(3-hydroxy-pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H), 7.87-7.82 (m, 3H), 7.45 (dd, 1H), 4.85 (s, 2H), 4.62-4.55 (m, 1H), 4.08-3.42 (m, 10H), 2.12-1.92 (m, 2H); MS (ion spray) 541 $(M+H)^+$.

EXAMPLE 1232 2-(4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methoxy-methyl-amide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86-7.81 (m, 3H), 7.45 (dd, 1H), 4.85 (s, 2H), 3.92 (s, 2H), 3.72 (s, 3H), 3.62 (m, 2H), 3.45 (m, 2H), 3.39 (s, 3H); MS (ion spray) 515 $(M+H)^+$.

EXAMPLE 1233 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropyl-methyl-amide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87- 7.81 (m, 3H), 7.66 (m, 1H), 7.45 (dd, 1H), 4.95-4.89 (m, 0.5), 4.82 (s, 2H), 4.38-4.22 (m, 0.5), 3.91 (s, 2H), 3.68-3.59 (m, 2H), 3.48-3.42 (m, 2H), 2.92 (s (broad), 3H), 1.24-1.15 (m, 6H); MS (ion spray) 527 $(M+H)^+$.

EXAMPLE 1234 ({2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carbonyl}-methyl-amino)-acetic acid ethyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.81 (m, 4H), 7.46 (dd,1H), 4.83 (s, 1H), 4.75 (s, 1H), 4.44 (s, 1H), 4.26-4.13 (m, 3H), 3.91 (s, 1H), 3.63-3.58 (m, 2H), 3.46-3.43 (m, 2H), 3.31 (s, 1.5), 3.15 (s, 1.5), 1.32-1.22 (m, 3H); MS (ion spray) 571 $(M+H)^+$.

EXAMPLE 1235 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxamide

MS (ion spray) 471 $(M+H)^+$.

EXAMPLE 1236 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methylamide

MS (ion spray) 485 $(M+H)^+$.

EXAMPLE 1237 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropylamide

MS (ion spray) 513 $(M+H)^+$.

When a {2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid methyl ester is treated with NaOH under the conditions previously employed then the product obtained is:

EXAMPLE 1238 {2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid.

^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.90-7.87 (m, 3H), 7.47 (dd, 1H), 7.17 (s, 1H), 4.80 (s, 2H), 3.93 (s, 2H), 3.75 (s, 2H), 3.60-3.58 (m, 2H), 3.50-3.48 (m, 2H); MS (Ion Spray) 486 $(M+H)^+$.

Amide bond formation using the conditions previously employed provides the following products using the amines shown

EXAMPLE 1239 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetamide

MS (ion spray) 485 $(M+H)^+$.

EXAMPLE 1240 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-methyl-acetamide

MS (ion spray) 499 $(M+H)^+$.

EXAMPLE 1241 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-isopropyl-acetamide

MS (ion spray) 527 $(M+H)^+$.

EXAMPLE 1242 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N,N-dimethyl-acetamide

MS (ion spray) 513 $(M+H)^+$.

EXAMPLE 1243 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one.

A: 5-Benzyloxycarbonylamino-3-oxo-pentanoic acid ethyl ester

Cbz-β-Alanine (5.0 g , 21.6 mmol) is dissolved in THF (10 mL). To this is added dropwise a solution of carbonyl diimidazole (3.5 g , 21.6 mmol) in THF (50 mL) and allowed to stir 16 hrs. This solution is then reduced to ~ 30 mL by rotary evaporation. In a separate flask (oven dried), isopropyl magnesium chloride in THF (2M) (16.2 mL, 32 mmol) is added and cooled to 0 °C and hydrogen ethyl malonate (4.28 g, 32.4 mmol) is added dropwise. The contents are allowed to stir at 0 °C for 30 min, allowed to warm to 25 °C and continue stirring for another 30 min, and finally warmed to 40 °C for 30 min. The contents are then cooled to 0 °C and the contents of the first flask are added dropwise. The reaction is allowed to gradually come to 25 °C and continue stirring for 4 hrs. The reaction is poured into 100 mL of ice cold 1 N H_3PO_4 and allowed to stir for 30 min. The contents are extracted (3 x 100 mL) with ethyl acetate. The combined organic layers are then washed (3 x 100 mL) with saturated sodium bicarbonate followed by (3 x 100 mL) with brine. The organic layer is dried over $MgSO_4$, filtered and reduced to an oil by rotary evaporation to provide 5-benzyloxycarbonylamino-3-oxo-pentanoic

acid ethyl ester. The product is used as is without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.25 (bm, 1H), 5.06 (s, 2H), 4.17 (q, 2H), 3.42 (m, 5H), 2.78 (t, 2H), 1.25 (t, 3H); MS (ion spray) 294 $(M+H)^+$.

B: 5-Benzyloxycarbonylamino-4-bromo-3-oxo-pentanoic acid ethyl ester

5-Benzyloxycarbonylamino-3-oxo-pentanoic acid ethyl ester (1.0 g, 3.4 mmol) is dissolved in glacial acetic acid (10mL) and pyridinium bromide perbromide (1.1 g, 3.4 mmol) of is added. The reaction stirred 16 hrs and then poured into H_2O (100 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layers are combined and washed with H_2O (2 x 100 mL) and with brine (2 x 100 mL). The organic layer is dried over MgSO4, filtered and reduced to an oil by rotary evaporation. The crude product is purified by flash chrom-atography on silica gel using 25% ethyl acetate / hexane as the eluent to provide 5-benzyloxycarbonylamino-4-bromo-3-oxo-pentanoic acid ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 5H), 5.27 (m, 1H), 5.09 (s, 2H), 4.67 (t, 1H), 4.17 (q, 2H), 3.72 (m, 4H), 1.27 (t, 3H); MS (ion spray) 372 $(M+H)^+$.

C: {5-(Benzyloxycarbonylamino-methyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester

A suspension of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide (200 mg, 0.5 mmol) and 5-benzyloxycarbonylamino-4-bromo-3-oxo-pentanoic acid ethyl ester (370 mg, 1.0 mmol) is heated at 90 °C in a mixture of toluene/t-butanol, 1:1 (5 mL) for 16 h. The reaction is concentrated and purified using column chromatography (silica, 2%MeOH/CH_2Cl_2) to provide {5-(benzyloxycarbonylamino-methyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.45 (dd, 1H), 7.32 (s, 5H), 7.45 (bt, 1H), 5.07 (s, 2H), 4.73 (s, 2H), 4.42 (d, 2H), 4.13 (q, 2H), 3.90 (s, 2H), 3.76 (s, 2H), 3.61-3.55 (m, 2H), 3.50-3.43 (m, 2H), 1.24 (t, 3H); MS (ion spray) 677 $(M+H)^+$.

D: {5-Aminomethyl-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester

{5-(Benzyloxycarbonylamino-methyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester (40 mg, 0.06 mmol) is treated with 30% HBr/HOAc (1 mL) for 7 h. Ether (10 mL) is added and the resulting precipitate is washed twice with ether. The resulting salt is partitioned between EtOAc (15 mL) and $NaHCO_3$ solution (10 mL). The organic phase is washed with NaHCO3 and brine (2 x 10 mL), dried ($MgSO_4$) and concentrated to provide {5-aminomethyl-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-

piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester. ^{1}H NMR (300 MHz, DMSO) δ 8.32 (d, 1H), 8.17 (s, 1H), 8.08-8.02 (m, 2H), 7.57 (dd, 1H), 4.62 (s, 2H), 4.02 (q, 2H), 3.81 (s, 2H), 3.74 (s, 2H), 3.64 (s, 2H), 3.48-3.35 (m, 4H), 2.48 (t, 3H); MS (ion spray) 543 $(M+H)^+$.

E: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one

{5-Aminomethyl-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester (12 mg, 0.02 mmol) is heated in EtOH (3 mL) for 3 days at 70 °C. The precipitate which is formed is filtered to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one. ^{1}H NMR (300 MHz, DMSO) δ 8.31 (d, 1H), 8.08-8.02 (m, 2H), 7.55 (dd, 1H), 4.67 (s, 2H), 4.36 (s (broad), 2H), 3.84 (s, 2H), 3.60-3.54 (m, 4H), 3.38 (t, 2H); MS (LC/MS-ESI) 496 $(M+H)^+$.

EXAMPLE 1244 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one.

A: 4-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester

Isonipecotic acid (19.6g, 76 mmol) is dissolved in THF (200 mL) and cooled to 0 °C and lithium aluminum hydride is added portionwise over 10 minutes. The reaction is allowed to stir at 25 °C for 16 h. The reaction is then cooled to 0 °C and water (6 mL) is added dropwise followed by 15% NaOH (6 mL). After 20 minutes, water (18 mL) is added and the reaction is stirred 30 min. The reaction is filtered, and the filtrate is concentrated and recrystallized from hexane to provide 4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester. mp 67-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (bd, 2H), 3.50 (d, 2H), 2.70 (dd, 2H), 1.73-1.60 (m, 3H), 1.45 (s, 9H), 1.14 (ddd, 2H); MS (ion spray) 216 $(M+H)^+$.

B: 4-Bromomethyl-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (2.30 g, 10.7 mmol) and carbon tetrabromide (4.43 g, 13.4 mmol) in CH_2Cl_2 (40 mL) is cooled to 0 °C. Triphenylphosphine (4.21g, 16.0 mmol) is added and the reaction is stirred at 25 °C for 1h. The reaction is concentrated and ether is added to the residue. The mixture is filtered and washed with ether. The filtrate is concentrated and purified by column chromatography (silica, 20% EtOAc/hexane) to provide 4-bromomethyl-piperidine-1-carboxylic acid tert-butyl ester as a crystaline solid upon standing. Mp 48-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (bm, 2H), 3.29 (d, 2H), 2.70 (dd, 2H), 1.85-1.73 (m, 3H), 1.46 (s, 9H), 1.28-1.13 (m, 2H); MS (EI) 277 (M)+.

C: 4-(1-tert-Butoxycarbonyl-piperidin-4-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester

Sodium hydride (60%, 0.27 g, 6.7 mmol) is added to a solution of 4-benzyloxycarbonyl-2-oxo-piperazine (1.58 g, 6.7 mmol) in dry DMF (40 mL). After 30 minutes 4-bromomethyl-piperidine-1-carboxylic acid tert-butyl ester (1.87g, 6.7 mmol) is added and the reaction is allowed to stir for 16h. The solvent is removed in vacuo and the residue is dissolved in ether and washed with NH_4Cl. The aqueous phase is back-extracted with ether and the combined ether fractions are washed with water and brine to provide 4-(1-tert-butoxycarbonyl-piperidin-4-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester which is used without futher purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.16 (d, 2H), 4.16 (s, 2H), 4.13 (br, 2H), 3.73-3.69 (m, 2H), 3.44-3.30 (m, 6H), 2.68 (bt, 2H), 1.85-1.73 (m, 1H), 1.58 (bd, 2H), 1.46 (s, 9H), 1.25-1.10 (m, 2H); MS (ion spray) 432 (M+H)+.

D: 4-(2-Oxo-piperazin-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-(1-tert-butoxycarbonyl-piperidin-4-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.3 g, 5.4 mmol) in methanol (75 mL) is purged with nitrogen and 10% Pd on carbon (0.3 g) is added, and the reaction is again purged with nitrogen. The reaction is placed on a Parr shaker under hydrogen for 16h. After the system is purged of hydrogen, the catalyst is filtered and washed with methanol. The filtrate is concentrated to provide 4-(2-oxo-piperazin-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester which is used without further purification. MS (EI) 298 (M+H)+.

E: 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 4-(2-oxo-piperazin-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester (1.44 g, 4.8 mmol) in CH_2Cl_2 (75 mL) and MeCN (10 mL) is added diisopropylethylamine (1.3 mL, 4.8 mmol) followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (1.29 g, 4.8 mmol), and the reaction is allowed to stir 16 h. The reaction is diluted with CH_2Cl_2 and washed with 1N HCl and NaHCO3, dried and concentrated. The residue is purified by column chromatography (silica, 40% EtOAc/ CH_2Cl_2) to provide 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.83 (m, 3H), 7.47 (dd, 1H), 4.1 (br, 2H), 3.86 (s, 2H), 3.46 (bs, 4H), 3.25 (br, 2H), 2.61 (t, 2H), 1.87-1.75 (m, 1H), 1.51 (d, 2H), 1.41 (s, 9H), 1.10 (ddd, 2H); MS (Ion spray) 528 $(M+H)^+$.

F: 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one

Trifluoroacetic acid (4 mL) is added to a solution of 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester (1.1 g, 2.0 mmol) in CH_2Cl_2 (15 mL). After 1 h the reaction is concentrated and the residue is dissolved in CH_2Cl_2 and washed with Na_2CO_3, dried ($MgSO_4$) and concentrated to provide 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.83 (m, 3H), 7.46 (dd, 1H), 3.86 (dd, 2H), 3.45 (s, 2H), 3.23 (d, 2H), 3.07 (d, 2H), 2.54 (dt, 2H), 2.39 (s, 1H), 1.83-1.75 (m, 1H), 1.56 (d, 2H), 1.24-1.11 (m, 2H); MS (Ion spray) 428 $(M+H)^+$.

EXAMPLE 1245 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid amide

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (20 mg, 0.047 mmol) in a mixture of 1,2-dichloroethane (1 mL) and THF (1 mL) is added trimethylsilyl isocyanate (0.006 mL, 0.05 mmol) and stirred 60 hours. The reaction is concentrated and purified by column chromatography (silica, 20% methanol/dichloromethane) to provide 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid amide. ^1H NMR (300 MHz, CD_3OD) d 8.09 (s, 1H), 8.02 (d, 2H), 7.53 (dd, 1H), 3.90 (d, 4H), 3.49 (d, 4H), 3.30-3.24 (m, 2H), 2.65 (dt, 2H), 1.49 (d, 2H), 1.12-0.97 (m, 2H); MS (Ion spray) 471 (M+H).

EXAMPLE 1246 2-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-acetamide

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (20 mg, 0.047 mmol) in N-methylpyrrolidinone (0.5 mL) is added 2-chloroacetamide (9 mg, 0.094 mmole) and diisopropylethylamine (0.016 mL, 0.094 mmole) and heated at 120 °C for 16 h. The reaction is concentrated and purified by column chromatography (silica, 5% methanol/dichloromethane) to provide 2-{4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-acetamide. ^1H NMR (300 MHz, $CDCl_3$) d 7.88-7.83 (m, 3H), 7.47 (dd, 1H), 6.98 (bs, 1H), 5.30 (bs, 1H), 3.86 (s, 2H), 3.46 (s, 4H), 3.28 (d, 2H), 2.95 (s, 2H), 2.82 (d, 2H), 2.06 (t, 2H), 1.69-1.50 (m, 3H), 1.33-1.25 (m, 2H); MS (Ion spray) 485 $(M+H)^+$.

EXAMPLE 1247 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (40 mg, 0.094 mmole) in n-butanol (1.0 mL) is added 2,4-dichloropyrimidine (14, 0.094 mmole) and diisopropylethylamine (0.016 mL, 0.094 mmole) and this mixture is heated at 110°C for 4 hours. The reaction is concentrated and purified by column chromatography (silica, 25% ethyl acetate/dichloromethane) to yield 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$) d 8.01 (d, 1H), 7.89-7.87 (m, 3H), 7.48 (dd, 1H), 6.35 (d, 1H), 4.41-4.20 (m, 2H), 3.87 (s, 2H), 3.48 (s, 4H), 3.28 (dd, 2H), 2.05-1.95 (m, 1H), 1.67 (d, 2H), 1.31-1.20 (m, 2H); MS (Ion spray) 542 $(M+H)^+$.

EXAMPLE 1248 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one (17 mg, 0.031 mmole) in ethanol (1 mL) is added a 40% solution of dimethylamine (11 mg, 0.094 mmole). This mixture is heated at 80 °C in a sealed tube 16h. The reaction is concentrated and lyophilized to provide 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$) d 7.93-7.84 (m, 4H), 7.48 (dd, 1H), 5.84 (d, 1H), 4.32 (d, 2H), 3.87 (s, 2H), 3.47 (s, 4H), 3.26 (d, 2H), 3.14 (s, 6H), 1.99-1.90 (m, 1H), 1.62 (d, 2H), 1.27-1.17 (m, 2H); MS (Ion spray) 549 $(M+H)^+$.

Using the procedures the following compounds can be prepared;

Example	Name
1249	(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one
1250	(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one
1251	(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one
1252	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1253	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1254	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-

	pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester
1255	(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1256	(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1257	4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester
1258	(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1259	(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1260	4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester
1261	(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1262	(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1263	4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester

EXAMPLE 1264 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one.

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one (0.40 g, 0.74mmol) in EtOH is added ethanolamine (0.089 mL, 1.5 mmol). The solution is heated to reflux for 18 h and evaporated to dryness. The residue is chromatographed eluting successively with 1%, 2% and 4% MeOH in CH_2Cl_2. Fractions containing only product are combined and the solvent evaporated. Trituration with ether afforded the title compound as a yellow solid: MS (ESI): *m/z* 565 (M^+ + H).

By substituting ethanolamine with the corresponding amine, the following products can similarly be prepared:

Example 1265

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1266

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1267

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1268

4-[(4-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-pyrimidin-2-yl)-methyl-amino]-butyric acid

Example 1269

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethoxy)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1270

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-{2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl}-piperidin-4-ylmethyl)-piperazin-2-one

Example 1271

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethylsulfanyl)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

EXAMPLE 1272 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (20 mg, 0.047 mmol) in n-butanol (0.5 mL) is added 6-chloronicotinamide (15 mg, 0.094 mmole) and diisopropylethylamine (0.016 mL, 0.094 mmole) and heated at 110 °C 16 h. The reaction is concentrated and purified by column chromatography (silica, 20% methanol/dichloromethane) to provide 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid. ^{1}H NMR (300

MHz, CD_3OD) δ 8.59 (d, 1H), 8.11-7.92 (m, 3H), 7.54 (dd,1H), 6.72 (d, 1H), 4.27 (d, 1H), 3.92 (s, 2H), 3.57-3.47 (m, 4H), 3.25 (d, 2H), 2.79-2.71 (dt, 2H), 1.96-1.80 (m, 1H), 1.50 (d, 2H), 1.29-1.06 (m, 2H); MS (Ion spray) 549 $(M+H)^+$.

Using the corresponding halide the following compounds can be similarly prepared:

EXAMPLE 1273 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrimidin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, 2H), 7.88-7.83 (m, 3H), 7.48 (d, 1H), 6.44 (t, 1H), 4.71 (d, 2H), 3.87 (s, 2H), 3.47 (s, 4H), 3.26 (d, 2H), 2.76 (dt, 2H), 2.00-1.91 (m, 1H), 1.62 (d, 2H), 1.26-1.21 (m, 2H) ; MS (Ion spray) 506 $(M+H)^+$

EXAMPLE 1274 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrazin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 2H), 7.89-7.84 (m, 4H), 7.48 (dd, 1H), 4.27 (d, 2H), 3.88 (s, 2H), 3.48 (s, 2H), 3.28 (d, 2H), 2.80 (t, 2H), 2.01-1.90 (m, 1H), 1.65 (d, 2H), 1.32 (m, 2H); MS (Ion spray) 506 $(M+H)^+$

EXAMPLE 1275 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (t, 1H), 7.89-7.84 (m, 3H), 7.49-7.41 (m, 2H), 6.63-6.56 (m, 2H), 4.23 (d, 2H), 3.88 (s, 2H), 3.48 (s, 4H), 3.27 (d, 2H), 2.73 (dt, 2H), 1.93-1.86 (m, 1H), 1.60 (t, 2H), 1.32-1.19 (m, 2H); MS (Ion spray) 505 $(M+H)^+$.

EXAMPLE 1276 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-carboxylic acid

^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.39-8.29 (m, 2H), 7.99-7.84 (m, 3H), 7.49-7.45 (m, 1H), 7.08 (q, 1H), 5.65 (s, 1H), 3.87 (d, 2H), 3.48 (d, 6H), 2.81 (t, 1H), 2.57 (dt, 1H), 1.85-1.76 (m, 1H), 1.73-1.69 (m, 2H), 1.43-1.37 (m, 2H); MS (Ion spray) 548 $(M+H)^+$.

EXAMPLE 1277 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.84 (m, 3H), 7.47 (dd, 1H), 7.37 (t, 1H), 6.12 (dd, 1H), 6.03 (dd, 1H), 4.24 (d, 2H), 3.88 (s, 2H), 3.84 (s, 3H), 3.48 (s, 4H), 3.27 (d, 2H), 2.71 (dt, 2H), 1.95-1.84 (m, 1H), 1.61 (d, 2H), 1.32-1.22 (m, 2H); MS (Ion spray) 535 $(M+H)^+$.

Preparation of the intermediate,
4-Bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl.

A: 6'-Methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester
In a round-bottom flask, 20 ml of anhydrous toluene is added and degassed several times from vacuum/N_2. 2-methoxy-5-bromopyridine (752 mg, 4.0 mmol), ethyl isonipecotate (740 mg, 4.8 mmol), sodium t-butoxide (537 mg, 5.6 mmol), $Pd_2(DBA)_3$ (73 mg, 2 mol%) and of BINAP (100 mg, 0.16 mmol) are added and heated to 70 °C under N_2 for 16 hrs. The reaction is cooled to r.t. and taken up in 100 ml of ethyl ether and washed with brine (2 x 50 ml). The ether is dried over $MgSO_4$, filtered and reduced to an oil under vacuum. The compound is purified by flash chromatography on silica gel using 20 % ethyl acetate / hexane as the eluent to provide 6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H), 7.28 (dd, 1H), 6.66 (d, 1H), 4.15 (q, 2H), 3.87 (s, 3H), 3.42 (dt, 2H), 2.71 (dt, 2H), 2.39 (m, 1H), 2.03 (m, 2H), 1.90 (m, 2H), 1.26 (t, 3H); MS (EI) 264 $(M)^+$.

B: (6'-Methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-methanol
A round bottom flask is charged with anhydrous THF (8 mL) and LAH (122 mg, 3.17 mmol) is added. The contents are placed under N_2 and cooled to 0 °C. To this is added a solution of 6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester (400 mg, 1.51 mmol) in THF (2 ml) over 5 min. The reaction is allowed to come to r.t. and continue to stir for an additional hour. 4 drops of H_2O are added, followed by 4 drops of 15% $NaOH_{(aq)}$ and allowed to stir at r.t. for 20 min. 0.5 mL of H_2O are added, and the contents are filtered through a pad of celite and washed with THF. The solution is reduced to an oil under vacuum, and purified by flash chromatography on silica gel using 3% methanol / methylene chloride as the eluent to provide (6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-methanol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 1H), 7.29 (dd, 1H), 6.66 (d, 1H), 3.88 (s, 3H), 3.53 (m, 4H), 2.65 (dt, 2H), 1.85 (m, 2H), 1.65 (m, 1H), 1.42 (m, 2H); MS (EI) 222 $(M)^+$.

C: 4-Bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl
(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-methanol (300 mg, 1.35 mmol) is dissolved in methylene chloride (10 mL). carbon tetrabromide (561 mg, 1.69 mmol) is added and dissolved. The solution is cooled to 0 °C and triphenylphoshine (529 mg, 2.02 mmol) is added portionwise. The reaction is allowed to come to r.t. and is stirred for 30 min. The volume is then reduced under vacuum to ~ 2 ml and purified by flash chromatography on silica gel

using 2% methanol / methylene chloride as the eluent to provide 4-bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl. ^{1}H NMR (300 MHz, CD_3OD) δ 7.74 (d, 1H), 7.43 (dd, 1H), 6.72 (d, 1H), 3.83 (s, 3H), 3.54 (m, 2H), 3.38 (d, 2H), 2.65 (dt, 2H), 1.94 (m, 2H), 1.75 (m, 1H), 1.44 (m, 2H); MS (EI) 284 $(M)^+$.

The above alkylating reagent, 4-bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl, can be used to provide:

EXAMPLE 1278 4-(6-Chloro-benzo[b]thiophene-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylmethyl)-piperazin-2-one
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.50-7.43 (m, 2H), 6.88 (dd, 1H), (d, 1H), 3.85 (s, 5H), 3.48-3.15 (m, 7H), 3.29-3.17 (m, 2H), 2.89-2.81 (m, 1H), 2.25-2.12 (m, 1H), 1.65-1.56 (m, 4H); MS (ion spray) 535 $(M+H)^+$.

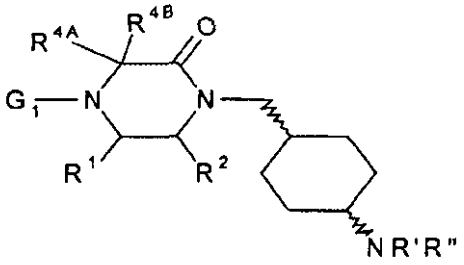
EXAMPLE 1279 O-Phenyl-1-cyano-3-{4-[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl} isourea
To a suspension of 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (0.90 g, 2.1 mmol) in 2-propanol (20 mL) is added diphenyl cyanocarbonimidate (0.50 g, 2.1 mmol). After stirring for 18 h, TLC (4% MeOH in CH_2Cl_2) indicated a mixture of starting material and primarily one faster migrating product. Additional diphenyl cyanocarbonimidate (0.50 g) is added and the reaction mixture is heated to 80 °C for 2 h. Upon cooling to rt the precipitate which formed is collected, washed with 2-propanol and air-dried to afford the title compound as an off- white solid; yield 0.48g. A sample is further purified by chromatography eluting successively with 1%, 2% and 4% MeOH in CH_2Cl_2 to afford a chromatographically pure white solid: MS (ESI): *m/z* 572 $(M^+ + H)$.

EXAMPLE 1280 Preparation of N,N Dimethyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine.
To a solution of O-phenyl-1-cyano-3-{4-[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl} isourea (0.10 g, 0.18 mmol) in MeOH (10 mL) is added 40% aqueous dimethylamine (10 mL) and the reaction is stirred at rt for 72 h. The solvents are evaporated and the residue is chromatographed eluting successively with 1% and 2% MeOH in CH_2Cl_2. Fractions containing only product are concentrated and the residue is triturated with ether to afford the title compound as a white solid; yield 17 mg: MS (ESI): *m/z* 523 $(M^+ + H)$.

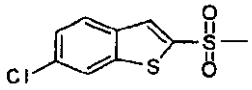
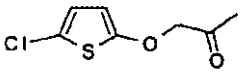
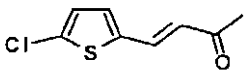
EXAMPLE 1281 Preparation of N-Methyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine.

The title compound is prepared as a white solid using the procedure of Example 3 except substituting methylamine for dimethylamine: MS (ESI): *m/z* 509 (M^+ + H).

Other, 4-(methylpiperin-1-yl) cyanoformamidine compounds can be prepared from intermediates having the structure of formula including but not limited to:



wherein G-1 includes but is not limited to


, 
, 
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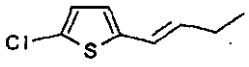
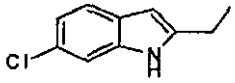

, and 
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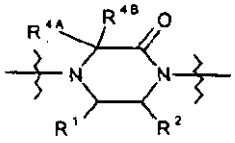
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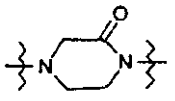
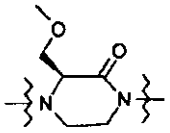
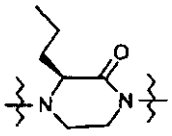
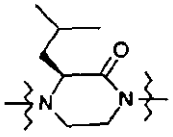
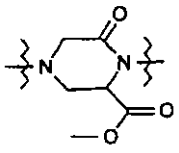
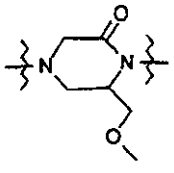

, 
, 


, 
, and 
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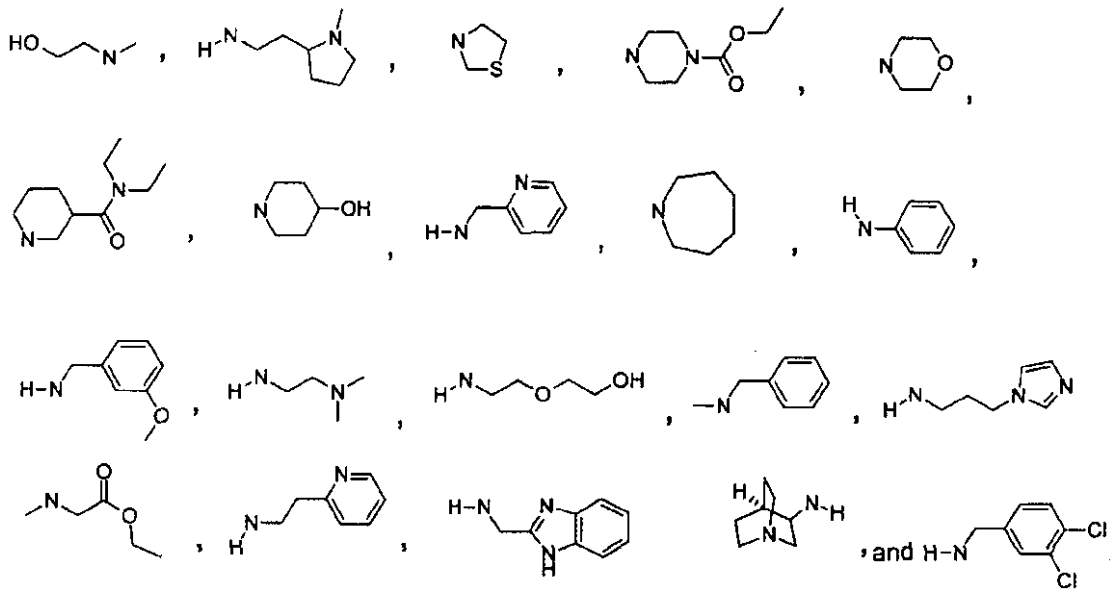


Example 1282 Preparation of N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-cyanoguanidine

a. Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine

8-Carboxaldehyde-1,4-dioxa-spiro[4.5]decane (4.4 g, 26 mmol), prepared according to the method of Pearson et al. (*J. Org. Chem.* 62, 1997, 5284), aminoacetaldehyde dimethyl acetal (3.3 g, 0.31 mmol), acetic acid (1.6 g, 0.26 mmol) and sodium cyanoborohydride (2.0 g, 0.31 mmol) are stirred in methanol (140 mL) for 6 h. The methanol is evaporated and the residue is partitioned between ethyl acetate (200 mL) and 1 N NaOH (100 mL). The organic phase is dried (Na_2SO_4) and is evaporated to provide the intermediate title compound as a yellow oil (7.2 g) which is used without further purification. MS (EI), 259 $[M]^+$.

b. {1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester

Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine (6.6 g, 26 mmol), (*S*)-(2-benzyloxycarbonylamino-3-methoxy)-propionic acid (7.2 g, 28 mmol), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (12 g, 31 mmol) and N,N-diisopropylethylamine (7.7 g, 60 mmol) are stirred in DMF (200 mL) for 18 h. The DMF is evaporated and the residue diluted with ethyl acetate (200 mL). The organic phase is washed with water (50 mL), 2 N HCl (50 mL), 1 N NaOH (50 mL), is dried ($MgSO_4$) and is evaporated to

provide the intermediate title compound as a yellow oil (13 g) which is used without further purification. MS (ES), 495 $[M+H]^+$.

c. 4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester

{1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester (12.8 g, 26 mmole) and *p*-toluenesulphonic acid monohydrate (0.74 g, 3.9 mmol) are placed in toluene (150 mL) and stirred at 60-70°C for 7 h. The mixture is evaporated and the residue is purified by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) to provide the intermediate title compound as a clear colorless oil (5.0 g, 45%). MS (ES), 431 $[M+H]^+$.

d. 1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one

4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester (4.7 g, 11 mmol) and 10% Pd on carbon (1.0 g) are stirred in methanol (150 mL) under a hydrogen atmosphere for 18 h. The mixture is filtered through Celite® and is evaporated to provide the intermediate title compound as a clear colorless oil (3.3 g, 11 mmol). MS (EI), 298 $[M]^+$.

e. 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one

1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one (3.3 g, 11 mmol), (5-chloro-thiophen-2-yloxy)-acetic acid (2.1 g, 11 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (3.9 g, 12 mmol) and triethylamine (3.3 g, 33 mmol) are stirred in DMF (100 mL) for 8 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with water, 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$) and is evaporated. The residue is purified by flash chromatography (silica gel, 4:1 ethyl acetate/hexanes) to provide the intermediate title compound as a clear colorless oil (2.8g, 54%). MS (ES), 473 $[M+H]^+$.

f. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one (2.8 g, 5.9 mmol) is placed in 80:20 acetic acid/water and heated at 65°C for 0.2 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with 1 N NaOH, is dried ($MgSO_4$) and is evaporated to provide the intermediate title compound as a clear colorless oil (2.4 g, 95%). MS (ES), 429 $[M+H]^+$.

g. 1-cis-[4-(Amino)-cyclohexylmethyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-piperazin-2-one and 1-trans-[4-(amino)-cyclohexylmethyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-piperazin-2-one

Sodium cyanoborohydride (0.075 g, 1.2 mmol) is added to a mixture of 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one (0.5 g, 1.2 mmol) and ammonium acetate (0.9 g, 12 mmol) in anhydrous methanol (20 mL). The mixture is stirred 18 h and is concentrated *in vacuo*. The residue is diluted with EtOAc (20 mL) and is washed with 1N NaOH. The organic phase is dried (Na_2SO_4) and is evaporated to provide the intermediate title compound as a mixture of cis and trans isomers (0.49 g, 98%) which is used without further purification. MS (ES), 430 $[M+H]^+$.

h. N-trans-({[4-(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-cyclohexyl)-N'-cyano-O-phenylisourea

N-(cis/trans)-({[4-(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-cyclohexyl)-N'-cyano-O-phenylisourea (0.49 g, 1.14 mmol) and diphenyl cyanocarbonimidate (0.28 g, 1.17 mmol) are stirred in *i*-propyl alcohol (5 mL) for 18 h. The mixture is concentrated *in vacuo* and is diluted with EtOAc (20 mL). The organic phase is washed with 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$) and is evaporated. The residue is purified by flash chromatography (silica gel, EtOAc) to provide the intermediate title compound as a white solid (0.33 g, 50%). MS (ES), 574 $[M+H]^+$.

The cis isomer is also isolated (0.1 g, 15%). MS (ES), 574 $[M+H]^+$.

i. N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-cyanoguanidine

N-trans-({[4-(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-2-oxo-piperazin-1-ylmethyl)-cyclohexyl)-N'-cyano-O-phenylisourea (0.025 g, 0.04 mmol) is stirred in a 7 N solution of ammonia in methanol (2 mL) for 18 h. The mixture is diluted with EtOAc (20 mL) and is washed with 1 N NaOH and brine. The organic phase is dried ($MgSO_4$) and is evaporated to provide the title compound as a colorless resin (0.014 g, 70%). MS (ES), 497 $[M+H]^+$.

The Following Compounds are also prepared in a similar manner to that described in Example 1282:

Example 1283

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N',N'-dimethyl-cyanoguanidine: MS (ES), 510 $[M+H]^+$.

Example 1284

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-methyl-cyanoguanidine: MS (ES), 524 $[M+H]^+$.

Example 1285

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-(2-hydroxyethyl)-N'-methyl-cyanoguanidine: MS (ES), 554 $[M+H]^+$.

EXAMPLE 1286 Preparation of 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one
and
4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one

A. Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine

8-Carboxaldehyde-1,4-dioxa-spiro[4.5]decane (4.4 g, 26 mmol), prepared according to the method of Pearson et al. (*J. Org. Chem.* 62, 1997, 5284), aminoacetaldehyde dimethyl acetal (3.3 g, 0.31 mmol), acetic acid (1.6 g, 0.26 mmol) and sodium cyanoborohydride (2.0 g, 0.31 mmol) are stirred in methanol (140 mL) for 6 h. The methanol is evaporated and the residue is partitioned between ethyl acetate (200 mL) and 1 N NaOH (100 mL). The organic phase is dried (Na_2SO_4) and is evaporated to provide the intermediate title compound as a yellow oil (7.2 g) which is used without further purification. MS (EI), 259 $[M]^+$.

B. {1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester

Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine (6.6 g, 26 mmol), (*S*)-(2-benzyloxycarbonylamino-3-methoxy)-propionic acid (7.2 g, 28 mmol), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (12 g, 31 mmol) and N,N-diisopropylethylamine (7.7 g, 60 mmol) are stirred in DMF (200 mL) for 18 h. The DMF is evaporated and the residue diluted with ethyl acetate (200 mL). The organic phase is washed with water (50 mL), 2 N HCl (50 mL), 1 N NaOH (50 mL), is dried ($MgSO_4$) and is evaporated to provide the intermediate title compound as a yellow oil (13 g) which is used without further purification. MS (ES), 495 $[M+H]^+$.

C. 4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester

{1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester (12.8 g, 26 mmole) and *p*-toluenesulphonic acid monohydrate (0.74 g, 3.9 mmol) are placed in toluene (150 mL) and stirred at 60-70°C for 7 h. The mixture is evaporated and the residue is purified by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) to provide the intermediate title compound as a clear colorless oil (5.0 g, 45%). MS (ES), 431 $[M+H]^+$.

D. 1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one

4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester (4.7 g, 11 mmol) and 10% Pd on carbon (1.0 g) are stirred in methanol (150 mL) under a hydrogen atmosphere for 18 h. The mixture is filtered through Celite® and is evaporated to provide the intermediate title compound as a clear colorless oil (3.3 g, 11 mmol). MS (EI), 298 $[M]^+$.

E. 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one

1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one (3.3 g, 11 mmol), (5-chloro-thiophen-2-yloxy)-acetic acid (2.1 g, 11 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (3.9 g, 12 mmol) and triethylamine (3.3 g, 33 mmol) are stirred in DMF (100 mL) for 8 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with water, 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$)

and is evaporated. The residue is purified by flash chromatography (silica gel, 4:1 ethyl acetate/hexanes) to provide the intermediate title compound as a clear colorless oil (2.8 g, 54%). MS (ES), 473 $[M+H]^+$.

F. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one (2.8 g, 5.9 mmol) is placed in 80:20 acetic acid/water and heated at 65°C for 0.2 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with 1 N NaOH, is dried ($MgSO_4$) and is evaporated to provide the intermediate title compound as a clear colorless oil (2.4 g, 95%). MS (ES), 429 $[M+H]^+$.

G. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one
and
4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one

4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one (0.07 g, 0.14 mmol), morpholine (0.025 g, 0.28 mmol), acetic acid (0.008 g, 0.14 mmol) and sodium cyanoborohydride (0.01 g, 0.17 mmol) are stirred in methanol (1 mL) for 48 h. The solvent is removed in vacuo and the residue is purified by flash column chromatography (silica gel, 98:2 dichloromethane/methanol) to provide the cis isomer compound as a colorless resin (0.01 g, 15%). MS (ES), 500 $[M+H]^+$.

The trans isomer is also isolated (0.02, g, 29%). MS (ES), 500 $[M+H]^+$.

The following compounds are also prepared in a similar manner to that descroibed in Example 1286.

Example 1287 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-{4-[(2-hydroxy-ethyl)-methyl-1-amino]-cyclohexylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one: MS (ES), 488 $[M+H]^+$.

EXAMPLE 1288 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[(2-hydroxy-ethyl)-methyl-1-amino]-cyclohexylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one:
MS (ES), 488 $[M+H]^+$.

EXAMPLE 1289 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one: MS (ES), 541 $[M+H]^+$.

EXAMPLE 1290 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one: MS (ES), 541 $[M+H]^+$.

EXAMPLE 1291 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one: MS (ES), 535 $[M+H]^+$.

EXAMPLE 1292 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one: MS (ES), 535 $[M+H]^+$.

EXAMPLE 1293 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 501 $[M+H]^+$.

EXAMPLE 1294 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 501 $[M+H]^+$.

EXAMPLE 1295 4-(4-cis-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester: MS (ES), 571 $[M+H]^+$.

EXAMPLE 1296 4-(4-trans-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester: MS (ES), 571 $[M+H]^+$.

EXAMPLE 1297 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 514 $[M+H]^+$.

EXAMPLE 1398 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 514 $[M+H]^+$.

EXAMPLE 1399 1-cis-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one MS (ES), 512 $[M+H]^+$.

EXAMPLE 1300 1-trans-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one:
MS (ES), 512 $[M+H]^+$.

EXAMPLE 1301 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one MS (ES), 521 $[M+H]^+$.

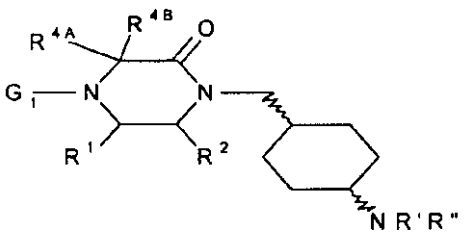
EXAMPLE 1302 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one:
MS (ES), 521 $[M+H]^+$.

EXAMPLE 1303 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one: MS (ES), 506 $[M+H]^+$.

EXAMPLE 1304 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one:
MS (ES), 506 $[M+H]^+$.

EXAMPLE 1305 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 518 $[M+H]^+$.
and
EXAMPLE 1306 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one:
MS (ES), 518 $[M+H]^+$.

Similarly, additional 1-(alkyl,arly)amino-4-methylcyclohexyl compounds can be prepared from intermediates having a structure



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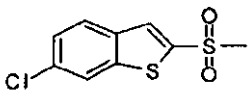
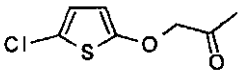
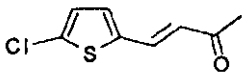
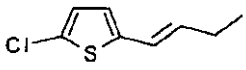
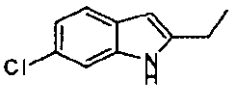
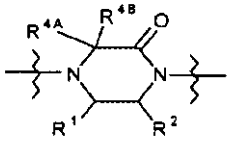
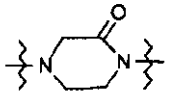
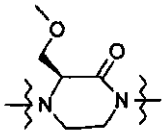
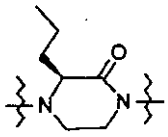
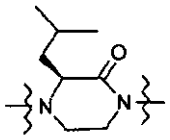
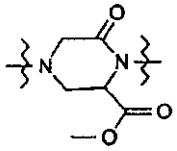
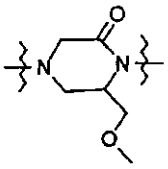
 ,  ,  ,

 , and  ;

 includes but is not limited to

 ,  , 

 ,  , and  ; and

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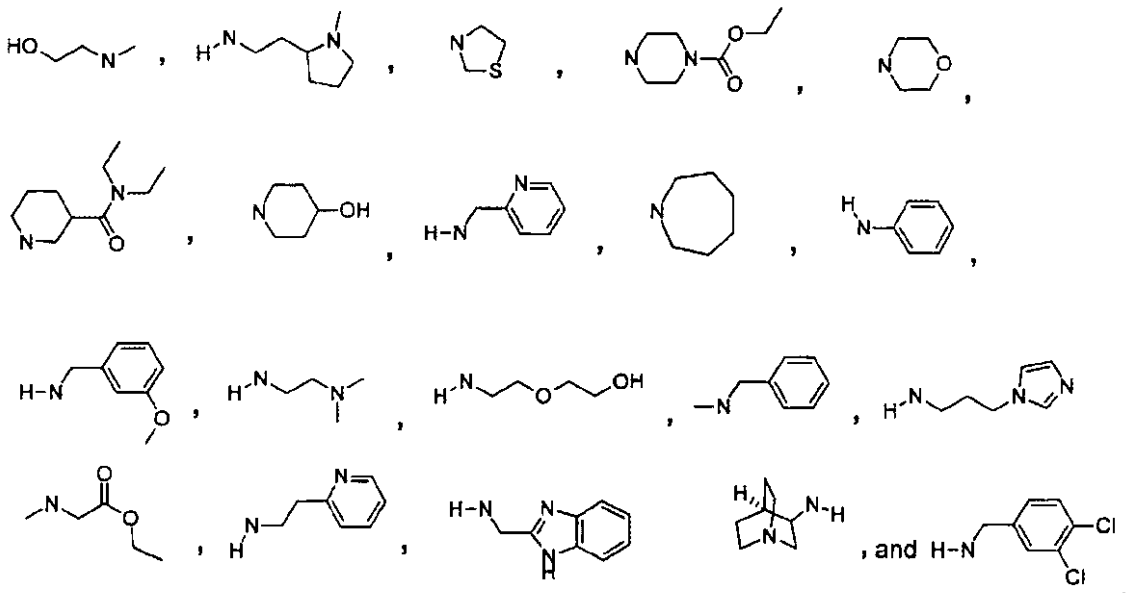


EXAMPLE 1307 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

A. 5-hydroxymethyl-2-methylthiopyrimidine

To a solution of 2-methylthiopyrimidine-5-carboxaldehyde (1.35 g, 8.7 mmol), prepared according to the method of Gupton et al. (*J. Het. Chem.* 28, 1991, 1281), in methanol (1 mL) at 0°C is added sodium borohydride (0.3 g, 7.9 mmol). The mixture is stirred for 0.5 h and is concentrated *in vacuo*. The residue is partitioned between EtOAc and 1 N NaOH. The organic phase is dried ($MgSO_4$) and is evaporated to yield the intermediate title compound as a yellow solid (1.18 g, 87%). MS (ES), 157 $[M+H]^+$.

B. 5-bromomethyl-2-methylthiopyrimidine

5-hydroxymethyl-2-methylthiopyrimidine (0.1 g, 0.61 mmol), triphenylphosphine (0.45 g, 1.7 mmol) and carbon tetrabromide (0.28 g, 0.85 mmol) are stirred in benzene (5 mL) for 24 h. The mixture is evaporated and the residue is purified by flash chromatography (silica gel, 4:1 hexanes/ethyl acetate) to provide the intermediate title compound as a white solid (0.08 g, 61%). MS (ES), 219/221 $[M+H]^+$ (Br).

C. 4-benzyloxycarbonyl-3-(*S*)-methoxymethyl-1-[(2-methylthiopyrimidin-5-yl)-methyl]-piperazine-2-one

4-Benzyloxycarbonyl-3-(*S*)-methoxymethyl-piperazine-2-one (0.1 g 0.37 mmol), 5-bromomethyl-2-methylthiopyrimidine (0.08 g, 0.37 mmol) and tetra-*n*-butylammonium bromide

(0.06 g, 0.19 mmol) are placed in dichloromethane (1 mL) and 50% aqueous NaOH (0.03 mL) and stirred for 4 h. The mixture is diluted with water and is extracted with dichloromethane (2 X 20 mL). The combined organic extracts are dried ($MgSO_4$) and are evaporated. The residue is purified by flash chromatography (silica gel, 98:2 dichloromethane/methanol) to provide the intermediate title compound as a colorless oil (0.05 g, 33%). MS (ES), 417 $[M+H]^+$.

D. 4-benzyloxycarbonyl-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

4-benzyloxycarbonyl-3-(*S*)-methoxymethyl-1-[(2-methylthiopyrimidin-5-yl)-methyl]-piperazine-2-one (0.045 g, 0.11 mmol) is dissolved in dichloromethane (3 mL) and cooled to -78°C. 57-86% 3-Chloroperoxybenzoic acid (0.095 g, 0.33 mmol) is added and the mixture is warmed to room temperature. The mixture is diluted with dichloromethane (20 mL) and is washed with dilute aqueous Na_2CO_3. The organic phase is dried (Na_2SO_4) and is evaporated. The crude residue is used without further purification. MS (ES), 449 $[M+H]^+$. The residue is placed in DMF (1 mL) and N,N-dimethylethylamine (0.05 g, 0.6 mmol) is added. The mixture is stirred for 4 h and is concentrated *in vacuo*. Purification by flash chromatography (silica gel, 9:1 dichloromethane/methanol) provided the intermediate title compound as a colorless resin (0.01 g, 20%). MS (ES), 457 $[M+H]^+$.

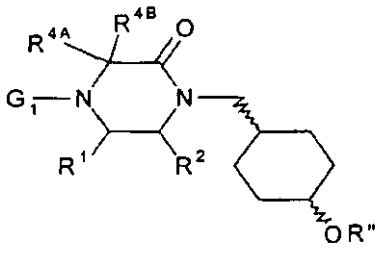
E. 1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

*4-Benzyloxycarbonyl-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(S)-*methoxymethyl-piperazine-2-one (0.01 g, 0.02 mmol) and 10% Pd on carbon (0.01 g) are stirred in acetic acid (3 mL) under a hydrogen atmosphere for 18 h. The mixture is filtered through Celite® and is evaporated to provide the intermediate title compound as a clear colorless oil (0.002 g). MS (ES), 323 $[M+H]^+$.

F. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

The title compound can be prepared by placing 1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one, (5-chloro-thiophen-2-yloxy)-acetic acid, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and triethylamine in DMF and stirring 8-16 h. The mixture is evaporated and is diluted with ethyl acetate. The organic phase is washed with water, 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$) and is evaporated. The residue is purified by flash chromatography (silica gel, 4:1 ethyl acetate/hexanes) to provide the title compound.

Similarly, 2-amino & alkoxy-4&5-substituted-methylpyrimidinyl compounds can be prepared from intermediates having a structure



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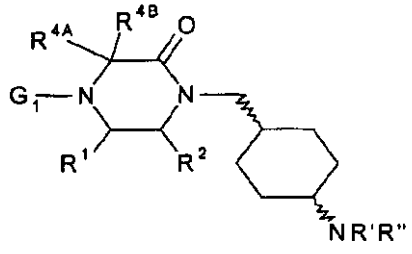

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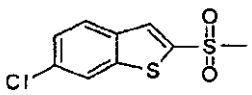

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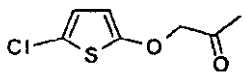

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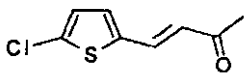

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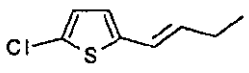

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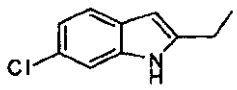

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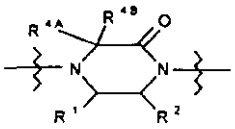

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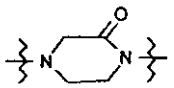

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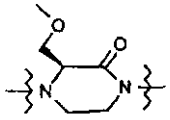

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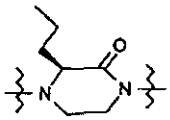

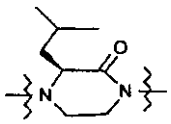

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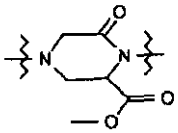

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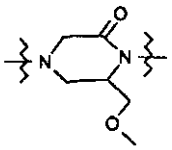

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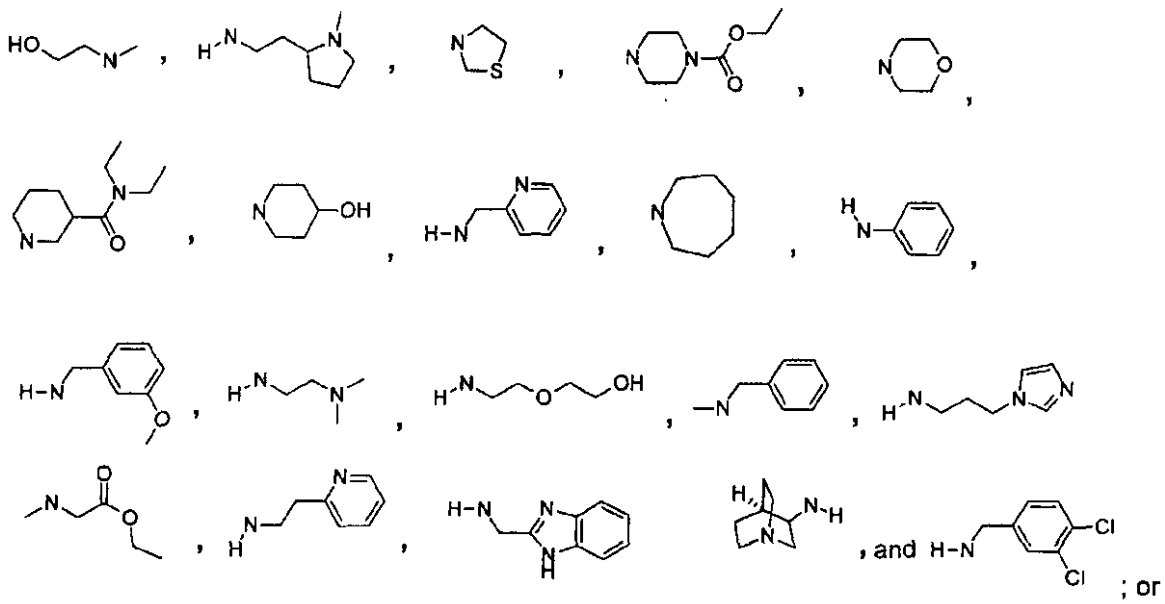

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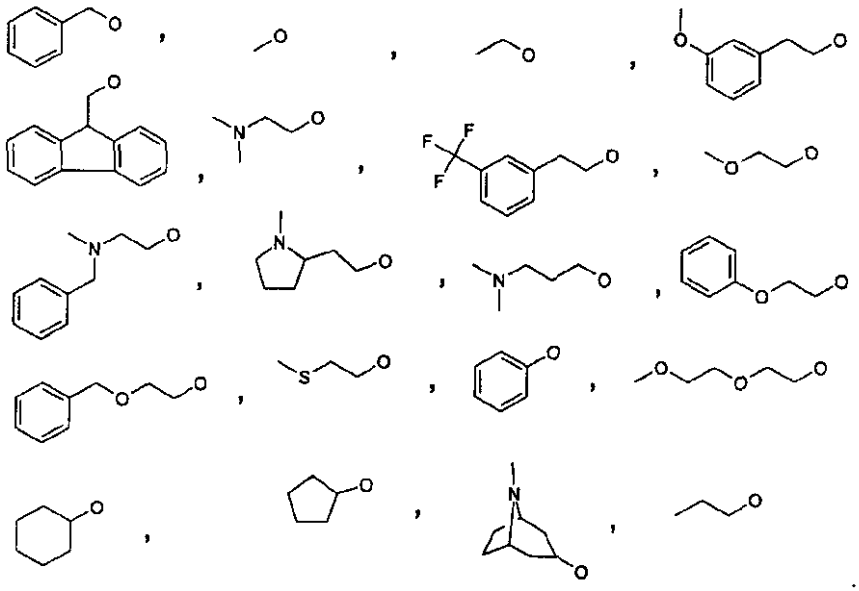


EXAMPLE 1308. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione.

A. Methyl 2-amino -4-hydroxymethlybenzoate.

To a solution of 16.0 g (76.6 mmole) of dimethyl aminoterephthalate in 200 ml of anhydrous THF cooled to -78°C is added 250 ml (250 mmole) of 1 M Super Hydride dropwise over 1 hour. The mixture is stirred for an additional 1.5 hours warming to 0°C (a little starting material on TLC is observed). The mixture is poured into 300 ml of cold water and extracted with ethyl acetate. The organic layer is washed with water and the two layers are allowed to

stand for 30 minutes. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is evaporated. The residue is dissolved in ethyl acetate and the solution is poured over a Buchner funnel containing silica gel, using 150 ml of ethyl acetate to wash the funnel. The filtrate is evaporated. The residue is dissolved in the minimum amount of ethyl acetate and the solution is diluted to the cloudy point with hexane. Additional hexane is added as the product precipitates. A total of 100 ml of hexane is added and the solid is collected and vacuum dried to give 8.4 g of the title intermediate material, 98-100°C mp; 61% yield. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (d, 1H), 6.67 (s, 1H), 6.60 (d, 1H), 5.75 (bs, 2H), 4.62 (s, 2H), 3.86 (s, 3H), 1.83 (bs, 1H). EI MS, $[M]^+$=181.

B. 7-Hydroxymethlyquinazolin-4-one.

A mixture of 2.0 g (19.1 mmole) of methyl 2-amino-4-hydroxymethlybenzoate in 4 ml of formamide is heated in an oil bath of 180°C for three hours. The mixture is cooled and triturated with 70 ml of boiling ethyl acetate. The ethyl acetate is then decanted from the dark oil and cooled in a freezer overnight to precipitate 0.7 g 205-12°C mp; 40% yield. ^{1}H NMR (d_6-DMSO, 300MHz) δ 8.08 (s, 1H), 8.06 (d, 1H), 7.60 (s, 1H), 7.45 (d, 1H), 5.48 (bs, 1H), 4.65 (s, 2H), 3.35 (bs, 1H). EI MS, $[M]^+$=176.

C. 4-Chloro-7-chloromethylquinazoline.

A mixture of 2.0 g (11.3 mmole) of 7-hydroxymethylquinazolin-4-one in 25 ml of phosphorus oxychloride is heated under reflux for 30 minutes. A very thick mixture is formed and the heating is continued for an additional 1.5 hours to give a solution. The phosphorus oxychloride is evaporated in a rotary evaporator and the residue is poured into ice water. The mixture is extracted with ether. The ether is dried over $MgSO_4$, filtered, and the filtrate evaporated. The residue is treated with 10 ml of ether and filtered. The filtrate is evaporated to afford 0.8 g of intermediate product which is used directly in the next step without further purification; 33% yield. ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.07 (s, 1H), 8.30 (d, 1H), 8.06 (s, 1H), 7.78 (d, 1H), 4.78 (s, 2H). EI MS, $[M]^+$=212, 214, 216 (Cl_2 pattern).

D. 4-Amino-7-chloromethylquinazoline.

To 15 ml of a saturated ethanolic ammonia solution is added 1.0 g (4.7 mmole) of 4-chloro-7-chloromethylquinazoline. The mixture is stirred at room temperature overnight. The precipitate which forms is collected to give 0.7 g of the title intermediate product, mp>300°C; 77% yield. ^{1}H NMR (d_6-DMSO, 300MHz) δ 8.38 (s, 1H), 8.20 (d, 1H), 7.78 (bs, 2H), 7.70 (s, 1H), 7.51 (d, 1H), 4.92 (s, 2H). EI MS, $[M]^+$=193, 195 (Cl pattern).

E. 3-(4-Chloro-phenyl)-(E)-propenal.

To a solution of 3-(4-chloro-phenyl)-prop-2-(E)-en-1-ol (2.33 g, 13.8 mmol, prepared as described in *J.Med. Chem.* 1997, 1827) in 50 ml of CH_2Cl_2 is added activated manganese (IV) oxide (4.80 g , 55.3 mmol) in three portions over 3 hours and the resulting suspension is stirred at room temperature overnight. After filtration through a pad of celite and concentration *in vacuo*, the crude residue is purified by column chromatography eluting with 10% EtOAc/hexanes to provide the title intermediate compound (0.80 g , 4.80 mmol) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.71 (d, 1H), 7.48 (m, 3H), 7.41 (dd, 2H), 6.68 (dd, 1H).

F. {2-[3-(4-Chloro-phenyl)-allylamino]-ethyl}-carbamic acid tert-butyl ester.

To a solution of N-Boc-ethylenediamine (0.63 g, 4.80 mmol) in 20mL of MeOH is added 3-(4-chloro-phenyl)-(E)-propenal (0.80 g, 4.80 mmol). After stirring for 3 hours at room temperature over 4A molecular sieves, $NaBH_4$ (0.19 g, 5.00 mmol) is added. The reaction mixture is stirred for 16 hours, then diluted with EtOAc and filtered through Celite plug. The solution is concentrated under reduced pressure. The residue is partitioned between EtOAc and H_2O and the layers are separated. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with H_2O, brine, then dried over $MgSO_4$, filtered and concentrated. The crude title product is purified by column chromatography, eluting with a gradient of 25% EtOAc/CH_2Cl_2 to 50% EtOAc/CH_2Cl_2, to provide the title intermediate compound (0.80g, 2.57 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.26 (s, 4H), 6.49 (d, 1H), 6.23 (dt, 1H), 4.96 (bs, 1H), 3.40 (m, 2H), 3.25 (m,, 2H), 2.76 (m, 2H), 1.60 (bs, 1H), 1.45 (s, 9H).

G. N-(2-tert-Butoxycarbonylamino-ethyl)-N-[3-(4-chloro-phenyl)-allyl]-oxalamic acid methyl ester.

To a solution of {2-[3-(4-chloro-phenyl)-allylamino]-ethyl}-carbamic acid tert-butyl ester (0.80 g, 2.57 mmol) in 15 ml of CH_2Cl_2 at 0°C is added triethylamine (0.54 mL , 3.85 mmol) and methyl chlorooxoacatate (0.25 mL, 2.70 mmol). The resulting mixture is stirred at 0°C for 1 h, then at room temperature for 1 h. The solution is partitioned between EtOAc and H_2O and the layers separated. The organic layer is washed with 1N HCl solution, H_2O, saturated $NaHCO_3$ solution and brine, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with 25% EtOAc/CH_2Cl_2 to provide the title intermediate compound (0.98g, 2.47 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.31 (m, 4H), 6.55 (dd, 1H), 6.14 (m, 1H), 4.88 (bs, 1H), 4.21, 4.10 (d, 2H, rotamers), 3.91, 3.86 (s, 3H, rotamers), 3.55, 3.44 (m, 2H, rotamers), 3.36 (m, 2H), 1.43 (s, 9H).

H. 1-[3-(4-Chloro-phenyl)-allyl]-piperazine-2,3-dione.

A solution of N-(2-tert-butoxycarbonylamino-ethyl)-N-[3-(4-chloro-phenyl)-allyl]-oxalamic acid methyl ester (0.49 g, 1.23 mmol) in 6 mL of EtOAc at 0 °C is saturated with HCl gas. The ice-bath is removed and the solution is stirred at room temperature for 30 min as a white

precipitate forms after about 5-10 min. After this time, the solution is concentrated to a white solid (0.41 g). The crude amine salt is suspended in 6 mL CH_2Cl_2 and 1.5 mL of MeOH. Triethylamine (0.5 mL, 3.53 mmol) is added and the resulting solution is stirred at room temperature overnight. The solution is concentrated under reduced pressure and partitioned between CH_2Cl_2 and H_2O. The aqueous layer is basified with 0.5N NaOH. The organic layer is washed with H_2O, brine, then dried over $MgSO_4$, filtered and concentrated. The title intermediate compound is obtained as a white solid (0.32 g, 1.21 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 7.82 (bs, 1H), 7.30 (s, 4H), 6.56 (d, 1H), 6.14 (dt, 1H), 4.27 (d, 2H), 3.58 (m, 4H).

I. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione.

To a solution of 1-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione (60 mg, 0.23 mmol) in 1.5 mL of DMF is added NaH (10 mg of a 60% dispersion in mineral oil, 0.24 mmol). The mixture is heated at 55°C for 20 min. To the solution is added 4-amino-7-chloromethyl-quinazoline (49 mg, 0.25 mmol), and the resulting mixture is heated at 55°C for 20 min as a white precipitate is formed. After this time, reaction mixture is quenched with a few drops of H_2O and MeOH, then concentrated. The crude product is purified by RP-HPLC, eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) over 30 minutes, and the appropriate product fractions are combined and lyopholized to provide the title compound (56 mg, 0.10 mmol) as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.78 (bs, 2H), 8.83 (s, 1H), 8.40 (s, 1H), 7.72 (d, 1H), 7.65 (s, 1H), 7.49 (d, 2H), 7.38 (d, 2H), 6.61 (d, 1H), 6.30 (dt, 1H), 4.80 (s, 2H), 4.18 (d, 2H), 3.59 (m, 4H). ISP MS, $[M+H]^+$=422.

EXAMPLE 1328. 1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione.

A. {2-[3-(5-Chloro-thiophen-2-yl)-allylamino]-ethyl}-carbamic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 1306, Part F from 3-(5-chloro-thiophen-2-yl)-(E)-propenal. ^1H NMR ($CDCl_3$, 300MHz) δ 6.77 (d, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 5.99 (dt, 1H), 4.95 (bs, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 2.76 (m, 2H), 1.48 (bs, 1H), 1.45 (s, 9H).

B. N-1-[3-(5-Chloro-thiophen-2-yl)-allylamino]-ethane-1,2-diamine hydrochloride.

A solution of {2-[3-(5-chloro-thiophen-2-yl)-allylamino]-ethyl}-carbamic acid tert-butyl ester (0.11 g, 0.35 mmol) in 20 mL of EtOAc at 0 °C is saturated with HCl gas. The ice-bath is removed and the solution is stirred at room temperature for 1 h. After this time, the solution is concentrated to a white solid (0.41 g). The title compound is obtained as a white solid (0.07 g, 0.27 mmol) and used as is in the following step. ^1H NMR ($CDCl_3$, 300MHz) δ 6.76 (d, 1H), 6.68 (d, 1H), 6.54 (d, 1H), 6.01 (dt, 1H), 3.38 (m, 2H), 2.82 (m, 2H), 2.71 (m, 2H), 1.40 (bs, 3H).

C. N-[3-(5-Chloro-thiophen-2-yl)-allyl]-N'-(4-pyridin-4-yl-benzyl)-ethane-1,2-diamine.

To a solution of N-1-[3-(5-chloro-thiophen-2-yl)-allylamino]-ethane-1,2-diamine hydrochloride (0.07 g, 0.27 mmol) in 10mL of MeOH is added 4-pyridin-4-yl-benzaldehyde (0.05 g, 0.27 mmol). After stirring for 16 h at room temperature over 4A molecular sieves, $NaBH_4$ (0.01 g, 0.27 mmol) is added. The reaction mixture is stirred for 5 h, filtered through a Celite plug and concentrated. The residue is partitioned between EtOAc and H_2O and the layers are separated. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with H_2O (3X), brine, then dried over $MgSO_4$, filtered and concentrated. The crude material is purified by column chromatography, eluting with a gradient of 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 with 2% NH_4OH present to provide the title compound (0.042g, 0.11 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 8.65 (d, 2H), 7.61, (d, 2H), 7.50 (d, 2H), 7.45 (d, 2H), 6.76 (d, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 6.00 (dt, 1H), 3.38 (s, 2H), 3.35 (d, 2H), 2.78 (s, 4H), 1.78 (bs, 2H).

D. 1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione.

To a solution of N-[3-(5-Chloro-thiophen-2-yl)-allyl]-N'-(4-pyridin-4-yl-benzyl)-ethane-1,2-diamine (0.037 g, 0.10 mmol) in 1.5 ml of EtOH is added dimethyl oxalate (0.012 g, 0.10 mmol). The resulting mixture is stirred at room temperature for 16 h, then heated at 50 °C for 16 h. The solution is concentrated. The crude product is purified by column chromatography, eluting with a gradient of 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to provide the title compound as a white solid (0.024 g, 0.04 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 8.68 (d, 2H), 7.63, (d, 2H), 7.50 (m, 2H), 7.43 (d, 2H), 6.79 (d, 1H), 6.672(d, 1H), 6.59 (d, 1H), 5.87 (dt, 1H), 4.76 (s, 2H), 4.20 (d, 2H), 3.48 (s, 4H). ISP MS, $[M+H]^+$=438, 440, Cl pattern.

The following 2,3-diketopiperazine compounds are prepared in a similar fashion using the procedures described above.

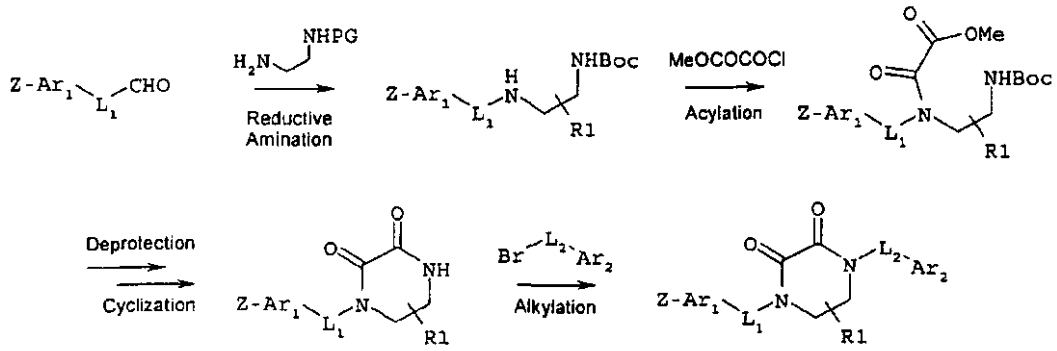
Example	Name	m/z [M+H]
1309	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione	ISP-452, Cl
1310	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione	ISP-421, Cl
1311	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione	ISP-484
1312	1-(3-carbamimidoyl-benzyl)-4-(4-carbamimidoyl-benzyl)-2,3 dioxopiperizine	ISP-379

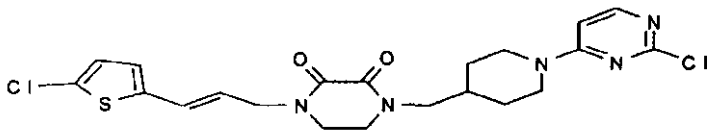
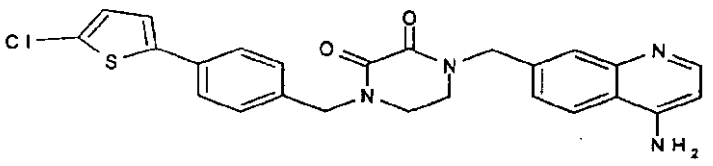
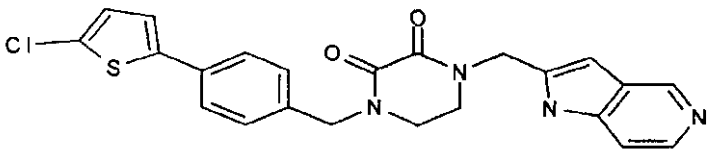
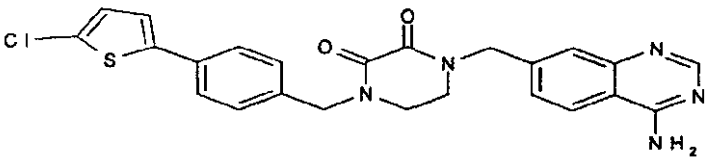
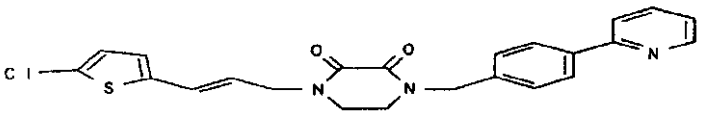
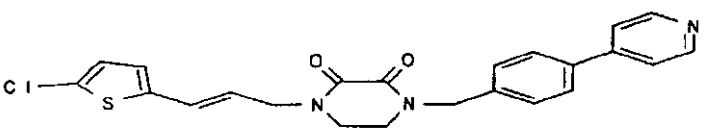
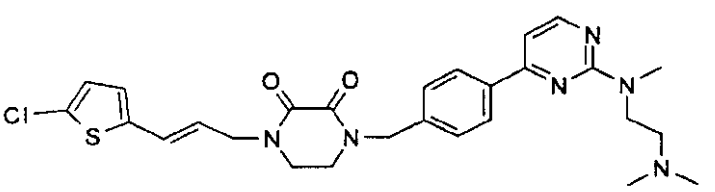
1313	Bis-1,4-(3-carbamimidoyl-benzyl)-2,3-dioxopiperizine	ISP-379
1314	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazine-2,3-dione	
1315	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-428, Cl
1316	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione	
1317	1-(4-Amino-quinolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione	
1318	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-427, Cl
1319	1-[3-(3-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1320	1-[3-(4-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	ISP-395, Cl
1321	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	ISP-401, Cl
1322	1-(6-chloro-benzo[b]thiophen-2-yl-methyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1323	1-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1324	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1325	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(thieno[3,2-b]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1326	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-2-yl-benzyl)-piperazine-2,3-dione	ISP-438, Cl
1327	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-2-yl)-benzyl]-piperazine-2,3-dione	ISP-454, Cl
1328	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione	ISP-438, Cl
1329	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-4-yl)-benzyl]-piperazine-2,3-dione	
1330	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-methoxy-pyridin-3-yl)-	ISP-468

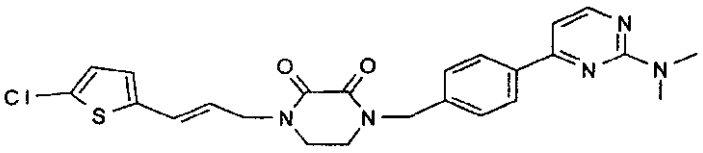
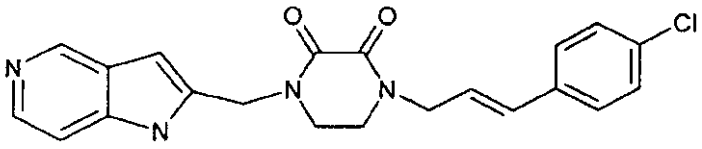
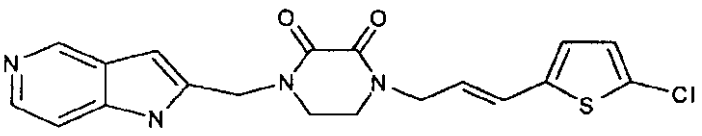
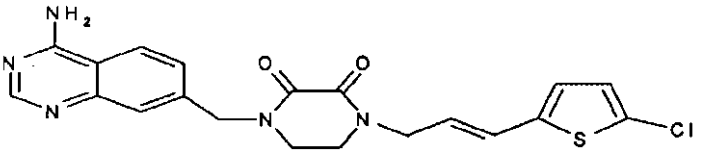
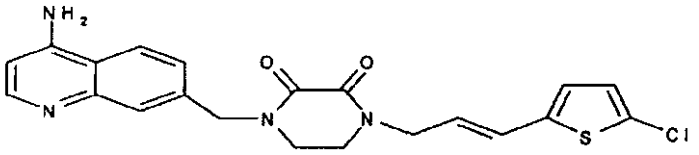
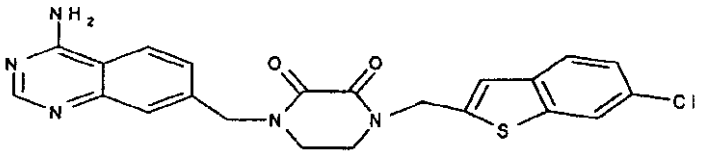
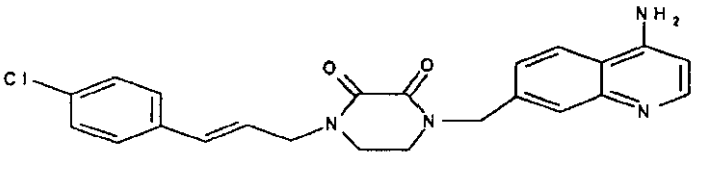
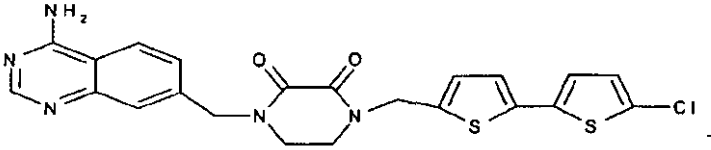
	benzyl]-piperazine-2,3-dione	
1331	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazine-2,3-dione	ISP-454
1332	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-benzyl]-piperazine-2,3-dione	ISP-482, Cl
1333	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzyl)-piperazine-2,3-dione	ISP-539, Cl
1334	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-cyclohexymethyl]-piperazine-2,3-dione	
1335	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-cyclohexylmethyl)-piperazine-2,3-dione	
1336	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methyl-piperazine-2,3-dione	
1337	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-ethyl-piperazine-2,3-dione	
1338	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-propyl-piperazine-2,3-dione	
1339	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-butyl-piperazine-2,3-dione	
1340	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-piperazine-2,3-dione	ISP-470, Cl
1341	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-isobutyl-piperazine-2,3-dione	
1342	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methoxymethyl-piperazine-2,3-dione	
1343	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid	
1344	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl ester	
1345	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid amide	
1346	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl amide	
1347	1-[4-(2-Chloro-pyrimidin-4-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-	ISP-473,

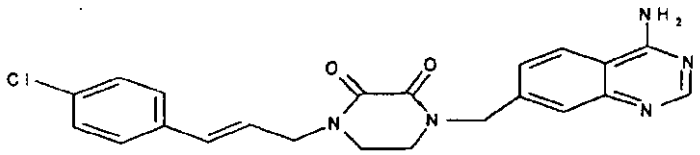
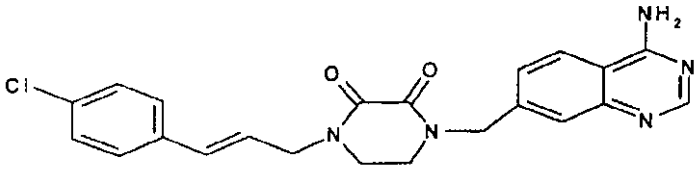
	allyl]-piperazine-2,3-dione	Cl
1348	1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione	ISP-478, Cl
1349	1-[4-(5-Chloro-thiophen-2-yl)-benzyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	ISP-451, Cl
1350	1-(4-Amino-quinolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione	ISP-477, Cl
1351	1-[1-(2-Chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-480, Cl
1352	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione	ISP-487, Cl
1353	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione	ISP-445, Cl
1354	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-3-yl-benzyl)-piperazine-2,3-dione	ISP-438, Cl
1355	1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione	ISP-479, Cl
1356	1-[4-(6-Amino-pyridin-3-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-453, Cl
1357	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-[4-(1-oxy-pyridin-3-yl)-benzyl]-piperazine-2,3-dione	ISP-454, Cl
1358	1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione	ISP-528, Cl
1359	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione	ISP-481, Cl
1360	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione	ISP-439, Cl
1361	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazine-2,3-dione	ISP-469, Cl

The following 2,3-diketopiperazine compounds are prepared in a similar fashion as in example 1308 and outlined in the following reaction scheme.

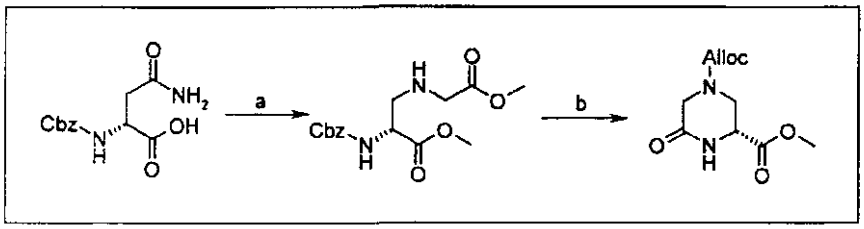


Example	structure	formula	molecular weight
1362		$C_{21}H_{23}Cl_2N_5O_2S$	480,42
1363		$C_{25}H_{21}ClN_4O_2S$	476,99
1364		$C_{23}H_{19}ClN_4O_2S$	450,95
1365		$C_{24}H_{20}ClN_5O_2S$	477,98
1366		$C_{23}H_{20}ClN_3O_2S$	437,95
1367		$C_{23}H_{20}ClN_3O_2S$	437,95
1368		$C_{27}H_{31}ClN_6O_2S$	539,1

1369		$C_{24}H_{24}ClN_5O_2S$	482,01
1370		$C_{21}H_{19}ClN_4O_2$	394,86
1371		$C_{19}H_{17}ClN_4O_2S$	400,88
1372		$C_{20}H_{18}ClN_5O_2S$	427,91
1373		$C_{21}H_{19}ClN_4O_2S$	426,92
1374		$C_{22}H_{18}ClN_5O_2S$	451,93
1375		$C_{23}H_{21}ClN_4O_2$	420,89
1376		$C_{22}H_{18}ClN_5O_2S_2$	484,00

1377		$C_{22}H_{20}ClN_5O2$	421,88
1378		$C_{22}H_{20}ClN_5O_2$	421,88

Scheme 1 A synthetic scheme of the C(6)-ester template.

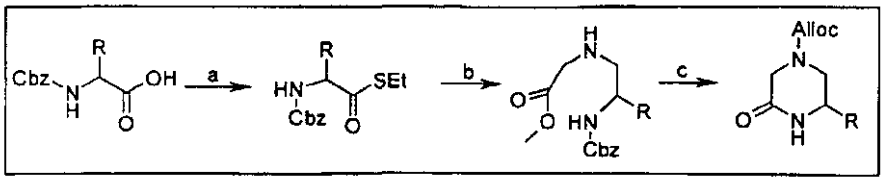


Reagents: (a) 1. PIFA, Py; 2. $SOCl_2$, MeOH; 3. $BrCH_2CO_2Me$. (b) 1. Pd on C, H_2; 2. Alloc-Cl, Et_3N.

Example 1379 (*R*)-5-Oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.

To a solution containing methyl (*R*)-6-oxopiperazine-2-carboxylate (1.32 g, 8.35 mmol), prepared by the method of Aebischer, in anhydrous dichloromethane (30 mL) at 0 °C was added triethylamine (1.26 g, 12.5 mmol) followed by allylchloroformate (1.20 g, 10.0 mmol). After 1 h, the reaction mixture was poured onto a 1:1 mixture of CH_2Cl_2/water (200 mL), acidified using 1N HCl and the layers were separated. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was chromatographed on silica gel (CH_2Cl_2 to 1% MeOH/CH_2Cl_2) to provide 1.22 g (60%) of (*R*)-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester as a viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (bs, 1H), 5.90 (m, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 4.05-4.26 (m, 3H), 3.80 (s, 3H), 3.72 (m, 2H) ppm. Mass Spectrum: (ISP loop) *m/z* 243 (M+H).

Scheme 2 A synthetic scheme of the C(6)-alkyl templates.



Reagents: (a). DCC, EtSH, CH_2Cl_2. (b). 1. TES, Pd/C, Acetone. 2. H_2N-Gly-OMe*HCl, $NaBH_3(CN)$, MeOH. (c). 1. Pd/C, MeOH, H_2. 2. Alloc-Cl, Et_3N, CH_2Cl_2.

Example 890: (*R*)-3-Isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester.

A. (*R*)-2-Benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester. To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-butyric acid (5.0 g, 20.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was added DMAP (258 mg, 2.0 mmol) followed by chilled EtSH (1.6 mL, 22.0 mmol). Dicyclohexylcarbodiimide (4.5 g, 22.0 mmol) was added in one portion and the reaction was complete after 30 min. The solid material was removed by vacuum filtration and the filtrate was concentrated. The crude product was purified by flash silica gel chromatography (hexane to 8:1 hexane/EtOAc) to provide (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.21 g, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 2.27 (m, 1H), 2.88 (q, *J* = 7.5 Hz, 2H), 4.35 (dd, *J* = 9.5, 4.6 Hz, 1H), 5.13 (s, 2H), 5.25 (br d, *J* = 9.5 Hz, 1H), 7.30-7.36 (m, 5H) ppm.

Using the appropriate amino acids the following compounds were prepared:

Example	Name	m/z(M+H)$^+$
1380	(*S*)-2-Benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester.	296
1381	(*R*)-2-Benzyloxycarbonylamino-4-methyl-pentanethioic acid S-ethyl ester.	310
1382	(*S*)-2-Benzyloxycarbonylamino-4-methyl-pentanethioic acid S-ethyl ester.	310
1383	(*S*)-2-Benzyloxycarbonylamino-thiopropionic acid S-ethyl ester.	268
1384	(*R*)- 2-Benzyloxycarbonylamino-3-methoxy-thiopropionic acid S-ethyl ester	298

1385	(*S*)- 2-Benzyloxycarbonylamino-3-methoxy-thiopropionic acid S-ethyl ester	298
1386	(*S*)-3-Benzyloxycarbonylamino-3-ethylsulfanylcarbonyl-propionic acid tert-butyl ester	368

B. (*R*)-(1-Formyl-2-methyl-propyl)-carbamic acid benzyl ester. To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.2 g, 17.6 mmol) in acetone (100 mL) was added Pd-on-C (10%, 233 mg). The heterogeneous mixture was cooled to 0 °C and Et_3SiH (8.4 mL, 53 mmol) was quickly added. After 30 min, the reaction mixture was filtered through a pad of celite and the filtrate concentrated and partitioned between hexane (200 mL) and acetonitrile (300 mL). The layers were separated and the ACN phase was washed once with hexane (100 mL) and then concentrated to afford crude (*R*)-(1-formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g) which was used directly without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (m, 1H), 4.31 (m, 1H), 5.09 (s, 2H), 5.45 (br, 1H), 7.30-7.45 (m, 5H), 9.65 (s, 1H) ppm.

C. (*R*)-(2-Benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester. To a solution containing crude (*R*)-(1-formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g, 17.6 mmol) in anhydrous MeOH (100 mL) at 0 °C was added glycine ethyl ester hydrochloride (9.5 g, 70.4 mmol). After 10 min, 1.0 M $NaCNBH_3$ in THF (27 mL, 27 mmol) was added and the heterogeneous reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was concentrated and the residue was partitioned between diethyl ether (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The layers were separated and the aqueous layer was extracted twice with diethyl ether (2 x 200 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product which was purified by flash silica gel chromatography (hexane/EtOAc, 2:1 to 1:1) which provided 4.2 g (74%) of (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.25 (t, J = 8.4 Hz, 3H), 1.62 (br s, 1H), 1.80 (m, 1H), 2.65-2.70 (m, 2H), 3.37 (ABq, Δ_{AB} = 32.3 Hz, J_{AB} = 17.4 Hz, 2H), 4.16 (q, J = 8.4 Hz, 2H), 5.14 (s, 2H), 7.28-7.36 (m, 5H) ppm. Mass Spectrum: (ion spray): *m/z* 323 (M+H).

The following examples were prepared according to the above procedure:

Example	Name	m/z(M+H)$^+$
1387	(*S*)-(2-Benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester.	323
1388	(*S*)-(2-Benzyloxycarbonylamino-4-methyl-pentylamino)-acetic acid methyl ester.	323
1389	(*R*)-(2-Benzyloxycarbonylamino-4-methyl-pentylamino)-acetic acid methyl ester.	323
1390	(*S*)-(2-Benzyloxycarbonylamino-propylamino)-acetic acid methyl ester.	295
1391	(*R*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid ethyl ester	325
1392	(*S*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid ethyl ester	325
1393	(*S*)-3-Benzyloxycarbonylamino-4-(methoxycarbonylmethyl-amino)-butyric acid tert-butyl ester.	395

D. (*R*)-6-Isopropyl-piperazin-2-one. To a Parr vessel charged with (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester (4.2 g, 13.0 mmol) in MeOH (130 mL) was added Pd-on-C (10%, 396 mmol). The reaction vessel was pressurized with 40 PSI hydrogen pressure and shaken for 4 h at ambient temperature. The reaction mixture was then filtered through celite and the filtrate concentrated to provide 1.77 g (95%) of (*R*)-6-isopropyl-piperazin-2-one as an off-white solid which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.68 (sept, *J* = 6.7 Hz, 1H), 2.67 (dd, *J* = 12.8, 8.9 Hz, 1H), 3.09-3.22 (m, 2H), 3.46 (ABq, Δ_{AB} = 34.3 Hz, J_{AB} = 17.5 Hz, 2H), 5.97 (br s, 1H) ppm.

The following examples were prepared according to the above procedure:

Example	Name	m/z(M+H)$^+$
1394	(*S*)-6-Isopropyl-piperazine-2-one.	142
1395	(*S*)-6-Isobutyl-piperazine-2-one.	157
1396	(*R*)-6-Isobutyl-piperazine-2-one.	157
1397	(*S*)-6-Methyl-piperazine-2-one.	
1398	(*R*)-6-Methoxymethyl-piperazin-2-one	144
1399	(*S*)-6-Methoxymethyl-piperazin-2-one	144

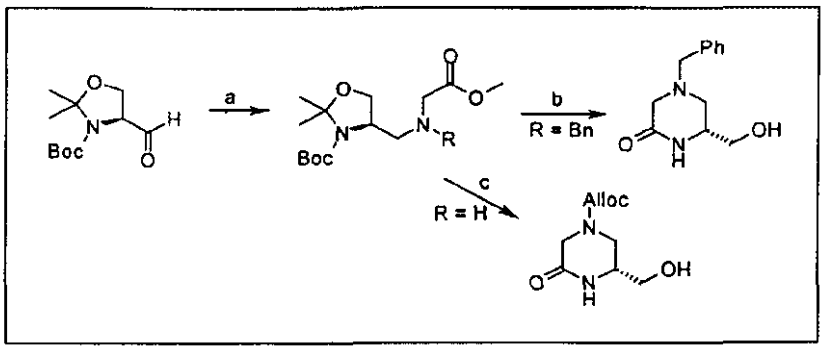
E. (*R*)-3-Isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester.

To a solution of (*R*)-6-isopropyl-piperazin-2-one (1.77 g, 12.5 mmol) in anhydrous CH_2Cl_2 (45 mL) at 0 °C was added triethylamine (2.6 mL, 18.7 mmol) followed by allyl chloroformate (1.6 mL, 15.0 mmol). The mixture was stirred at 0 °C for 30 min and at ambient temperature for 30 min then was partitioned between CH_2Cl_2 (30 mL) and water (75 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL) and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated on to silica gel. The mixture was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH/CH_2Cl_2 →2%→4%) to provide 2.62 g (93%) of (*R*)-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) d 6.85-7.08 (m, 1H), 5.82-5.99 (m, 1H), 5.19-5.33 (m, 2H), 4.60 (d,*J* = 5.6 Hz, 2H), 4.21 (d, *J* = 18.4 Hz, 1H), 3.97 (d, *J* = 18.4 Hz, 1H), 3.71-3.90 (m, 1H), 3.16-3.37 (m, 2H), 1.69-1.81 (m, 1H), 0.94-1.01 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 226 $(M+H)^+$.

The following examples were prepared according to the above procedure:

Example	Name	m/z(M+H)$^+$
1400	(*S*)-3-Isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	226
1401	(*S*)-3-Isobutyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	241
1402	(*R*)-3-Isobutyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	241
1403	(*S*)-3-Methyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	199
1404	(*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester	229
1405	(*S*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester	229
1406	(*S*)-3-tert-Butoxycarbonylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester	298

Scheme 3 A synthetic scheme of the *C*(6)-Hydroxymethylketopiperazine.



Reagents: (a) 1. $RNHCH_2CO_2Me$, $NaB(OAc)_3H$, 4A MS. (b) Sat'd HCl / MeOH; K_2CO_3. (c) 1. Alloc-Cl, Et_3N, CH_2Cl_2. 2. Sat'd HCl / MeOH; K_2CO_3.

Example 1407 (*R*)-4-Benzyl-6-hydroxymethyl-piperazin-2-one

A: (*R*)-4-[(Benzyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester. To a mixture of the Garner's aldehyde 1 (Garner, P., Park, J. - M. Org. Synthesis 1991, 70, 18) (31 g, 135 mmol), *N*-benzyl glycine ethyl ester (28.7 g, 149 mmol) and powdered 4Å MS (40 g) in 1,2-dichloroethane (300 mL) was added sodium triacetoxy-borohydride (43 g, 203 mmol) at 0 °C. After 12 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution, filtered through Celite, and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 10 : 1 to 3 : 1) provided 42.6 g (78%) of (*R*)-4-[(benzyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 4.14 (q, *J* = 6.9 Hz, 2H), 4.1-3.9 (m, 3H), 3.85-3.7 (m, 2H), 3.41-3.24 (m, 2H), 3.0 (d, *J* = 12.5 Hz, 1H), 2.68-2.55 (m, 1H), 1.57 (m, 3H), 1.47 (s, 9H), 1.45 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 407 $(M+H)^+$.

B: (*R*)-4-Benzyl-6-hydroxymethyl-piperazin-2-one. A solution of (*R*)-4-[(benzyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (42.6 g, 105 mmol) in MeOH (500 mL) was bubbled with anhydrous HCl gas for 30 min at 0°C. After 15 h at ambient temperature, the mixture was concentrated under reduced pressure and treated with K_2CO_3 (100 g, 0.72 mol) in MeOH (500 mL). Stirring was continued until the pH of the aliquot was basic (~24 h) after which the suspension turned colorless. The mixture was filtered, and the filtrate was concentrated and chromatographed on SiO_2 (5% to 15% MeOH in CH_2Cl_2) to afford 23 g (100%) of (*R*)-4-benzyl-6-hydroxymethyl-piperazin-2-one as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 6.95 (s, 1H), 3.68-3.6 (m, 2H), 3.58-3.45 (m, 4H), 3.17 (d, *J* = 14 Hz, 1H), 3.11 (d, *J* = 14 Hz, 1H), 2.71 (dd, *J* = 10.0, 3.5 Hz, 1H), 2.56 (dd, *J* = 9.5, 4.5 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 221 $(M+H)^+$.

Example 1408 (*R*)-3-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester

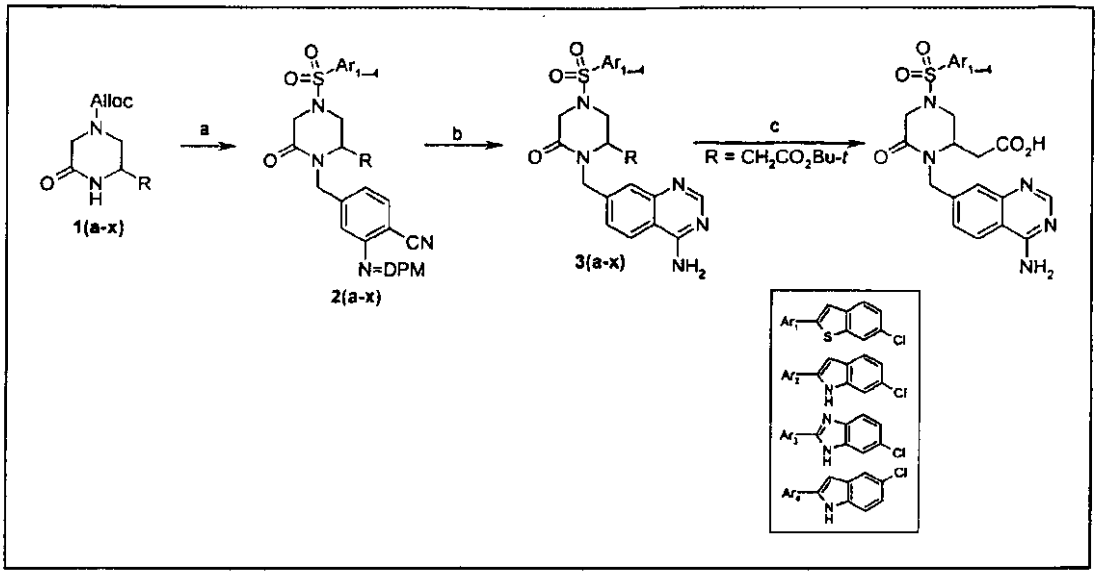
A: (*R*)-4-[(Ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester A solution of glycine methyl ester hydrochloride (26 g, 208 mmol) and Et_3N (28 mL, 203 mmol) in MeOH (200 mL) at 0 °C was treated with the Garner's aldehyde 1 (12 g, 52 mmol), followed by addition of a 1.0 M solution of $NaBH_3CN$ in THF (60 ml, 60 mmol.). After 3 hours at ambient temperature, the reaction mixture was concentrated and diluted with EtOAc and sat $NaHCO_3$ solution. The organic phase was separated, dried ($MgSO_4$), filtered, and

concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 2 : 1 to 1 : 2) provided 14.5 g (92%) of (*R*)-4-[(ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 2H). 3.75 (m, 1H), 3.7 (s, 3H), 3.45 (s, 2H), 2.7 (m, 2H), 1.5 (m, 15H) ppm. Mass Spectrum: (ESI) *m/z* 303 $(M+H)^+$.

B. (*R*)-3-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*R*)-4-[(ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (14.5 g, 48 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added triethylamine (12 mL, 86 mmol) followed by allylchloroformate (6.6 mL, 63 mmol). After 1 h at ambient temperature, the reaction mixture was diluted with saturated NH_4Cl and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to provide 15.4 g (83%) of (*R*)-4-[(allyloxycarbonyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester as a viscous oil. Mass Spectrum: (ESI) *m/z* 387 $(M+H)^+$.

A solution of (*R*)-4-[(allyloxycarbonyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (15.4 g, 40 mmol) in CH_2Cl_2 (20 mL) and TFA (150 mL) was stirred for 12 h at ambient temperature. The mixture was concentrated under reduced pressure (azeotrophic evaporation with toluene) and treated with excess K_2CO_3 in MeOH (300 mL). Stirring was continued until the pH of the aliquot was basic (~24 h). The mixture was filtered, and the filtrate was concentrated and chromatographed on SiO_2 (5% to 20% MeOH in CH_2Cl_2) to afford 6 g (70%) of (*R*)-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.97-5.88 (m, 1H), 5.35-5.24 (m, 2H), 4.62 (d, *J* = 5.7 Hz, 2H), 4.2-4.1 (m, 2H), 3.8-3.4 (m, 5H), 2.65 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 214 $(M+H)^+$.

Scheme 4 A synthetic scheme of the C(6)-substituted sulfonamide inhibitors.



Reagents: (a). 1. NaH, 4-bromomethyl-2-diphenylmethyleneaminobenzonitrile, THF. 2. $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, 3. sulfonyl chloride, Et_3N, CH_2Cl_2, (b). 1. c-HCl , MeOH; 2. Triazine, AcOH, EtOH, reflux. (c). TFA, CH_2Cl_2.

Example 1409 (*R*)-1-(4-Amino-quinazolin-7-yl-methyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one.

A. (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*R*)-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.60 g, 11.5 mmol) in anhydrous THF (30 mL) and anhydrous DMF (2 mL) at 0 °C was added sodium hydride (600 mg, 60% dispersion in mineral oil, 14.95 mmol). The mixture was stirred at 0 °C for 15 min until gas evolution ceased, then 2-(benzyhydrylidene-amino)-4-bromomethyl-benzonitrile (4.41 g, 12.1 mmol) was added. The reaction was allowed to warm slowly to ambient temperature over 3 h and the now black solution was quenched with saturated aqueous NH_4Cl (100 mL) and partitioned between water (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (2 x 250 mL) and the combined organic phases were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1%MeOH/CH_2Cl_2→1.8%→2%) to afford 4.98 g (83%) of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a sticky brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.17-7.52 (m, 10H), 6.86 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.58 (s, 1H), 5.83-5.98 (m, 1H), 5.18-5.42 (m, 3H), 4.61 (d, *J* = 5.5 Hz, 2H), 4.20-4.31 (m, 1H), 3.92-4.16 (m, 2H),

3.71 (d, *J* = 15.1 Hz, 1H), 2.70-2.78 (m, 2H), 1.87-2.02 (m, 1H), 0.94 (d,*J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 521 $(M+H)^+$.

B (*R*)-2-(Benzhydrylidene-amino)-4-(2-isopropyl-6-oxo-piperazin-1-ylmethyl)-benzonitrile. To a solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.0 g, 3.85 mmol) in anhydrous CH_2Cl_2 (40 mL) at ambient temperature was added morpholine (1.6 mL, 19.2 mmol) followed by *tetrakis* (triphenyl phosphine) palladium (444 mg, 0.385 mmol). The yellow solution was stirred for 1 h then concentrated on to silica gel and flash column chromatographed (CH_2Cl_2→1%MeOH/CH_2Cl_2 →2%) to provide 1.4 g (83%) of (*R*)-2-(benzhydrylidene-amino)-4-(2-isopropyl-6-oxo-piperazin-1-ylmethyl)-benzonitrile as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.19-7.69 (m, 9H), 6.86 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.60 (d, *J* = 1.0 Hz, 1H), 5.31 (d, *J* = 15.4 Hz, 1H), 3.85 (d, *J* = 15.5 Hz, 1H), 3.72 (t, *J* = 4.6 Hz, 1H), 3.43-3.59 (m, 1H), 2.82-2.91 (m, 2H), 2.42-2.48 (m,1H), 1.96-2.05 (m, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 437 $(M+H)^+$.

C (*R*)-2-(Benzhydrylidene-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-(2-isopropyl-6-oxo-piperazin-1-ylmethyl)-benzonitrile (0.61 g, 1.4 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added diisopropylethylamine (320 μL, 1.82 mmol) followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (375 mg, 1.4 mmol). The reaction was stirred at ambient temperature for 1 h then concentrated on to silica gel and flash column chromatographed (Hexane:EtOAc, 4:1→2:1) to provide 681 mg (73%) of (*R*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.86 (m, 3H), 7.72 (d, *J* = 7.0 Hz, 2H), 7.32-7.52 (m, 5H), 7.09-7.27 (m, 5H), 6.77 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.53 (d, *J* = 1.1 Hz, 1H), 5.30 (d, *J* = 15.2 Hz, 1H), 4.03-4.16 (m, 1H), 3.75 (d, *J* = 15.2 Hz, 1H), 3.57 (d, *J* = 16.7 Hz, 1H), 2.82-2.90 (m, 1H), 2.63 (dd, *J* = 12.3, 3.7 Hz, 1H), 2.07-2.17 (m, 1H), 0.93-1.04 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 667 $(M+H)^+$.

Examples:

Example	Name	m/z$(M+H)^+$
1410	(*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	651
1411	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-	750

	oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	
1412	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	750
1413	(*S*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	667
1414	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	651
1415	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	750
1416	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	750
1417	(*R*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	681
1418	(*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	665
1419	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	764
1420	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	764
1421	(*S*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	681
1422	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	665
1423	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	764
1424	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl	764

	ester	
1425	(*S*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-methyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	
1426	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-methyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	
1427	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	
1428	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	
1429	(*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	653
1430	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	653
1431	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxymethyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	752
1432	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxymethyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	752
1433	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxymethyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	752
1434	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid tert-butyl ester	739

Example 1435 (*R*)-2-Amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]benzonitrile. To a solution of (*R*)-2-(benzyhdrylidene-amino)-4-[4-(6-*chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile* (681 mg, 1.02 mmol) in MeOH (15 mL) and THF (3 mL) at 0 °C was added concentrated HCl (10 drops). The solution was stirred at 0 °C for 15 min then concentrated to dryness and the residue purified by flash silica gel chromatography (CH_2Cl_2→1%MeOH/CH_2Cl_2→2%) to provide 481 mg (94%) of (*R*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]benzonitrile as a crunchy white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-

7.88 (m, 3H), 7.46 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.23-7.30 (m, 1H), 6.55 (s, 1H), 6.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.30 (d, *J* = 15.3 Hz, 1H), 4.37 (s, 2H), 4.08-4.22 (m, 1H), 3.78-3.90 (m, 2H), 3.57-3.69 (m, 1H), 3.10-3.18 (m, 1H), 2.78 (dd, *J* = 12.5, 4.0 Hz, 1H), 2.18-2.29 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 503 $(M+H)^+$.

Example 1436: (*R*)-1-(4-Amino-quinazolin-7-yl-methyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one. To a suspension of (*R*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]benzonitrile (468 mg, 0.93 mmol) in abs. EtOH (12 mL) was added glacial acetic acid (540 µL, 9.31 mmol) and triazine (775 mg, 9.31 mmol). The mixture was warmed to reflux (became homogeneous) stirred for 16 h, cooled and concentrated to dryness. The crude product was purified by reverse phase HPLC on a 2" Dynamax C18 column (10→100% ACN in H_2O/0.1% TFA) to provide 365 mg (61%) of (*R*)-1-(4-amino-quinazolin-7-yl-methyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one as a white, lyophilized solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (br s, 2H), 8.75 (s, 1H), 8.24-8.34 (m, 2H), 8.19 (s, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.53-7.62 (m, 3H), 5.07 (d, *J* = 16.4 Hz, 1H), 4.45 (d, *J* = 16.3 Hz, 1H), 4.06 (d, *J* = 16.4 Hz, 1H), 3.83 (d, *J* = 16.2 Hz, 1H), 3.63 (d, *J* = 16.2 Hz, 1H), 3.34-3.45 (m, 1H), 3.02 (AB quartet, *J* = 12.6, 3.6 Hz, 1H), 2.11-2.22 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm. Mass Spectrum: (ESI): *m/z* 530 $(M+H)^+$.

The following examples were prepared according to the above procedure:

Example 1437 (*R*)-1-(4-Aminoquinazolin-7-yl-methyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (bs, 2H); 8.76 (s, 1H); 8.29 (d, *J* = 8.6 Hz, 1H); 7.65-7.73 (m, 2H); 7.55-7.62 (m, 2H); 7.40 (d, *J* = 8.7 Hz, 1H); 5.05 (d, *J* = 16.2 Hz, 1H); 4.47 (d, *J* = 16.2 Hz, 1H); 4.13 (d, *J* = 16.6 Hz, 1H); 3.80-3.93 (m, 2H); 3.35-3.65 (m, 1H); 3.18 (AB q, *J* = 12.9, 3.6 Hz, 1H), 2.09-2.19 (m, 1H); 0.99 (d, *J* = 6.8 Hz, 3H); 0.93 (d, *J* = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 514 $(M+H)^+$.

Example 1438 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.96 (dd, *J* = 15.9, 6.85 Hz, 6H), 2.19 (m, 1H), 3.02 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.40 (m, 2H), 3.82 (d, *J* = 12.4 Hz, 1H), 4.03 (d, *J* = 16.3 Hz, 1H), 4.47 (d, *J* = 16.3 Hz, 1H), 5.06 (d, *J* = 16.3 Hz, 1H), 7.55 (m, 3H), 8.06 (d, *J* = 8.6 Hz, 1H), 8.20 (s, 1H), 8.28

(d, J = 8.6 Hz, 1H), 8.33 (d, J = 1.9 Hz, 1H), 8.76 (s, 1H), 9.71 (br.s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 530 $(M+H)^+$.

Example 1439 (*S*)-1-(4-Aminoquinazolin-7-yl-methyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.96 (dd, J = 17.84, 6.86 Hz, 6H), 2.15 (m, 1H), 3.18 (dd, J = 12.8, 3.5 Hz, 2H), 3.88 (m, 3H), 4.13 (d, J = 16.5 Hz, 1H), 4.47 (d, J = 16.3 Hz, 1H), 5.06 (d, J = 16.3 Hz, 1H), 7.40 (dd, J = 8.7, 1.8 Hz, 1H), 7.57 (s, 1H), 7.60 (d, J = 8.65 Hz, 1H), 7.74 (m, 2H), 8.29 (d, J = 8.54 Hz, 1H), 8.76 (s, 1H), 9.71 (br. s, 2H) ppm. Mass Spectrum: (ESI)*m/z* 514 $(M+H)^+$.

Example 1440 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 17.6, 6.4 Hz, 6H), 1.41 (m, 1H), 1.60 (m, 1H), 1.74 (m, 1H), 3.06 (d, J = 10.0 Hz, 1H), 3.42 (d, J = 8.8 Hz, 1H), 3.65 (d, J = 16.2 Hz, 1H), 3.73 (s, 1H), 4.05 (d, J = 16.2 Hz, 1H), 4.41 (d, J = 16.6 Hz, 1H), 5.02 (d, J = 16.6 Hz, 1H), 7.53 (s, 1H), 7.58 (dd, J = 8.6, 2.0 Hz, 2H), 8.06 (d, J = 8.6 Hz, 1H), 8.22 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H), 8.77 (s, 1H), 9.74 (s, 2H) ppm. Mass Spectrum: (ESI)*m/z* 544 $(M+H)^+$.

Example 1441 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (500 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 24.0, 6.6 Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, J = 10.2 Hz, 1H), 3.43 (m, 1H), 3.80 (d, J = 12.7 Hz, 1H), 3.89 (s, 1H), 3.93 (d, J = 9.8 Hz, 1H), 4.18 (d, J = 16.1 Hz, 1H), 4.42 (d, J = 16.6 Hz, 1H), 5.04 (d, J = 16.6 Hz, 1H), 7.41 (dd, J = 8.8, 2.0 Hz, 1H), 7.56 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 544 $(M+H)^+$.

Example 1442 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 17.6, 6.4 Hz, 6H), 1.41 (m, 1H), 1.74 (m, 1H), 3.06 (d, J = 10.0 Hz, 1H), 3.42 (d, J = 8.8 Hz, 1H), 3.65 (d, J = 16.2 Hz, 1H), 3.73 (s, 1H), 4.05 (d, J = 16.2 Hz, 1H), 4.41 (d, J = 16.6 Hz, 1H), 5.02 (d, J = 16.6 Hz, 1H), 7.53 (s, 1H), 7.58 (dd,

J = 8.6, 2.0 Hz, 2H), 8.06 (d, *J* = 8.6 Hz, 1H), 8.22 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 8.77 (s, 1H), 9.74 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 544 $(M+H)^+$.

Example 1443 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (500 MHz, d_6-DMSO) ↗ 0.82 (dd, *J* = 24.0, 16.6 Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, *J* = 10.2 Hz, 1H), 3.43 (m, 1H), 3.80 (d, *J* = 12.7 Hz, 1H), 3.89 (s, 1H), 3.93 (d, *J* = 9.8 Hz, 1H), 4.18 (d, *J* = 16.1 Hz, 1H), 4.42 (d, *J* = 16.6 Hz, 1H), 5.04 (d, *J* = 16.6 Hz, 1H), 7.41 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.56 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 528 $(M+H)^+$.

Example 1444 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (500 MHz, d_6-DMSO) ↗ 0.82 (dd, *J* = 24.0, 6.6 Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, *J* = 10.2 Hz, 1H), 3.43 (m, 1H), 3.80 (d, *J* = 12.7 Hz, 1H), 3.89 (s, 1H), 3.93 (d, *J* = 9.8 Hz, 1H), 4.18 (d, *J* = 16.1 Hz, 1H), 4.42 (d, *J* = 16.6 Hz, 1H), 5.04 (d, *J* = 16.6 Hz, 1H), 7.41 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.56 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* =2.0 Hz, 1H), 8.62 (s, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 562 $(M+H)^+$.

Example 1445 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 8.37 (d, *J* = 10.2 Hz, 2H), 8.19 (s, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.73 (br. s, 2H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.50 (s, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 5.06 (d, *J* = 15.8 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 3.98 (d, *J* = 16.0 Hz, 1H), 3.77 (d, *J* = 16.0 Hz, 1H), 3.62-3.48 (m, 2H), 3.21 (d, *J* = 9.2 Hz, 1H), 1.25 (d, *J* = 6.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 502 $(M+H)^+$.

Example 1446
(*S*)-1-(4-Aminoquinazolin-7-yl-methyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 9.80 (d, *J* = 6.2 Hz, 2H), 8.82 (s, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 7.84 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.60 (s, 1H), 7.47 (d, *J* = 8.7 Hz,

1H), 4.98 (d, J = 16.5 Hz, 1H), 4.60 (d, J = 16.5 Hz, 1H), 4.19 (d, J = 16.4 Hz, 1H), 3.96 (d, J = 16.4 Hz, 1H), 3.60 (m, 3H), 1.26 (d, J = 6.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 486 $(M+H)^+$.

Example 1447 (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid tert-butyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.86-7.88 (m, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 0.55 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 1.2 Hz, 1H), 7.46 (dd, J = 8.6, 1.8 Hz, 1H), 7.33 (dd, J = 8.5, 1.6 Hz, 1H), 5.36 (d, J = 15.7 Hz, 1H), 4.24 (d, J = 17.1 Hz, 1H), 4.11 (d, J = 15.7 Hz, 1H), 3.95 (d, J = 12.4 Hz, 1H), 3.80-3.88 (m, 1H), 3.59 (d, J = 16.7 Hz, 1H), 2.86-2.98 (m, 2H), 2.65 (dd, J = 16.8, 2.5 Hz, 1H) 1.43 (s, 9H) ppm. Mass Spectrum: (ESI) *m/z* 602 $(M+H)^+$.

Example 1448 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 2H), 8.77 (s, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 8.6 Hz, 1H), 8.21 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.54-7.62 (m, 2H), 7.50 (s, 1H), 4.95 (d, J = 16.5 Hz, 1H), 4.59 (d, J = 16.6 Hz, 1H), 4.02 (d, J = 16.5 Hz, 1H), 3.45-3.80 (m, 3H), 3.09-3.19 (m, 4H) ppm. Mass Spectrum: (ESI) *m/z* 532 $(M+H)^+$.

Example 1449 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 8.44 (s, 1H), 8.36 (s, 1H), 8.21-8.09 (m, 5H), 7.58 (dd, J = 11.0, 1.3 Hz, 1H), 7.49 (s, 1H), 7.36 (d, J = 8.5 Hz, 1H), 5.06 (d, J = 16.0 Hz, 1H), 4.49 (d, J = 16.0 Hz, 1H), 4.04 (d, J = 16.1 Hz, 1H), 3.79-3.72 (m, 2H), 3.58-3.49 (m, 3H), 3.21 (s, 3H), 3.14 (d, J = 10.3 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 532 $(M+H)^+$.

Example 1450 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (d, J = 5.8 Hz, 2H), 8.78 (s, 1H), 8.31 (d, J = 8.6 Hz, 1H), 7.68-7.79 (m, 2H), 7.52-7.61 (m, 2H), 7.40 (dd, J = 8.7, 1.9 Hz, 1H), 4.94 (d, J = 16.6 Hz, 1H), 4.59 (d, J = 16.6 Hz, 1H), 4.14 (d, J = 16.4 Hz, 1H), 3.82-3.94 (m, 2H), 3.63-3.68 (m, 1H), 3.43-3.52 (m, 2H), 3.32 (dd, J = 12.6, 3.4 Hz, 1H), 3.14 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 516 $(M+H)^+$.

Example 1451 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (bs, 2H); 8.78 (s, 1H); 8.30 (d, *J* = 8.6 Hz, 1H); 7.73 (bs, 2H); 7.51-7.62 (m, 2H); 7.37-7.44 (m, 2H); 4.94 (d, *J* = 16.5 Hz, 1H); 4.59 (d, *J* = 16.5 Hz, 1H); 4.15 (d, *J* = 16.5 Hz, 1H); 3.90 (d, *J* = 16.5 Hz, 1H); 3.83 (s, 1H); 3.62-3.68 (m, 1H); 3.41-3.52 (m, 2H); 3.32 (AB q, *J* = 12.7, 3.5 Hz, 1H); 3.14 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 516 $(M+H)^+$.

Example 1452 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one. (RPR 252864A)

For examples where the aryl sulfonamide contains an indole moiety, the compounds were constructed using the above sequence but a Boc-deprotection step was employed at the last step:

A solution of (*R*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-isopropyl-5-oxo-piperazine-1-sulfonyl]-6-chloro-indole-1-carboxylic acid tert-butyl ester (102 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with trifluoroacetic acid 1 mL) and the solution was allowed to warm to ambient temperature and stir for 16 h. The mixture was concentrated to dryness then purified by reverse phase HPLC on a 1" Dynamax, C18 column (5→100% ACN in H_2O/0.1% TFA) to provide 27 mg (25%) of (*R*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one as a white lyophilized solid. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.48 (s, 1H), 9.61 (br s, 2H), 8.74 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.45-7.52 (m, 2H), 7.12-7.20 (m, 2H), 5.03 (d, *J* = 16.4 Hz, 1H), 4.45 (d, *J* = 16.8 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 3.79 (d, *J* = 12.2 Hz, 1H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.30-3.37 (m, 1H), 2.88 (AB quartet, *J* = 12.4, 3.9 Hz, 1H), 2.10-2.18 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 513 $(M+H)^+$.

The following examples were prepared according to the above procedure:

Example 1453 (*R*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.54 (s, 1H), 9.62 (br. s, 2H), 8.74 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.45-7.61 (m, 3H), 7.34 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.11 (d, *J* =

1.4 Hz, 1H), 5.05 (d, *J* = 16.3 Hz, 1H) 4.45 (d, *J* = 16.3 Hz, 1H), 4.02 (d, *J* = 16.4 Hz, 1H), 3.79 (d, *J* = 16.4 Hz, 1H), 3.55 (d, *J* = 16.4 Hz, 1H), 3.31-3.33 (m, 1H), 2.39 (AB quartet, *J* = 12.5, 3.6 Hz, 1H), 2.08-2.20 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 513 $(M+H)^+$.

Example 1454 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.95 (dd, *J* = 18.8, 6.8 Hz, 6H), 2.15 (m, 1H), 2.89 (dd, *J* = 12.6, 3.7 Hz, 1H), 3.35 (m, 1H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.80 (d, *J* = 12.3 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 4.44 (d, *J* = 16.3 Hz, 1H), 5.03 (d, *J* = 16.3 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 7.31 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.51 (m, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 2.1 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 9.59 (br. s, 2H), 12.53 (s, 1H) ppm. Mass Spectrum (ESI)*m/z* 513 $(M+H)^+$.

Example 1455 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.95 (dd, *J* = 18.7, 6.8 Hz, 6H), 2.15 (m, 1H), 2.89 (dd, *J* = 12.7, 3.7 Hz, 1H), 3.32 (m, 1H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.83 (d, *J* = 12.3 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 4.45 (d, *J* = 16.3 Hz, 1H), 5.04 (d, *J* = 16.3 Hz, 1H), 7.15 (m, 2H), 7.48 (d, *J* = 0.84 Hz, 1H), 7.49 (s, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.76 (s, 1H), 9.71 (s, 2H), 12.49 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 513 $(M+H)^+$.

Example 1456 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.4, 6.4 Hz, 6H), 1.40 (m, 1H), 1.55 (m, 1H), 1.70 (m, 1H), 2.93 (d, *J* = 10.4 Hz, 1H), 3.19 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.4 Hz, 1H), 4.05 (d, *J* = 16.3 Hz, 1H), 5.00 (d, *J* = 16.6 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.48 (d, *J* = 4.6 Hz, 1H), 7.50 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.74 (s, 1H), 9.63 (s, 2H) ppm. Mass Spectrum (ESI)*m/z* 527 $(M+H)^+$.

Example 1457 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.8, 6.4 Hz, 6H), 1.40 (m, 1H), 1.58 (m, 1H), 1.70 (m, 1H), 2.92 (d, *J* = 10.2 Hz, 1H), 3.20 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.2

Hz, 1H), 4.04 (d, *J* = 16.3 Hz, 1H), 4.38 (d, *J* = 16.5 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 9.52 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 527 $(M+H)^+$.

Example 1458 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.4, 6.4 Hz, 6H), 1.40 (m, 1H), 1.55 (m, 1H), 1.70 (m, 1H), 2.93 (d, *J* = 10.4 Hz, 1H), 3.19 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.4 Hz, 1H), 4.05 (d, *J* = 16.3 Hz, 1H), 4.38 (d, *J* = 16.6 Hz, 1H), 5.00 (d, *J* = 16.6 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.48 (d, *J* = 4.6 Hz, 1H), 7.50 (s, 1H), 7.57 (d, 8.6 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.74 (s, 1H), 9.63 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 527 $(M+H)^+$.

Example 1459 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.8, 6.4 Hz, 6H), 1.40 (m, 1H), 1.58 (m, 1H), 1.70 (m, 1H), 2.92 (d, *J* = 10.2 Hz, 1H), 3.20 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.2 Hz, 1H), 4.04 (d, *J* = 16.3 Hz, 1H), 4.38 (d, *J* = 16.5 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 7.49 (s, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 9.57 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 527 $(M+H)^+$.

Example 1460 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.60 (s, 1H), 9.56 (br. s, 2H), 8.75 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.82 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.52 (br. s, 2H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.13 (s, 1H), 4.95 (d, *J* = 16.7 Hz, 1H), 4.53 (d, *J* = 16.7 Hz, 1H), 3.99 (d, *J* = 16.2 Hz, 1H), 3.64 (d, *J* = 16.3 Hz, 2H), 3.16 (d, *J* = 9.5 Hz, 2H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 485 $(M+H)^+$.

Example 1461 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.5 (s, 1H), 9.54 (br. s, 2H), 8.75 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.52 (s, 2H), 7.19 (br. s, 2H), 4.95 (d, J = 16.5 Hz, 1H), 4.52 (d, J = 16.5 Hz, 1H), 4.00 (d, J = 16.4 Hz, 1H), 3.64 (d, J = 16.2 Hz, 2H), 3.14 (d, J = 9.5 Hz, 2H), 1.21 (d, J = 6.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 485 $(M+H)^+$.

Example 1462 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

Example 1463 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.55 (s, 1H), 9.67 (bs, 2H), 8.75 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 1.7 Hz, 1H), 7.45-7.59 (m, 3H), 7.31 (dd, J = 8.8, 1.9 Hz, 1H), 7.11 (d, J = 1.4 Hz, 1H), 4.94 (d, J = 16.5 Hz, 1H), 4.56 (d, J = 16.6 Hz, 1H), 4.03 (d, J = 16.3 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.42-3.66 (m, 4H), 3.15 (s, 3H), 3.02 (AB q, J = 12.3, 3.1 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 515 $(M+H)^+$.

Example 1464 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.53 (d, J = 1.7 Hz, 1H), 9.74 (d, J = 14.3 Hz, 2H), 8.73 (s, 1H), 8.30 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.47-7.59 (m, 3H), 7.11-7.18 (m, 2H), 4.94 (d, J = 16.7 Hz, 1H), 4.55 (d, J = 16.4 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.43-3.64 (m, 4H), 3.14 (s, 3H), 3.02 (AB q, J = 12.3, 3.29 Hz, 1H) ppm Mass Spectrum: (ESI) *m/z* 515 $(M+H)^+$.

Example 1465 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

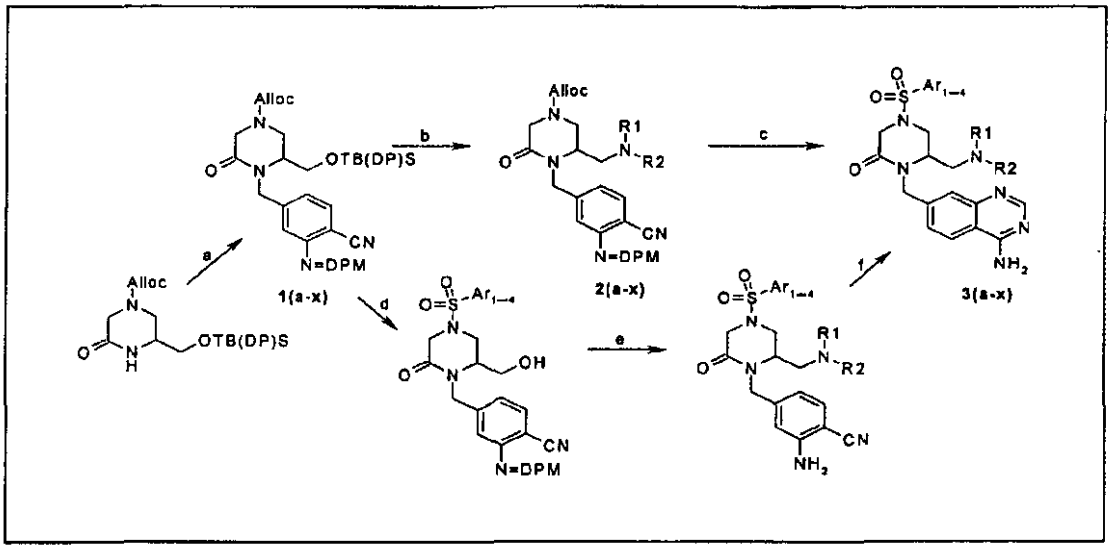
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H); 9.63 (bs, 2H); 8.75 (s, 1H); 8.27 (d, J = 8.5 Hz, 1H); 7.73 (d, J = 8.6 Hz, 1H); 7.56 (d, J = 8.8 Hz, 1H); 7.48 (s, 2H); 7.13-7.20 (m, 2H); 4.95 (d, J = 16.5 Hz, 1H); 4.56 (d, J = 16.7 Hz, 1H); 4.03 (d, J = 15.9 Hz, 1H); 3.76 (d, J = 12.7 Hz, 1H); 3.44-3.65 (m, 4H); 3.16 (s, 3H); 3.00 (AB q, J = 11.7, 2.6 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 515 $(M+H)^+$.

Example 1466 (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid

A: (*S*)-[2-(4-Amino-quinazolin-7-ylmethyl)-5-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid. To a solution of (*S*)-[2-(4-amino-quinazolin-7-ylmethyl)-5-(6-chloro-

benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid tert-butyl ester (58 mg, 0.096 mmol) in CH_2Cl_2 cooled to 0°C was added TFA (1 mL). After stirring for 30 min. at 0°C the reaction was allowed to warm to room temperature. After stirring for 2 h the solvent was concentrated and the residue dissolved in water. Lyophilization afforded 53 mg (82%) of (*S*)-[2-(4-amino-quinazolin-7-ylmethyl)-5-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.52 (bs, 2H), 8.74 (s, 1H), 8.34 (d, *J* = 1.8 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.50-7.60 (m, 3H), 5.02 (d, *J* = 16.4 Hz, 1H), 4.50 (d, *J* = 16.4 Hz, 1H), 3.72-3.81 (m, 2H), 3.63 (d, *J* = 16.2 Hz, 1H), 3.14-3.21 (m, 1H), 2.70-2.80 (m, 2H) ppm. Mass Spectrum: (ESI)*m/z* 546 $(M+H)^+$.

Scheme 5 A synthetic scheme of the C(6)-alkylaminomethyl substituted sulfonamide inhibitors.



Reagents: (a). NaH, 4-Bromomethyl-2-diphenylmethyleneaminobenzonitrile, THF. (b). 1. TBAF, THF. 2. SO3-Py, DMSO. 3. amines, $NaB(OAc)_3H$, 4A MS. (c). 1. $Pd(PPh_3)_4$, morpholine, CH_2Cl_2. 2. "Sulfonyl chloride", Et_3N, CH_2Cl_2. 3. c-HCl, MeOH. 4. 1,3,5-Triazine, AcOH, EtOH, reflux. (d). 1. see (c.1-2, b.1) (e). 1. Dess-Martin. 2. see (b3, c.3) (f) see (c.4).

Example 1467 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one (RPR257023A)

A: (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxy methyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*R*)-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (5.2 g, 11.5 mmol) in a mixture of 5:1 THF:DMF (120 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.6 g, 15 mmol) followed after 15 min by 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (4.7

g, 12.7 mmol). After 2 h at ambient temperature the reaction mixture was diluted with saturated NH_4Cl, and extracted with EtOAc. The extracts were washed with water (twice), dried ($MgSO_4$), filtered and concentrated. The crude residue was used in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 747 $(M+H)^+$.

B: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(4-methyl-piperazin-1-ylmethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. A solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxy methyl)-5-oxo-piperazine-1-carboxylic acid allyl ester in THF (100 mL) was treated with a 1.0 M solution of TBAF in THF (17 mL, 17 mmol). After 0.5 h at ambient temperature, the reaction mixture was diluted with saturated NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (hexanes / EtOAc, 1:1 to 1:5) to yield 4.3 g (50%) of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. Mass Spectrum: (ESI) *m/z* 509 $(M+H)^+$.

A solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.4 g, 4.7 mmol) in DMSO (8 mL) and Et_3N (4 mL) at 0 °C was treated with SO_3.Py (3.76 g, 24 mmol). After 20 h at ambient temperature, the mixture was diluted with water, and extracted with EtOAc. The extracts were washed with saturated NH_4Cl solution and water, dried ($MgSO_4$) and concentrated. The crude (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (~2.3 g) was used in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 507 $(M+H)^+$.

To a mixture of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (100 mg, 0.2 mmol), N-methylpiperazine (0.066 mL, 0.59 mmol) and powdered 4Å MS (0.1 g) in 1,2-dichloroethane (2 mL) at 0 °C was added sodium triacetoxy-borohydride (0.13 g, 0.6 mmol). After 20 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (2% to 10% MeOH in CH_2Cl_2) provided 50 mg (43%) of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(4-methyl-piperazin-1-ylmethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.1 Hz, 2H), 7.5-7.1 (m, 9H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 6.0-5.85 (m, 1H), 5.35-5.23 (m, 3H), 4.7-4.55 (m, 2H), 4.5-4.5 (m, 1H), 4.23 (d, *J* = 15 Hz, 1H), 4.0-3.8 (m, 2H), 3.0-2.8 (m, 2H), 2.5-2.3 (m, 10H), 2.28 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 591 $(M+H)^+$.

C: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one. Tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.02 mmol) was added to a solution of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(4-methyl-piperazin-1-ylmethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (50 mg, 0.085 mmol) and morpholine (0.074 mL, 0.85 mmol) in CH_2Cl_2 (5 mL). After 1 h at ambient temperature, the reaction mixture was concentrated and chromatographed on SiO_2 (5% to 15% MeOH inCH_2Cl_2) to provide 40 mg (93%) of (*S*)-2-(benzhydrylidene-amino)-4-[2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile: Mass Spectrum: (ESI) *m/z* 507 $(M+H)^+$.

To a solution of (*S*)-2-(benzhydrylidene-amino)-4-[2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (40 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added Et_3N (0.055 mL, 0.4 mmol), followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (30 mg, 0.12 mmol). After 1 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extracts were washed with saturated NH_4Cl solution and brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was used in the next reaction without further purification. Mass Spectrum: (ESI)*m/z* 737 $(M+H)^+$.

Concentrated HCl (12M, 5 drops) was added to a solution of (*S*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile in MeOH (5 mL) at 0 °C. After 1 h at ambient temperature, the reaction mixture was concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (10% to 20% MeOH in CH_2Cl_2) to provide 20 mg (44%) of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile. Mass Spectrum: (ESI) *m/z* 573 $(M+H)^+$.

To a solution of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (20 mg, 0.035 mmol) in absolute ethanol (3 mL) was added 1,3,5-triazine (28 mg, 0.35 mmol) and acetic acid (0.02 mL, 0.35 mmol). The solution was heated to a reflux. After 48 h, the solution was concentrated and the resulting crude product was chromatographed on SiO_2 (10% to 30% MeOH in CH_2Cl_2) to provide 15 mg (71%) of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one. Mass Spectrum: (ESI) *m/z* 600 $(M+H)^+$.

The following compounds were prepared according to the above procedures using the appropriate amines and sulfonyl chlorides.

Example	Compound Name	*m/z* (M+H)
1468	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzo imidazole-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one	555
1469	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one	
1470	(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-piperazin-2-one	602

Example 1471 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one (RPR257982A).

A: (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (2.5 g, 7.62 mmol) in a mixture of THF (40 mL) and DMF (2 mL) at 0°C was added NaH 60% dispersion in mineral oil (400 mg, 9.91 mmol). After stirring for 10 min 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (2.81 g, 7.62 mmol) was added in one portion. More NaH (63 mg, 1.5 mmol) was added after 1 h. After stirring for an additional 1 h the reaction was quenched with aq. NH_4Cl and extracted with ether. The ether was washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) afforded 3.90 g (82%) of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.3 Hz, 2H), 7.38-7.50 (m, 4H), 7.25-7.28 (m, 3H), 7.17 (br s, 2H), 6.86 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.59 (s, 1H), 5.84-5.98 (m, 1H), 5.20-5.35 (m, 3H), 4.60 (s, 2H), 4.27-4.39 (m, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 3.90 (d, *J* = 15.2 Hz, 2H), 3.54 (br s, 2H), 3.00-3.05 (m, 1H), 2.84-2.95 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 623 $(M+H)^+$.

B: (*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine -1-carboxylic acid allyl ester (3.90 g, 6.27 mmol) and morpholine (2.75 mL, 31 mmol) in CH_2Cl_2 (60 mL) was added $(PPh_3)_4Pd$ (728 mg, 0.630 mmol). After stirring for 20 min the

reaction was chromatographed on SiO_2 (CH_2Cl_2 to 2% MeOH / CH_2Cl_2) to give 3.0 g (89%) of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow oil. Mass Spectrum: (ESI) *m/z* 539 $(M+H)^+$.

To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (3.0 g, 5.57 mmol) and DIPEA (1.3 mL, 7.24 mmol) in CH_2Cl_2 at 0 °C was added 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (1.50 g, 5.57 mmol). The reaction was allowed to warm to ambient temperature for 16 h and was concentrated. Chromatography on SiO_2 (Hexanes to 2:1 Hexanes / EtOAc) afforded 3.29 g (76%) of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. Mass Spectrum: (ESI) *m/z* 769 $(M+H)^+$.

To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (3.16 g, 4.11 mmol) in THF (20 mL) at 0 °C was added TBAF (5.4 mL of a 1 M solution in THF, 5.4 mmol). After 15 min. the reaction was complete and chromatography on SiO_2 (CH_2Cl_2 to 2% MeOH / CH_2Cl_2) afforded 2.42 g (90%) of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow foam. ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.87 (m, 1H), 7.82 (d, *J* = 2.9 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 2H), 7.37-7.51 (m, 6H), 7.09-7.23 (m, 5H), 6.81 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.55 (d, *J* = 1.3 Hz, 1H), 4.98 (d, *J* = 15.1 Hz, 1H), 4.20 (d, *J* = 16.6 Hz, 1H), 4.03 (d, *J* = 15.1 Hz, 1H), 3.94 (d, *J* = 12.3 Hz, 1H), 3.59-3.72 (m, 2H), 3.51 (d, *J* = 16.7 Hz, 1H), 3.12-3.19 (m, 1H), 2.65 (dd, *J* = 12.4, 3.17 Hz, 1H), 2.23 (t, *J* = 5.4 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 655 $(M+H)^+$.

C: (*S*)-2-Amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile (1.3 g, 2.0 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin Periodinane (1.77 g, 4.1 mmol). After stirring for 30 min the reaction was chromatographed on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) to afford 975 mg (75%) of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-formyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.25 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.66-8.01 (m, 8H), 7.11-7.48 (m, 5H), 6.76 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.51 (d, *J* = 1.2 Hz, 1H), 5.20 (d, *J* = 15.1 Hz, 1H), 4.17-4.28 (m, 2H), 3.84 (d, *J* = 15.1 Hz, 1H), 3.40-3.52 (m, 2H), 2.82 (dd, *J* = 12.8, 4.0 Hz, 1H) ppm.

To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-formyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile (440 mg, 0.674 mmol), 4-(1-pyrrolidinyl)-piperidine (422 mg, 2.73 mmol), and 4Å molecular sieves (725 mg) in 1,2-dichloroethane (10 mL) was added $NaBH(OAc)_3$ (432 mg, 2.04mmol). After stirring for 16 h the molecular sieves were filtered off and washed with CH_2Cl_2. The filtrate was then washed with aq. NH_4Cl, followed by brine, dried over Na_2SO_4, filtered, and concentrated to give 289 mg (54%) of (*S*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. Mass Spectrum: (ESI) m/z 791 $(M+H)^+$.

To a solution of (*S*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile (289 mg, 0.365 mmol) in a mixture of MeOH (4 mL) and THF (2 mL) at 0°C was added conc. HCl (3 drops). After stirring for 20 min, $NaHCO_3$ was added and the reaction was concentrated to dryness. The residue was chromatographed on SiO_2 (CH_2Cl_2 to 5% MeOH / CH_2Cl_2) to afford 96 mg (42%) of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.79-7.87 (m, 3H), 7.43 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.33-6.40 (m, 1H), 5.14 (d, *J* = 15.1 Hz, 1H), 4.24 (d, *J* = 16.1 Hz, 1H), 3.94-4.09 (m, 2H, 3.73 (br s, 1H), 3.54-3.69 (m, 2H), 3.48 (d, *J* = 16.6 Hz, 1H), 3.30-3.38 (m, 2H), 2.72-3.06 (m, 5H), 2.64-2.70 (m, 1H), 2.19-2.32 (m, 2H), 1.97-2.15 (m, 8H) ppm. Mass Spectrum: (ESI) *m/z* 627 $(M+H)^+$.

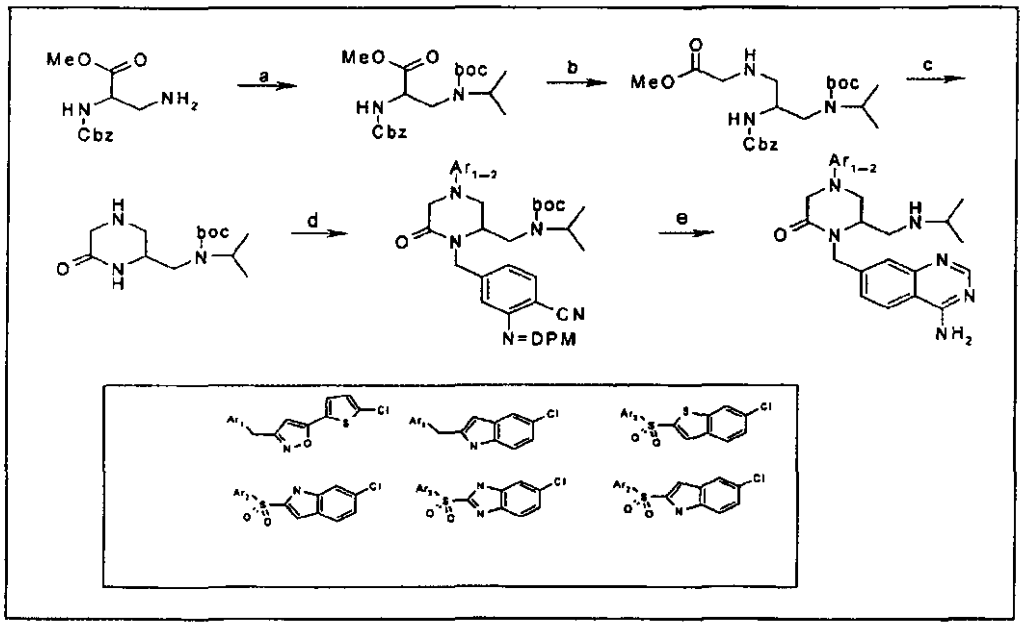
D: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one. A mixture of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile (96 mg, 0.153 mmol), HOAc (88 μL, 1.53 mmol), and 1,3,5-triazine (143 mg, 1.76 mmol) in absolute EtOH (6 mL) was refluxed overnight. The crude material was purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to give 106 mg (90%) of the TFA salt of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 8.61 (s, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.97-8.05 (m, 2H), 7.62 (dd, 8.6, 1.4 Hz, 1H), 7.49-7.57 (m, 2H), 5.14 (d, *J* = 16.5 Hz, 1H), 4.60 (d, *J* = 16.4 Hz, 1H), 4.17-4.32 (m, 2H), 3.70-3.76 (m, 1H), 3.57-3.67 (m, 3H), 3.09-

3.18 (m, 5H), 2.94-3.05 (m, 2H), 2.75-2.79 (m, 1H), 2.33-2.48 (m, 2H) ppm. Mass Spectrum: (ESI) *m/z* 654 $(M+H)^+$.

The following compounds were prepared according to the above procedures using the appropriate amines and 6-chloro-benzo[b]thiophene-2-sulfonyl chloride.

Example	Compound Name	*m/z* (M+H)
1472	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-[([1,3]dioxolan-2-ylmethyl-methyl-amino)-methyl]-piperazin-2-one	617
1473	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one	654
1474	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-[(2-isopropoxy-ethylamino)-methyl]-piperazin-2-one	603
1475	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-[(cyclopentyl-methyl-amino)-methyl]-piperazin-2-one	599

Scheme 6 A synthetic scheme of the C(6)-isopropyl substituted inhibitors.



Reagents: (a) 1. Acetone, $NaBH_3CN$, MeOH; 2. Boc_2O, DMAP, THF; (b) 1. "$CaBH_4$", EtOH; 2. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; 3. Gly-OMe.HCl, $NaBH_3CN$, MeOH; (c) H_2, MeOH, 10% Pd / C; (d) 1. Alloc-Cl, Et_3N, CH_2Cl_2; 2. NaH, 2-(benzyhydrylidene-amino)-4-bromomethyl-

benzonitrile, THF; 3. $Pd(PPh_3)_4$, Morpholine, CH_2Cl_2; 4. Sulfonyl chloride / Aryl bromide, Et_3N, CH_2Cl_2; (e) 1. Conc. HCl, MeOH; 2. 1,3,5-Triazine, AcOH, EtOH, Reflux.

Example 1476. (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropylaminomethyl)piperazin-2-one

A: (*S*)-3-Amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride. Thionyl chloride (4.48 mL, 61.34 mmol) was added cautiously to anhydrous methanol (50 mL) at 0 °C. After 5 min, 3-amino-2-benzyloxycarbonylamino-propionic acid (14.6 g, 61.34 mmol) was added. The heterogeneous mixture was allowed to warm to ambient temperature (became homogeneous) then warmed to reflux for 2.5 h. The cooled mixture was concentrated and dried *in vacuo* to afford 16 g (90%) of (*S*)-3-amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride as a white solid which was used without purification. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 3.08 (m, 1H), 3.20 (m, 1H), 3.65 (s, 3H) 4.42 (m, 1H), 5.05 (s, 2H), 7.3 (br. s, 5H), 7.89 (d, J = 8.3 Hz, 1H), 8.20 (br. s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 253 $(M+H)^+$.

B: (*S*)-2-Benzyloxycarbonylamino-3-isopropylamino-propionic acid methyl ester. To a solution of (*S*)-3-amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride (5 g, 17.33 mmol) in anhydrous MeOH (50 mL) at 0 °C was added acetone (1.15 mL, 15.6 mmol) followed by sodium cyanoborohydride (26 mL, 1.0 M / THF, 26 mmol). The mixture was stirred at ambient temperature for 4 h then acetone (0.5 mL, 13 mmol) was added and the mixture was left to stir for a further 16 h. The mixture was concentrated to dryness then partitioned between aqueous $NaHCO_3$ (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford a grey oil.

The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH / CH_2Cl_2) to afford 2.96 g (58%) of (*S*)-2-benzyloxycarbonylamino-3-isopropylamino-propionic acid methyl ester as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ↗ 0.99 (d, J = 6.3 Hz, 6H), 1.15 (m, 1H), 2.75 (m, 1H), 2.91 (dd, J = 12.5, 4.5 Hz, 1H), 3.03 (dd, J = 12.5, 4.5 Hz, 1H), 3.70 (s, 3H), 4.40 (m, 1H), 5.10 (s, 2H), 5.70 (m, 1H), 7.30 (br. s, 5H) ppm. Mass Spectrum: (ESI) m/z 294 $(M+H)^+$.

C: (*S*)-2-Benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propionic acid methyl ester. To a solution of (*S*)-2-benzyloxycarbonylamino-3-isopropylamino-propionic acid methyl ester (2.96 g, 10.07 mmol) in anhydrous THF (50 mL) at 0 °C was added DMAP (100

mg) followed by Boc-anhydride (2.42 g, 11.07 mmol). The solution was allowed to stir at ambient temperature for 16 h then was concentrated to dryness. The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→5%) to afford 5.0 g (65%) of (*S*)-2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propionic acid methyl ester as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.16 (d,*J* = 3.8 Hz, 6H) 1.45 (s, 9H), 3.40 (m, 2H), 3.70 (s, 3H), 4.00 (m, 1H), 4.40 (br. s, 1H), 5.50 (s, 2H), 6.10 (br. s, 1H), 7.30 (br. s, 5H) ppm. Mass Spectrum: (ESI) *m/z* 394 M^+.

D: (*S*)-[2-(tert-Butoxycarbonyl-isopropyl-amino)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester. To a stirring suspension of freshly ground sodium borohydride (1.92 g, 50.76 mmol) in abs. EtOH (100 mL) at -40 °C was added calcium chloride (2.82 g, 25.38 mmol). The heterogeneous mixture was stirred at -20 °C for 45 min then a solution of (*S*)-2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propionic acid methyl ester (5.0 g, 12.69 mmol) in abs. EtOH (50 mL) was added via pipette. The mixture was stirred at -20 °C for 1 h then was quenched with water (200 mL) and acidified cautiously to ~pH 3 with 2N HCl. The mixture was then extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic phases were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated to afford a colourless oil.

The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→5%) to afford 4.14 g (95%) of (*S*)-[2-(tert-butoxycarbonyl-isopropyl-amino)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester as a colourless oil. ^{1}H NMR (300 MHz, CDCl3) ↗ 1.19 (dd, *J* = 18.7, 6.7 Hz, 6H), 1.45 (s, 9H), 3.10 (m, 1H), 3.50 (m, 2H), 3.61 (m, 2H), 4.00 (m, 1H), 4.20 (m, 1H), 5.10 (s, 2H), 5.50 (m, 1H), 7.30 (br. s, 5H) ppm. Mass Spectrum: (ESI) *m/z* 366 M^+.

E: (*S*)-[2-Benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propylamino]-acetic acid methyl ester. To a solution of oxalyl chloride (1.18 mL, 13.57 mmol) in anhydrous CH_2Cl_2 (40 mL) at -78 ° C was added DMSO (1.93 mL, 27.14 mmol) dropwise. The solution was stirred at -78 °C for 10 min then a solution of (*S*)-[2-(tert-butoxycarbonyl-isopropyl-amino)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester (4.14 g, 11.31 mmol) in anhydrous CH_2Cl_2 (80 mL) was added via pipette. The reaction was stirred at -78 °C for 1 h then triethylamine (7.88 mL, 56.55 mmol) was added and the reaction stirred at 0 °C for 10 min. The mixture was partitioned between $NaHSO_4$ (200 mL) and CH_2Cl_2 (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford (*S*)-[2-(tert-butoxycarbonyl-

isopropyl-amino)-1-formyl-ethyl]-carbamic acid benzyl ester as a yellow oil which was used immediately without purification.

To a solution of (*S*)-[2-(tert-butoxycarbonyl-isopropyl-amino)-1-formyl-ethyl]-carbamic acid benzyl ester (11.31 mmol) in anhydrous MeOH (80 mL) at 0 °C was added glycine methyl ester hydrochloride (5.68 g, 45.24 mmol). The solution was stirred at 0 °C for 10 min then sodium cyanoborohydride (16.97 mL, 1.0 M / THF, 16.97 mmol) was added and the heterogeneous mixture was warmed to ambient temperature and stirred for 16 h. The mixture was concentrated to dryness and partitioned between aqueous $NaHCO_3$ (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford 4.75 g (96%) of *(S)*-[2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propyl amino]-acetic acid methyl ester as a colourless oil which was used in the next step without purification. Mass Spectrum (ESI) *m/z* 438 $(M+H)^+$.

F: (*S*)-Isopropyl-(6-oxo-piperazin-2-ylmethyl)-carbamic acid tert-butyl ester. A solution of *(S)*-[2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propyl amino]-acetic acid methyl ester (2.58 g, 5.9 mmol) in MeOH (150 mL) was placed in a large Parr bottle and treated with 10% palladium on carbon (300 mg) under N_2 atmosphere. The mixture was hydrogenated at 40 psi for 5 h then filtered through celite. The filtrate was concentrated to afford 1.60 g (100%) of (*S*)-isopropyl-(6-oxo-piperazin-2-ylmethyl)-carbamic acid tert-butyl ester as a grey oil which was used without further purification. Mass Spectrum (ESI) *m/z* 272 $(M+H)^+$.

G: (*S*)-3-[(tert-Butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*S*)-isopropyl-(6-oxo-piperazin-2-ylmethyl)-carbamic acid tert-butyl ester (1.6 g, 5.9 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added triethylamine (1.23 mL, 8.85 mmol) followed by allyl chloroformate (0.75 mL, 7.08 mmol). The solution was stirred at ambient temperature for 16 h then partitioned between $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash silica gel chromatography and dried in vacuo to afford 1.51 g (72%) of (*S*)-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) ↗ 1.12 (dd, *J* = 6.8, 3.7 Hz, 6H), 1.45 (s, 9H), 3.10 (m, 1H), 3.20 (m, 2H), 3.70 (m, 2H), 3.85 (m, 2H), 4.11 (ABq,*J* = 47.2, 18.2 Hz, 2H), 4.62 (d, *J* = 5.6 Hz, 2H), 5.30 (m, 2H), 5.90 (m, 1H) ppm. Mass Spectrum: (ESI)*m/z* 356 $(M+H)^+$.

H: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*S*)-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester (1.51 g, 4.25 mmol) in a mixture of anhydrous THF (100 mL) and anhydrous DMF (10 mL) at 0 °C was added sodium hydride (0.2 g, 60% dispersion / oil, 5.1 mmol). The mixture was stirred at 0 °C for 30 min until gas evolution ceased, then 2-(benzyhydrylidene-amino)-4-bromomethyl-benzonitrile (1.75 g, 4.68 mmol) was added. The brown mixture was stirred at 0-10 °C for 3 h then partitioned between saturated aqueous NH_4Cl (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford a brown oil. The crude product was purified by flash silica gel chromatography to afford 2.76 g (100%) of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.15 (m, 6H), 1.45 (s, 9H), 2.65 (m, 1H), 3.00 (m, 1H), 3.35 (m, 2H), 3.50 (m, 1H), 3.90 (m, 9H), 4.32 (d, *J* = 18.5 Hz, 1H), 4.63 (d, *J* = 5.5 Hz, 2H), 5.30 (m, 2H), 5.95 (m, 1H), 6.80 (br. s, 1H), 7.0 (br. s, 1H), 7.20 (br. s, 5H), 7.40 (br. s, 5H), 7.80 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 650 $(M+H)^+$.

I: (*S*)-{1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester. To a solution of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester (2.76 g, 4.28 mmol) in anhydrous CH_2Cl_2 (250 mL) was added morpholine (1.87 mL, 21.4 mmol) followed by *tetrakis* (triphenylphosphine) palladium (495 mg, 0.43 mmol). The yellow solution was stirred at ambient temperature for 1 h then concentrated on to silica gel and flash column chromatographed (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→3%→5%) to afford 1.9 g (79%) of (*S*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.08 (t, *J* = 6.8 Hz, 6H), 1.45 (s, 9H), 2.42 (m, 1H), 2.69 (m, 1H), 2.90 (m, 2H), 3.18 (m, 1H), 3.57 (d, *J* = 9.7 Hz, 2H), 3.71 (m, 1H), 3.90 (br. s, 1H), 4.04 (d, *J* = 15.2 Hz, 1H), 5.07 (d, *J* = 15.2 Hz, 1H), 6.75 (br. s, 1H), 6.90 (m, 1H), 7.15-7.45 (m, 10H), 7.75 (m, 1H) ppm. Mass Spectrum: (ESI) m/z 566 $(M+H)^+$.

J: (*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester. To a solution of

(*S*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester (1 g, 1.77 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C was added triethylamine (0.37 mL, 2.66 mmol) followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.57 g, 2.12 mmol). The solution was stirred at 0 °C for 2 h and at ambient temperature for 1 h then partitioned between water (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford 1.41 g (100%) of (*S*)-[1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester as a yellow foam which was used without further purification. Mass Spectrum: (ESI) *m/z* 796 $(M+H)^+$.

The following compounds were prepared according to the above procedures, using the appropriate sulfonyl chlorides or aryl bromides.

Example	Name	m/z(M+H)$^+$
1477	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(5-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	879
1478	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	879
1479	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	780
1480	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(5-chloro-1H-indol-2yl-methyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	829
1481	(S)-{1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester	763

Example 1482: (*S*)-[1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester. To a solution of (*S*)-[1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (1.41 g, 1.77 mmol) in a mixture of MeOH (20 mL) and THF (50 mL) at 0 °C was added conc. HCl (10 drops). The

mixture was stirred at 0 °C for 1 h then concentrated to dryness and flash column chromatographed on silica gel (CH_2Cl_2→1% MeOH / CH_2Cl_2→5%) to afford 1.11 g (100%) of (*S*)-[1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester as a yellow gum. Mass Spectrum: (ESI) *m/z* 632 $(M+H)^+$.

Example 1483: (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester.

To a suspension of (*S*)-[1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (1.11g, 1.77 mmol) in abs. EtOH (50 mL) were added 1,3,5-triazine (1.43 g, 17.7 mmol) and glacial acetic acid (1.01 mL, 17.7 mmol). The mixture was warmed to reflux (became homogeneous) and stirred for 16 h. The cooled mixture was concentrated to dryness and flash column chromatographed on silica gel (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→5%) to afford 0.8 g (68%) of (*S*)-[1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester as a yellow foam. ^1H NMR (300 MHz, $CDCl_3$) ↗ 1.23 (t, *J* = 6.6 Hz, 6H), 1.45 (s, 9H), 2.80 (br. s, 1H), 3.30 (m, 1H), 3.85 (m, 3H), 4.28 (d, *J* = 16.7 Hz, 1H), 5.39 (d, *J* = 15.4 Hz, 1H), 7.45 (dd, *J* = 8.6, 1.9 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.84 (m, 3H), 8.40 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 659 $(M+H)^+$.

Example 1484 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropylaminomethyl)-piperazin-2-one.

To a solution of (*S*)-[1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (0.8 g, 1.22 mmol) in anhydrous CH_2Cl_2 at 0 °C was added trifluoroacetic acid (5 mL). The solution was stirred, capped for 16 h then concentrated to dryness and purified by reverse-phase HPLC on a 2" Dynamax C18 column (10→80% ACN / H_20 /0.1% TFA). Appropriate fractions were combined and lyophilized to afford 0.58 g (86%) of the TFA salt of (*S*)-1-(4-aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl aminomethyl)-piperazin-2-one as a white solid. ^1H NMR (300 MHz, DMSO-$_6$) ↗ 1.22 (dd, *J* = 6.5, 2.1 Hz, 6H), 3.22 (m, 3H), 3.72 (m, 3H), 4.01 (s, 1H), 4.07 (d, *J* = 15.6 Hz, 1H), 4.38 (d, *J* = 16.7 Hz, 1H), 5.12 (d, *J* = 16.7 Hz, 1H), 7.58 (s, 1H), 7.59 (s, 1H), 7.60 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 8.19 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.36 (s, 1H), 8.50 (br. s, 1H), 8.72, (s, 1H), 9.49 (br. s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 559 $(M+H)^+$.

The following compounds were prepared according to the above procedures:

Example 1485 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}HNMR (300 MHz, DMSO-d_6) ↗ 1.20 (d, *J* = 6.41 Hz, 6H), 3.45 (m, 5H), 3.76 (m, 1H), 3.93 (d, *J* = 16.5 Hz, 1H), 4.15 (m, 1H), 4.39 (d, *J* = 16.6 Hz, 1H), 5.12 (d, *J* = 16.6 Hz, 1H), 7.43 (d, *J* = 6.6 Hz, 1H), 7.56 (s, 2H), 7.79 (m, 2H), 8.28 (d, *J* = 8.59 Hz, 1H), 8.45 (m, 1H), 8.70 (s, 2H), 9.52 (br. S, 2H) ppm. Mass Spectrum: (ESI) *m/z* 542 (M^+).

Example 1486 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 1.20 (m, 6H), 3.15 (m, 1H), 3.32 (m, 1H), 3.50 (m, 3H), 3.75 (m, 1H), 3.92 (d, *J* = 13.1 Hz, 1H), 4.10 (d, *J* = 16.3 Hz, 1H), 4.36 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 7.09 (s, 1H), 7.35 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.54 (m, 3H), 7.80 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.47 (m, 1H), 8.64 (m, 1H), 8.72 (br. s, 1H), 12.58 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 542 $(M+H)^+$.

Example 1487 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 1.20 (m, 6H), 3.38 (m, 5H), 3.72 (m, 1H), 3.90 (d, *J* = 13.0 Hz, 1H), 4.10 (d, *J* = 16.2 Hz, 1H), 4.36 (d, *J* = 16.2 Hz, 1H), 5.12 (d, *J* = 17.0 Hz, 1H), 7.20 (m, 2H), 7.51 (m, 3H), 7.75 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.45 (m, 1H), 8.59 (m, 1H), 8.71 (br. s, 1H), 12.53 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 542 $(M+H)^+$.

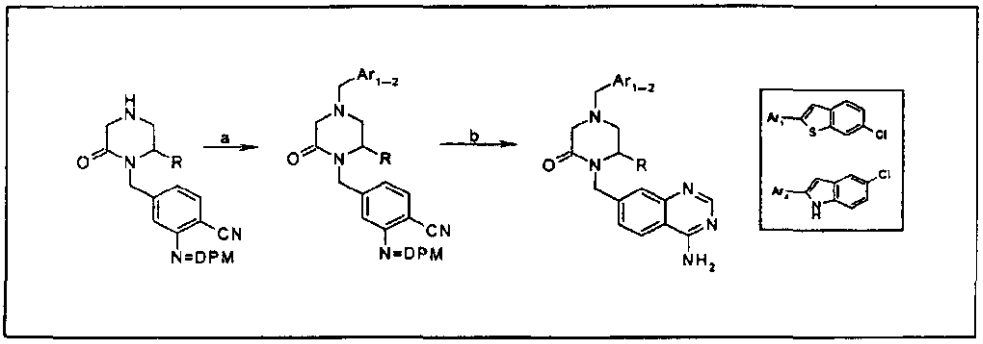
Example 1488 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (500 MHz, DMSO-d_6) ↗ 1.15 (dd, *J* = 15.93, 6.59 Hz, 6H), 2.70 (dd, *J* = 12.63, 3.29 Hz, 1H), 3.06 ((m, 2H), 3.20 (d, *J* = 12.09 Hz, 1H), 3.28 (m, 1H), 3.47 (d, *J* = 17.20 Hz, 1H), 3.57 (m, 1H), 3.59 (m, 2H), 4.37 (d, *J* = 16.48 Hz, 1h), 5.15 (d, *J* = 16.48 Hz, 1H), 7.04 (dd, *J* = 8.51, 1.92 Hz, 1H), 7.33 (d, *J* = 8.79 Hz, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.55 (s, 1H), 7.60 (dd, *J* = 8.78, 1.10 Hz, 1H), 8.36 (d, *J* = 8.24 Hz, 3H), 8.78 (s, 1H), 9.70 (m, 2H) ppm. Mass Spectrum: (ESI) *m/z* 492 $(M+H)^+$.

Example 1489 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-[5-(5-chlorothiophen-2-yl)isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (600 MHz, DMSO-d_6) ↗ 1.23 (dd, *J* = 10.0, 6.50 Hz, 6H), 2.70 (d, *J* = 10.4 Hz, 1H), 3.20 (m, 3H), 3.40 (m, 1H), 3.60 (m, 3H), 3.84 (dd,*J* = 33.9, 14.5 Hz, 2H), 4.41 (d, *J* = 16.7 Hz, 1H), 5.21 (d, *J* = 16.7 Hz, 1H), 6.95 (s, 1H), 7.31 (d,*J* = 4.0 Hz, 1H), 7.62 (m, 3H), 8.40 (m, 3H), 8.85 (s, 1H), 9.81 (br. S, 1H) ppm. Mass Spectrum: (ESI) *m/z* 526 (M+H)$^+$.

Scheme 7 A synthetic scheme of the C(6)-alkylaminomethyl substituted alkyl inhibitors.



Reagents: (a) Aryl bromide, K_2CO_3, DMF. (b) 1. Conc. HCl, MeOH 2. Triazine, AcOH, EtOH, Reflux. (c) TFA, CH_2Cl_2.

Example 1490. (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid (RPR 257329A).

A: (*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-tert-butoxy carbonylmethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester. To a suspension of (*S*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-yl}-acetic acid tert-butyl ester(265 mg, 0.52 mmol) and K_2CO_3 (133 mg, 0.96 mmol) in acetonitrile (1 mL) at 0°C was added 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester (253 mg, 0.73 mmol). After warming to ambient temperature over 16 h the reaction was partitioned between EtOAc and water. The water was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) afforded 300 mg (75%) of (*S*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano]-3-tert-butoxy carbonylmethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester as a yellow glass. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.0 Hz, 1H), 7.77 (d, *J* = 6.5 Hz, 2H), 7.38-7.47 (m, 4H), 7.23-7.29 (m, 4H), 7.17-7.21 (m, 3H), 6.84 (d*J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.48 (s, 1H), 5.05 (d, *J* = 15.5 Hz, 1H), 3.97 (d, *J* = 14.3 Hz, 1H), 3.78-3.89 (m, 2H), 3.58 (d, *J* = 16.3 Hz, 1H), 3.41-3.49 (m, 1H), 2.99 (d,*J* = 16.7 Hz, 1H), 2.71-2.87 (m, 2H), 2.29-2.42 (m, 2H), 1.67 (s, 9H), 1.26 (s, 9H) ppm. Mass Spectrum: (ESI)*m/z* 772 (M+H)$^+$.

B: (*S*)-2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl] -5-chloro-indole-1-carboxylic acid tert-butyl ester. To a solution of (*S*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-tert-butoxy carbonyl methyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester (300 mg, 0.388 mmol) in a mixture of MeOH (10 mL) and THF (2 mL) at 0 °C was added conc. HCl (7 drops). After stirring for 1 h the reaction was stopped and flash column chromatographed on silica gel (CH_2Cl_2→8% MeOH / CH_2Cl_2) to afford 170 mg (72%) of (*S*)-2-[4-(3-amino-4-cyano-benzyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester as a yellow gum. Mass Spectrum: (ESI) *m/z* 608 $(M+H)^+$.

A solution of (*S*)-2-[4-(3-amino-4-cyano-benzyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (170 mg, 0.28 mmol), glacial acetic acid (160 μL, 2.80 mmol) and 1,3,5-triazine (225 mg, 2.80 mmol) in absolute EtOH (4 mL) was heated to reflux for 16 h. The mixture was concentrated to dryness then flash column chromatographed on silica gel (CH_2Cl_2→8% MeOH / CH_2Cl_2) to afford 101 mg (58%) of (*S*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro -indole-1-carboxylic acid tert-butyl ester as an off-white glass. ^1H NMR (300 MHz, CD_3OD) δ 8.36 (s, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.46-7.56 (m, 2H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.22 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.60 (s, 1H), 5.21 (d, *J* = 15.7 Hz, 1H), 4.34 (d, *J* = 15.6 Hz, 1H), 4.18 (d, *J* = 13.6 Hz, 1H), 3.58-3.73 (m, 2H), 3.17 (d, *J* = 16.8 Hz, 1H), 2.73-2.89 (m, 2H), 2.48-2.61 (m, 2H), 1.70 (s, 9H), 1.08 (s, 9H) ppm. Mass Spectrum: (ESI)*m/z* 635 $(M+H)^+$.

C: (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid (RPR 257329A). A solution of (*S*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro -indole-1-carboxylic acid tert-butyl ester (101 mg, 0.159 mmol) in CH_2Cl_2 (5 mL) and TFA (1 mL) was stirred for 16 h. The mixture was concentrated to dryness and the crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA). The appropriate product fractions were combined and lyophilized to afford 34 mg (36%) of the TFA salt of (*S*)-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid as a white solid. ^1H NMR (300 MHz, CD_3OD) ↗ 10.68 (s, 1H), 8.64 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.66 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.34 (s, 1H), 5.18 (d, *J* = 16.3 Hz, 1H), 4.51 (d, *J* = 16.3 Hz, 1H), 3.71-3.89 (m, 3H), 3.56 (d, *J* = 17.8 Hz, 1H), 3.02-3.17 (m, 3H), 2.61-2.75 (*m*, 2H) ppm. Mass Spectrum (ESI) *m/z* 479 $(M+H)^+$.

The following compounds were prepared according to the above procedure:

Example 1491 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (s, 1H); 8.33 (s, 1H); 8.12 (d, *J* = 8.5 Hz, 1H); 7.72 (bs, 2H); 7.44 (d, *J* = 15.6 Hz, 1 H); 7.25-7.32 (m, 2H); 7.00 (dd, *J* = 8.6, 2.0 Hz, 1H); 6.29 (s, 1H); 5.05 (d , *J* = 15.4 Hz, 1H); 4.23 (d, *J* = 15.7 Hz, 1H); 3.81 (d, *J* = 13.3 Hz, 1H); 3.57 (d, *J* = 13.8 Hz, 1H); 3.40 (d, *J* = 16.2 Hz, 1H); 3.21-3.34 (m, 1H); 3.10-3.18 (m, 1H); 3.04 (d,*J* = 16.5 Hz, 1H); 2.66-2.74 (m, 1H); 2.31-2.39 (m, 1H); 1.22-1.30 (m, 1H); 1.06-1.19 (m, 1H); 0.70 (d,*J* = 6.5 Hz, 3H); 0.62 (d, *J* = 6.3 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 477 $(M+H)^+$.

Example 1492 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (DMSO-d_6) ↗ 11.30 (s, 1H), 9.74 (s, 2H), 8.79 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.58 (m, 3H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.35 (s, 1H), 5.02 (d, *J* = 16.5 Hz, 1H), 4.38 (d, *J* = 16.5 Hz, 1H), 3.95 (br d, 1H), 3.82 (d, 1H), 3.60 (d, 1H), 3.40 (d, 1H), 3.29 (br d, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 1.90 (m, 1H), 1.29 (m, 2H), 0.71 (dd,*J* = 21.1, 6.0 Hz, 6H) ppm. Mass Spectrum (ESI) *m/z* 477 $(M+H)^+$.

Example 1493 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, CD_3OD) ↗ 8.65 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 1.9 Hz, 1H), 7.70 (m, 2H), 7.58 (s, 1H), 7.30 (m, 2H), 5.11 (d,*J* = 16.4 Hz, 1H), 4.52 (d, *J* = 16.4 Hz, 1H), 4.02 (dd, *J* = 13.9, 0.86 Hz, 1H), 3.86 (d, *J* = 14.1 Hz, 1H), 3.63 (d, *J* = 16.7 Hz, 1H), 3.40 (m, 1H), 3.19 (d, *J* = 16.8 Hz, 1H), 3.0 (m, 1H), 2.60 (m, 1H), 2.08 (m, 1H), 1.32 (m, 2H), 0.80 (dd,*J* = 13.7, 5.9 Hz, 6H) ppm. Mass Spectrum: (ESI) *m/z* 494 $(M+H)^+$.

Example 1494 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, CD_3OD) ↗ 8.65 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.59 (s, 1H), 7.32 (dd,*J* = 8.5, 1.9 Hz, 1H), 7.29 (s, 1H), 5.12 (d, *J* = 16.4 Hz, 1H), 4.53 (d, *J* = 16.4 Hz, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 3.88 (d, *J* = 14.0 Hz, 1H), 3.65 (d, *J* = 16.7 Hz, 1H), 3.40 (d, *J* = 9.3 Hz, 1H), 3.22 (d, *J* = 16.7 Hz, 1H), 3.00 (d, *J* = 12.1

Hz, 1H), 2.68 (m, 1H), 2.08 (m, 1H), 1.35 (m, 2H), 0.81 (dd,*J* = 23.0, 5.9 Hz, 6H) ppm. Mass Spectrum: (ESI) *m/z* 494 $(M+H)^+$.

Example 1494 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-methoxymethyl-piperazin-2-one.

^{1}H NMR (DMSO-d_6) ↗ 11.31 (s, 1H), 9.75 (d, *J* = 5.5 Hz, 2H), 8.79 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.55 (m, 3H), 7.06 (d, *J* = 1.9 Hz, 1H), 7.03 (d, *J* = 1.7 Hz, 1H), 6.38 (s, 1H), 4.96 (d, *J* = 16.6 Hz, 1H), 4.61 (d, *J* = 16.6 Hz, 1H), 3.88 (q, *J* = 13.9 Hz, 2H), 3.40-3.62 (m, 4H), 3.28 (m, 1H), 3.07 (s, 3H), 3.01 (m, 1H), 2.72 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 465 $(M+H)^+$.

Example 1495 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-*methoxymethyl-piperazin-2-one.*

^{1}H NMR (DMSO-d_6) ↗ 11.31 (s, 1H), 9.75 (d, *J* = 5.7 Hz, 1H), 8.79 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.55 (m, 3H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.04 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.38 (s, 1H), 4.95 (d, *J* = 16.6 Hz, 1H), 4.60 (d, *J* = 16.6 Hz, 1H), 3.88 (q, *J* = 13.9 Hz, 2H), 3.40-3.60 (m, 4H), 3.20 (m, 1H), 2.72 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 465 $(M+H)^+$.

Example 1496 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one.

^{1}H NMR (300 MHz, CD_3OD) ↗ 11.10 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.58 (s, 1H), 7.32 (m, 2H), 5.07 (d,*J* = 16.4 Hz, 1H), 4.76 (d, *J* = 16.4 Hz, 1H), 3.97 (ABq, *J* = 32.9, 14.6 Hz, 2H), 3.55-3.70 (m, 4H), 3.19 (s, 3H), 3.10 (m, 2H), 2.72 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 481 M^+.

Example 1497 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one

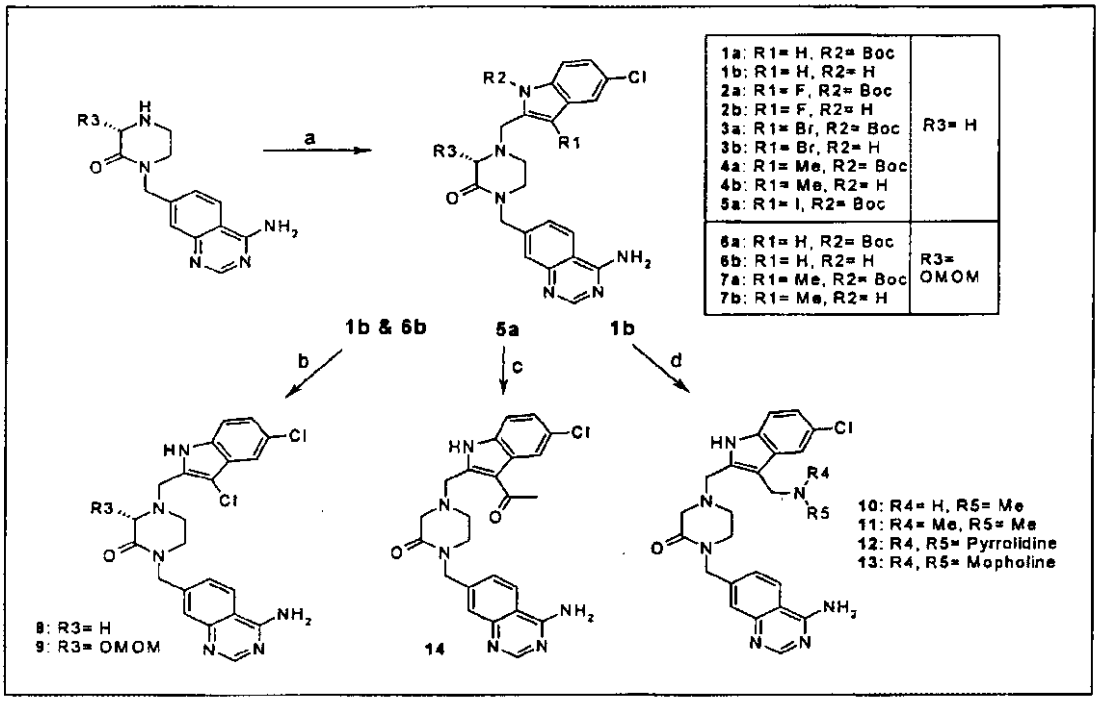
^{1}H NMR (300 MHz, CD_3OD) ↗ 8.65 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.58 (s, 1H), 7.32 (m, 2H), 5.07 (d,*J* = 16.5 Hz, 1H), 4.76 (d, *J* = 16.5 Hz, 1H), 3.99 (ABq, *J* = 33.0, 14.1 Hz, 2H), 3.58-3.70 (m, 4H), 3.19 (s, 3H), 3.15 (m, 2H), 2.76 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 482 $(M+H)^+$.

Example 1498 (*R/S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

^{1}H NMR (300 MHz, CD_3OD) δ 8.63 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 7.64 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.26 (d, *J* = 8.6, 1H), 7.01 (dd, *J* = 8.6, 2.0 Hz, 1H),

6.32 (s, 1H), 5.38 (d, J = 16.4 Hz, 1H), 4.28 (d, J = 16.4 Hz, 1H), 4.17-4.22 (m, 1H), 3.68-3.89 (m, 2H), 3.58 (d, J = 16.9 Hz, 1H), 3.47 (d, J = 12.0 Hz, 1H), 3.16 (d, J = 16.7 Hz, 1H), 2.73-2.80 (m, 1H) ppm. Mass Spectrum: (ESI) m/z 465 $(M+H)^+$.

Scheme 8 A synthetic scheme of the C(3')- substituted indolylmethyl inhibitors.



Reagents: (a). 1. $ArCH_2Br$, K_2CO_3, DMF 2. (a->b) TFA, CH_2Cl_2 (b). NCS (c). 1. $Pd(PPh_3)_4$, CuI, TEA, TMSCCH, DMF 2. K2CO3 (d). Amine, formaldehyde, dioxane/AcOH.

Example 1499. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one

A: 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. To a solution of 1-(4-Amino-quinazolin-7-ylmethyl)-piperazin-2-one (500 mg, 1.94 mmol) in DMSO (15 mL) was added K_2CO_3 (423 mg, 3.01 mmol) followed by 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester (744 mg, 2.16 mmol). After stirring for 16 h the reaction was partitioned between water and EtOAc. The EtOAc was washed with water, then brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 8% MeOH / CH_2Cl_2) afforded 924 mg (92%) of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester as a pale crunchy solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.92 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 1.0 Hz, 1H), 7.40-7.47 (m, 2H), 7.19 (dd, J = 8.9, 2.1 Hz, 1H), 6.50 (s,

1H), 5.87 (br s, 2H), 4.75 (s, 2H), 3.94 (s, 2H), 3.37 (s, 2H), 3.30 (t,*J* = 4.9 Hz, 2H), 2.77 (t, *J* = 5.6 Hz, 2H), 1.64 (s, 9H) ppm.

B: 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (RPR 210312A). To a solution of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (400 mg, 0.76 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL). After stirring for 16 h, chromatography on SiO_2 (CH_2Cl_2 to 20% MeOH / CH_2Cl_2) afforded 393 mg (>100%) of 1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one as an off white solid. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 11□□ □s, □□), 9.64 (br s, 2H), 8.77 (s, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 7.53-7.62 (m, 2H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.33 (s, 1H), 4.70 (s, 2H), 3.78 (s, 2H), 3.26-3.34 (m, 2H), 3.22 (s, 2H), 2.76 (s, 2H) ppm.

Example 1500 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one

A solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (115 mg, 0.273 mmol) in MeOH (3 mL) was treated with NCS (35 mg, 0.262 mmol) and stirred for 90 min. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 55 mg (41%) of the TFA salt of 1-(4-amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 11□□ (s, 1H), 9.73 (br s, 2H), 8.79 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.55 (s, 1H), 7.45-7.45 (m, 2H), 7.15 (dd,*J* = 8.6, 2.0 Hz, 1H), 4.70 (s, 2H), 4.44 (s, 2H), 3.82 (s, 2H), 3.32 (br s, 4H) ppm. Mass Spectrum: (ESI)*m/z* 455 $(M+H)^+$.

Example 1501 4-(3-Acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one

A: 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-trimethylsilanyl ethynyl-indole-1-carboxylic acid tert-butyl ester.

To a mixture of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-iodo-indole-1-carboxylic acid tert-butyl ester (190 mg, 0.29 mmol), copper(I) iodide (10 mg, 0.046 mmol), and *bis*(triphenylphosphine)-palladium dichloride (12 mg, 0.17 mmol) in Et_3N (1.5 mL) and DMF (0.5 mL) was added (trimethylsilyl)acetylene (100 μL, 0.70 mmol). After stirring for 16 h the reaction was partitioned between water and EtOAc. The aqueous phase was

extracted with EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 8% MeOH / CH_2Cl_2) afforded 133 mg (74%) of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-trimethylsilanyl ethynyl-indole-1-carboxylic acid tert-butyl ester as a brown solid. Mass Spectrum: (ESI) m/z 617 $(M+H)^+$.

B: 4-(3-Acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one. To a solution of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-trimethylsilanylethynyl-indole-1-carboxylic acid tert-butyl ester (133 mg, 0.215 mmol) in MeOH (5 mL) was added K_2CO_3 (513 mg, 3.71 mmol). After stirring for 6 h the reaction was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 50% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 22 mg (15%) of the TFA salt of 4-(3-acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 8□□□ □s, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 7.69 (dd, J = 8.5, 1.5 Hz, 1H), 7.65 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 8.7, 2.0 Hz, 1H), 4.27 (s, 2H), 3.47-3.54 (m, 6H), 3.01-3.06 (m, 2H), 2.68 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 463 $(M+H)^+$.

Example 1502 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-pyrrolidin-1-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one

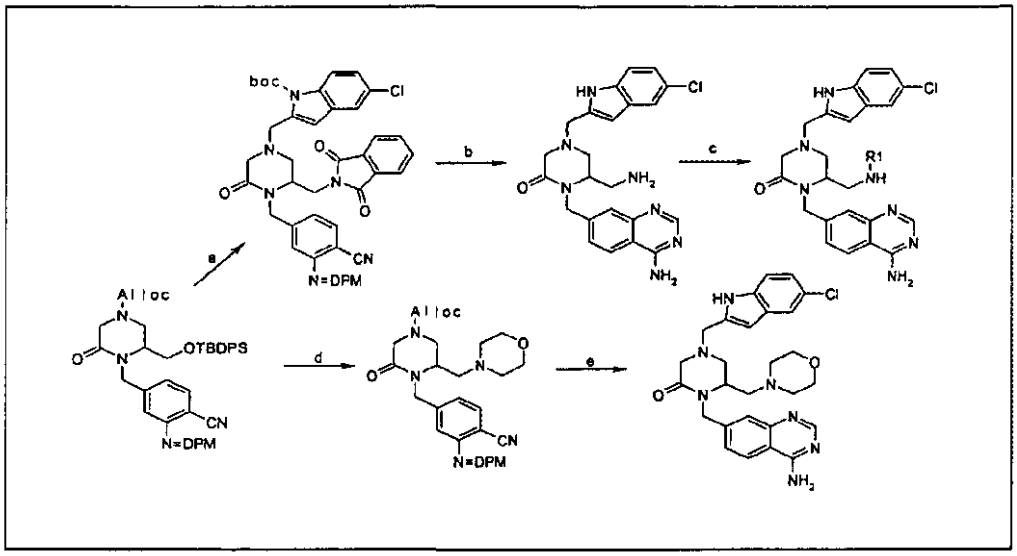
To a solution of formaldehyde (40 mg, 0.47 mmol) in a mixture of HOAc (1 mL) and dioxane (4 mL) at 0 °C was added pyrrolidine (36 μL, 0.43 mmol). After stirring for 5 min 1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (107 mg, 0.254 mmol) was added in one portion. The reaction was allowed to warm to ambient temperature and after stirring for 2.5 h was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 70 mg (47%) of the TFA salt of 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-pyrrolidin-1-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 11□□ (s, 1H), 9.78 (d, J = 1.7 Hz, 2H), 8.79 (s, 1H), 8.39 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.56-7.64 (m, 2H), 7.38 (d, J = 8.6 Hz, 1H), 7.12

(dd, J = 8.6, 1.8 Hz, 1H), 4.71 (s, 2H), 4.54 (s, 2H), 3.95 (s, 2H), 3.29 (s, 6H), 3.12 (br s, 2H), 2.82 (s, 2H, 1.95 (br s, 2H), 1.83 (br s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 504 $(M+H)^+$.

The following compounds were prepared using appropriate indole precursors as described in above examples:

Example	Compound Name	m/z (M+H)
1503	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-bromo-5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	499
1504	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-piperazin-2-one	434
1505	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-morpholin-4-ylmethyl-1*H*-indol-2-ylmethyl)-piperazin-2-one	520
1506	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one	463
1507	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-dimethylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one	477
1508	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one	478
1509	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-fluoro-1H-indol-2-ylmethyl)-piperazin-2-one	438
1510	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one	499

Scheme 9 A synthetic scheme of the C(6)-alkylaminomethyl substituted indolylmethyl inhibitors.



Reagents: (a) 1. $Pd(PPh_3)_4$, morpholine, CH_2Cl_2. 2. K_2CO_3, 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert butyl ester, DMF. 3. TBAF, THF. 4. Phthalimide, PPh_3, DEAD, THF. (b) 1. c-HCl, MeOH. 2. 1,3,5-Triazine, AcOH, EtOH, reflux. 3. TFA, CH_2Cl_2. 4. Hydrazine, EtOH. (c) Et_3N, electrophiles, CH_2Cl_2. (d) 1. TBAF, THF. 2. SO_3-Py, DMSO. 3. Amine, $NaB(OAc)_3H$, 4A MS, MeOH. (e) see (a.1-2), (b.1-2,4).

Example 1511 (*S*)-6-Aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one

A: (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile.

Tetrakis(triphenylphosphine)palladium (470 mg, 0.38 mmol) was added to a solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxy-methyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (2.8 g, 3.8 mmol) and morpholine (1.7 mg, 19 mmol) in CH_2Cl_2 (30 mL). After 30 min at ambient temperature, the reaction mixture was concentrated and chromatographed on SiO_2 (1% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to provide 2.6 g (100%) of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as an oil. Mass Spectrum: (ESI) *m/z* 677 $(M+H)^+$.

B: (*R*)-2-[4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

To a mixture of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (1.08 g, 1.6 mmol) and K_2CO_3 (0.66 g, 4.8 mmol) in DMF (3 mL) at 0 °C was added 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert butyl ester (0.67 g, 1.95 mmol). After 1 h at ambient temperature, the reaction mixture was diluted with EtOAc

and water, and extracted with EtOAc. The combined organic extracts were washed twice with water and brine, dried ($MgSO_4$), filtered, and concentrated to afford crude (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester which was used in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 940 $(M+H)^+$.

C: (*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester. A solution of (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester in THF (20 mL) was treated with a 1.0 M solution of TBAF in THF (5 mL, 5 mmol). The reaction mixture was stirred for 1 h at ambient temperature, diluted with brine and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated and chromatographed on SiO_2 (1% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to yield 2.46 g (94%) of (*R*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 688 $(M+H)^+$.

D: (*R*)-2-[4-[3-(Benzhydrylidene-amino)-4-cyanobenzyl]-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. In a 100 mL flask were placed (*R*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester (0.22 g, 0.32 mmol), triphenylphosphine (0.25 g, 0.96 mmol) and phthalimide (0.19 g, 1.28 mmol). Toluene (2 mL) and THF (2 mL) were added and the suspension was treated with DEAD (0.15 mL, 0.96 mmol) at -50 °C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 48 h. The solution was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 5:1 to 1:1) to provide 240 mg (93%) of (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyanobenzyl]-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 817 $(M+H)^+$.

E: (*R*)-2-[4-(3-Amino-4-cyano-benzyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Concentrated HCl (12M, 5 drops) was added to a solution of (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (0.24 g, 0.3 mmol) in MeOH (5 mL) at 0 °C. After 2 h at 0 °C, the

reaction mixture was concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on silica gel (hexanes/EtOAc, 3:1 to 1:1) to afford 0.13 g (67%) of (*R*)-2-[4-(3-amino-4-cyano-benzyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin -1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 653 $(M+H)^+$.

F: (*R*)-2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. To a solution of (*R*)-2-[4-(3-amino-4-cyano-benzyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (130 mg, 0.2 mmol) in absolute ethanol (7 mL) was added 1,3,5-triazine (162 mg, 2 mmol) and acetic acid (0.11 mL, 2 mmol). After the solution was heated to a reflux for 20 h, the solution was cooled and concentrated. The resulting crude product was chromatographed on SiO_2 (1% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to provide 100 mg (74%) of (*R*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 679 $(M+H)^+$.

G: (*R*)-2-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione. Excess TFA (~30% in CH_2Cl_2) was added to a solution of (*R*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (100 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 3 h at ambient temperature, the reaction mixture was concentrated to give the crude residue which was chromatographed on SiO_2 (2% CH_2Cl_2 to 20% MeOH in CH_2Cl_2) to afford 90 mg (100%) of (*R*)-2-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione. Mass Spectrum: (ESI) *m/z* 580 $(M+H)^+$.

H: (*S*)-6-Aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (RPR257001A). A mixture of (*R*)-2-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione (1.0 g, 1.5 mmol) in MeOH (30 mL) was treated with hydrazine monohydrate (30 mL, 75 mmol). After 12 h at ambient temperature, the reaction mixture was concentrated and dissolved in 0.1% TFA-containing acetonitrile and water, making 40 mL solution for a prep HPLC injection. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to

80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 0.91 g (89%) of (*S*)-6-aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one as a white solid. Mass Spectrum: (ESI) *m/z* 450 $(M+H)^+$.

Example 1512 (*S*)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-acetamide

To a solution of (*S*)-6-aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (15 mg, 0.022 mmol) and excess Et_3N in DMF (0.5 mL) was added acetic anhydride (0.008 mL) at 0 °C. After 1 h at ambient temperature, the reaction mixture was diluted with water and acetonitrile to make 10 mL of the solution. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 11 mg (82%) of (*S*)-N-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-acetamide as a white solid. Mass Spectrum: (ESI) *m/z* 492 $(M+H)^+$.

The following compounds were prepared by the coupling reactions of the C(6)-aminomethyl templates with appropriate electrophiles as described in above examples.

Example	Compound Name	*m/z* (M+H)
1513	(*S*)-Furan-2-carboxylic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide	544
1514	(*S*)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-formamide	477
1515	(*S*)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-ethyl-urea	521
1516	(*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-urea	492
1517	(*S*)-5-Bromo-thiophene-2-sulfonic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide	675
1518	(*S*)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-phenyl-urea	569
1519	(*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-	536

	6-oxo-piperazin-2-ylmethyl]-carbamic acid isopropyl ester	
1520	(*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-carbamic acid methyl ester	507
1521	(*S*)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-methanesulfonamide	528

Example 1522 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one

A: (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester. A solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.4 g, 4.7 mmol) in DMSO (8 mL) and Et_3N (4 mL) at 0 °C was treated with SO_3.Py (3.76 g, 24 mmol). After 20 h at ambient temperature, the mixture was diluted with water, and extracted with EtOAc. The combined organic extracts were washed with saturated NH_4Cl solution and water, dried ($MgSO_4$), concentrated. The crude (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (~2.3 g) was used for next reactions without further purification. Mass Spectrum: (ESI) *m/z* 507 $(M+H)^+$.

B: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. To a mixture of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (0.25 g, 0.49 mmol), morpholine (0.21 mL, 2.5 mmol) and powdered 4Å MS (0.5 g) in 1,2-dichloroethane (5 mL) was added sodium triacetoxy-borohydride (0.31 g, 1.5 mmol) at 0 °C. After 12 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was chromatographed on SiO_2 (2% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to afford 210 mg (73%) of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. Mass Spectrum: (ESI) *m/z* 578 $(M+H)^+$.

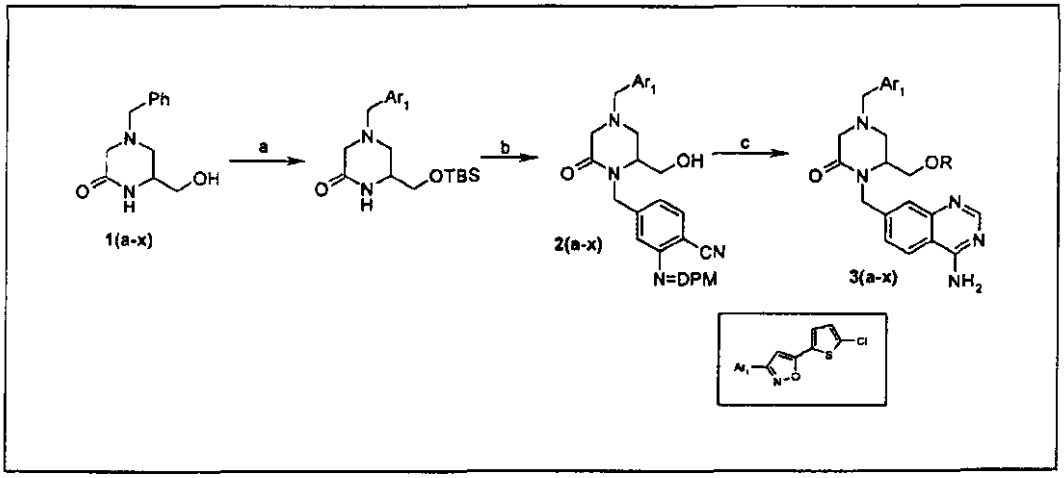
C: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid. Alloc deprotection of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester was carried out as described in previous examples using *tetrakis*(triphenylphosphine)palladium and morpholine, to

afford (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid in 100% yield. Mass Spectrum: (ESI) *m/z* 494 $(M+H)^+$.

D: (*S*)-2-[4-(3-Amino-4-cyano-benzyl)-3-morpholin-4-ylmethyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Coupling of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester with 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert butyl ester and deprotection of the diphenyl methylene group by HCl/MeOH were performed as described in previous examples to provide (*S*)-2-[4-(3-amino-4-cyano-benzyl)-3-morpholin-4-ylmethyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester in 43% yield. Mass Spectrum: (ESI) *m/z* 593 $(M+H)^+$.

E: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one (RPR256996A). The aminoquinazoline formation and the subsequent Boc deprotection were carried out as described in previous examples to afford (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one. Mass Spectrum: (ESI) *m/z* 520 $(M+H)^+$.

Scheme 10 A synthetic scheme of the C(6)-alkoxymethyl substituted isoxazolylmethyl inhibitors.



Reagents: (a). 1. TBSCl, Imidazole. 2. $Pd(OH)_2$, MeOH, H_2. 3. NaH, Ar1CH_2Br, THF. (b). 1. NaH, 4-bromomethyl-2-diphenylmethyleneaminobenzonitrile, THF. 2. TBAF, THF. (c). 1. NaH, RBr, THF. 2. c-HCl, MeOH. 3. 1,3,5-Triazine, AcOH, EtOH, reflux.

Example 1523 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one

A: (*R*)-4-Benzyl-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one. A solution of (*R*)-4-benzyl-6-hydroxymethyl-piperazin-2-one (9 g, 41 mmol) and imidazole (4.2 g, 62 mmol) in CH_2Cl_2 (80 mL) at 0 °C was treated with TBSCl (6.24 g, 42 mmol). After 1 h at ambient temperature, the mixture was concentrated, diluted with EtOAc, and filtered to remove most of the triethylamine hydrochloride. Concentration of the solution provided 12.8 g (93%) of the crude (*R*)-4-benzyl-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one which was used for the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 335 $(M+H)^+$.

B: (*R*)-6-(tert-Butyl-dimethyl-silanyloxymethyl)-piperazin-2-one. To a solution of (*R*)-4-benzyl-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one (2.1 g, 6.3 mmol) in MeOH (80 mL) was added 10% palladium hydroxide on C (0.3 g). The reaction mixture was hydrogenated at ambient temperature under a balloon of H_2 for 20 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated to afford 1.36 g (88%) of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one. Mass Spectrum (ESI) *m/z* 245 $(M+H)^+$.

C: (*R*)-6-(tert-Butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one. To a mixture of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one (1.36 g, 5.6 mmol) and K_2CO_3 (3.1 g, 22 mmol) in anhydrous DMF (10 mL) at 0 °C was added 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole (1.72 g, 6.2 mmol). After 2 h at ambient temperature, the reaction mixture was diluted with EtOAc and water, and the layers were separated. The organic phase was washed twice with water, brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to provide 2.55 g (100%) of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one. ^1H NMR (300 MHz, $CDCl_3$) δ □□27 (d, *J* = 4.2 Hz, 1H), 6.95 (d, *J* = 4.2 Hz, 1H), 6.35 (s, 1H), 6.09 (s, 1H), 3.7-3.45 (m, 5H), 3.33 (d, *J* = 16 Hz, 1H), 3.14 (d, *J* = 16 Hz, 1H), 2.76 (dd, *J* = 15, 3.6 Hz, 1H), 2.4-2.33 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H) ppm. Mass Spectrum: (ESI) *m/z* 442 $(M+H)^+$.

D: (*R*)-2-(Benzhydrylidene-amino)-4-{2-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one (2.55 g, 5.7 mmol) in a mixture of 5:1 THF:DMF (25 mL) at 0 °C was added NaH (a 60% dispersion in mineral oil, 0.32 g, 8 mmol) followed by 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (2.35 g, 6.3 mmol). After 0.5 h at 0°C, the reaction mixture was diluted with saturated NH_4Cl, and extracted with EtOAc. The combined organic extracts

were washed with water (twice), dried ($MgSO_4$), filtered and concentrated. The crude (*R*)-2-(benzhydrylidene-amino)-4-{2-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile was used directly in the next reaction without further purification.

E: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. A solution of (*R*)-2-(benzhydrylidene-amino)-4-{2-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile in THF (30 mL) was treated with a 1.0 M solution of TBAF in THF (7 mL, 7 mmol). The reaction mixture was stirred for 0.5 h at ambient temperature, concentrated and chromatographed on SiO_2 (CH_2Cl_2 to 4% MeOH in CH_2Cl_2) to yield 3.3 g (95%) of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. ^1H NMR (300 MHz, $CDCl_3$) δ □□79 (d, *J* = 7.2 Hz, 2H), 7.6-7.2 (m, 10 H), 6.95 (d, *J* = 4.1 Hz, 1H), 6.90 (d, *J* = 6.9 Hz, 1H), 6.62 (s, 1H), 6.31 (s, 1H), 5.15 (d, *J* = 15.4 Hz, 1H), 3.96 (d, *J* = 15.4 Hz, 1H), 3.75-3.6 (m, 5H), 3.2-2.9 (m, 3H), 2.51 (dd, *J* = 11.7, 2.8 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 622 $(M+H)^+$.

F: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (0.15 g, 0.24 mmol) in THF/DMF (5:1, 6 mL) at 0 °C were added 60% NaH in mineral oil (26 mg, 0.68 mmol), followed, after 15 min, by the addition of MeI (0.018 mL, 0.29 mmol). After 1 h at ambient temperature, the mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile was used directly in the next reaction without further purification.

G: (*R*)-2-Amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. Concentrated HCl (12M, 5 drops) was added at 0 °C to a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile in MeOH (5 mL). After 1 h at ambient temperature, the reaction mixture was concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on silica gel

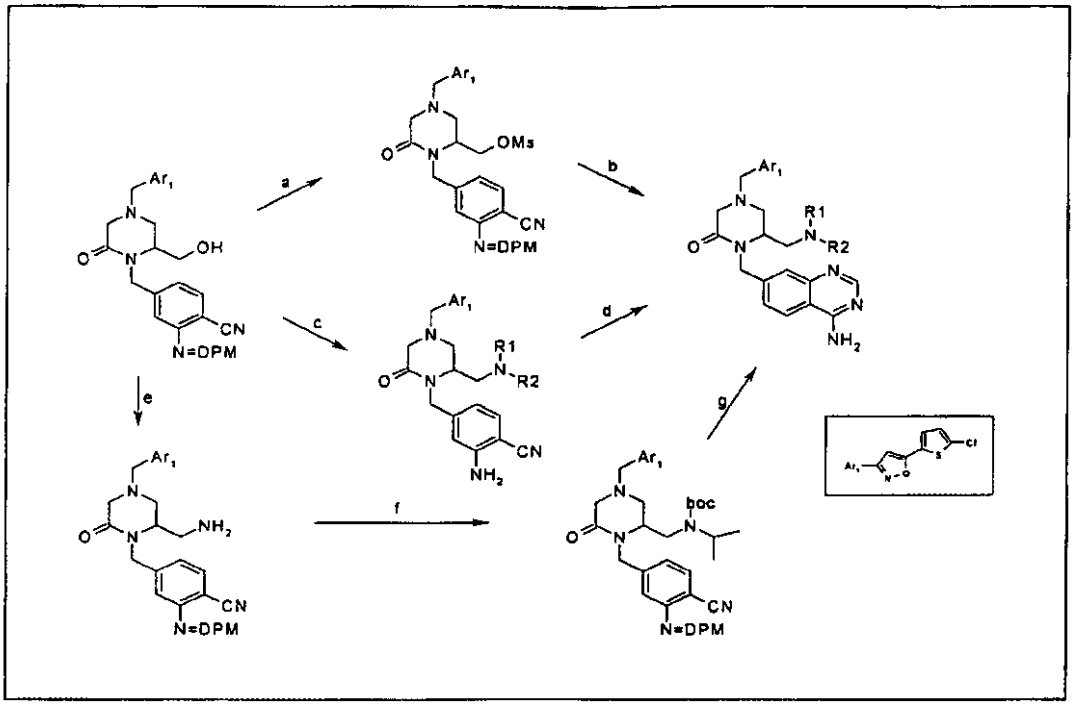
(CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to provide 90 mg (79%) of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. Mass Spectrum: (ESI) *m/z* 472 $(M+H)^+$.

H: (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one (RPR257852A). To a solution of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (90 mg, 0.19 mmol) in absolute ethanol (3 mL) was added 1,3,5-triazine (0.16 g, 1.9 mmol) and acetic acid (0.11 mL, 1.9 mmol). The solution was heated to reflux. After 15 h, the solution was concentrated and diluted with water and acetonitrile to make 10 mL of solution. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to give 75 mg (79%) of (*R*)-1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one as a white solid. Mass Spectrum: (ESI) *m/z* 499 $(M+H)^+$.

The following compounds were prepared by the O-alkylation reaction of the C(6)-hydroxymethyl templates with appropriate electrophiles as described in above examples.

Example	Compound Name	*m/z* (M+H)
1524	(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-ethoxymethyl-piperazin-2-one	513
1525	(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-6-benzyloxymethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one	575

Scheme 11 A synthetic scheme of the C(6)-alkylaminomethyl substituted isoxazoylmethyl inhibitors.



Reagents: (a) Ms_2O, Et_3N, CH_2Cl_2. (b) 1. Amine, DMF, 80 °C. 2. c-HCl, MeOH; 3. 1,3,5-Triazine, AcOH, EtOH, reflux. (c) 1. PDC. 2. amines, $NaB(OAc)_3H$, 4A MS, MeOH. 3. see (b.2). (d) see (b.3). (e) 1. Phthalimide, PPh_3, DEAD, THF. 2. Hydrazine. (f) 1. acetone, $NaB(OAc)_3H$, 4A MS. 2. Boc_2O ,THF. (g) 1.see (b.2-3), 2. TFA, CH_2Cl_2.

Example 1526 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one

A: (*R*)-Methanesulfonic acid 1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (1.89 g, 3.04 mmol) and Et_3N (2.1 mL, 15.2 mmol) in CH_2Cl_2 (25 mL) was added methane sulfonic anhydride (815 mg, 4.68 mmol). After stirring for 3 h the CH_2Cl_2 was concentrated and the residue was partitioned between EtOAc and water. The EtOAc was washed with water, followed by brine, dried over Na_2SO_4, filtered and concentrated to afford 1.9 g (89%) of (*R*)-methanesulfonic acid 1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl ester as a yellow foam. ^1H NMR (300 MHz, $CDCl_3$) δ 7□□□ (d, *J* = 7.1 Hz, 2H), 7.14-7.52 (m, 10H), 6.94 (d, *J* = 4.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.63 (d, *J* = 1.3 Hz, 1H), 6.35 (s, 1H), 5.12 (d, *J* = 15.1 Hz, 1H), 4.41 (dd, *J* = 10.0, 8.9 Hz, 1H), 4.05-4.16 (m, 1H), 3.91 (d, *J* = 15.1 Hz, 1H), 3.68 (d, *J* = 3.5 Hz, 2H), 3.53 (d, *J* = 16.7 Hz, 1H), 3.21-3.29 (m, 1H), 2.94-3.14 (m, 2H), 2.94 (s, 3H), 2.32-2.38 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 700 $(M+H)^+$.

B: (*S*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile. A mixture of (*R*)-methanesulfonic acid 1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl ester (1.5 g, 2.14 mmol), pyrrolidine (2 mL, 24 mmol), and K_2CO_3 (1.55 g, 11.2 mmol) was heated to 80 °C for 2 h. The reaction was diluted with EtOAc which was then washed with water, followed by brine, dried over Na_2SO_4, filtered and concentrated to afford 1.5 g (>100%) of crude (*S*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile as an oil. Mass Spectrum: (ESI) *m/z* 675 $(M+H)^+$.

C: (*S*)-2-Amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile. (*S*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile (1.5 g, 2.14 mmol) was dissolved in a mixture of MeOH (20 mL) and CH_2Cl_2 (5 mL) at 0 °C and was treated with TFA (4 mL). The reaction was allowed to warm to ambient temperature and after stirring for 2 h was chromatographed on SiO_2 (CH_2Cl_2 to 10% MeOH / CH_2Cl_2) to give 880 mg (85% over two steps) of (*S*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile as a brown gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.29 (m, 2H,), 6.93 (d, *J* = 4.0 Hz, 1H), 6.73 (d, *J* = 1.0 Hz, 1H), 6.56 (*dd*, *J* = 8.0, 1.4 Hz, 1H), 6.29 (s, 1H), 4.94 (*d*, *J* = 15.1 Hz, 1H), 4.11 (d, *J* = 15.0 Hz, 1H), 3.72-3.89 (m, 1H), 3.69-3.74 (m, 2H), 3.59 (d, *J* = 17.9 Hz, 1H), 3.27 (d, *J* = 12.7 Hz, 1H), 2.58-2.65 (m, 6H), 2.01-2.07 (m, 4H) ppm.

D: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one A solution of (*S*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile (880 mg, 1.72 mmol), HOAc (950 μL, 16.6 mmol), and 1,3,5-triazine (1.40 g, 17.2 mmol) in absolute EtOH (20 mL) was heated to reflux for 16 h. Chromatography on SiO_2 (CH_2Cl_2 to 20% MeOH / CH_2Cl_2) afforded 800 mg (86%) of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.3 (br s, 1H), 9.81 (d, *J* = 29.3 Hz, 2H), 8.79 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 7.54-7.65 (m, 3H), 7.27 (d, *J* = 4.0 Hz, 1H), 6.96 (s, 1H), 5.18 (d, *J* = 16.6 Hz, 1H), 4.41 (d, *J* = 16.6 Hz, 1H), 3.39-3.88 (m, 8H), 3.08-3.39 (m, 2H), 2.75 (d, *J* = 11.2 Hz, 1H), 1.80-1.98 (m, 4H) ppm. Mass Spectrum: (ESI) *m/z* 538 $(M+H)^+$.

Example 1527 (*R*)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine and (6R)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide

A: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-formyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (0.8 g, 1.3 mmol) and 4A MS (1 g) in CH_2Cl_2 (20 mL) was added PDC (0.98 g, 2.6 mmol). After 1 h at ambient temperature, the reaction mixture was chromatographed on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) to afford 520 mg (65%) of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-formyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile.

B: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-formyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (280 mg, 0.45 mmol), 2-aminoethyl isopropyl ether (230 mg, 2.3 mmol), and 4Å molecular sieves (300 mg) in 1,2-dichloroethane (3 mL) was added $NaBH(OAc)_3$ (290 mg, 1.35 mmol). After stirring for 16h the molecular sieves were filtered off, and washed with CH_2Cl_2. The filtrate was then washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to give (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile which was used for next reaction without further purification.

C: (*R*)-2-Amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile in a mixture of MeOH (4 mL) and CH_2Cl_2 (1 mL) at 0 °C was added conc. HCl (5 drops). After stirring for 20 min, the reaction was concentrated, and diluted with saturated $NaHCO_3$ solution and EtOAc. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on silica gel (CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to provide 80 mg (33%) of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. Mass Spectrum: (ESI) *m/z* 543 $(M+H)^+$.

D: (*R*)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine and (*R*)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide. To a solution of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile (80 mg, 0.15 mmol) in absolute ethanol (5 mL) was added 1,3,5-triazine (0.13 g, 2.2 mmol) and acetic acid (0.1 mL, 2.2 mmol). The solution was heated to 90 °C for 20 h and concentrated. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) to give 10 mg (11%) of (*R*)-N-{1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine. Mass Spectrum: (ESI) *m/z* 597 $(M+H)^+$, and 25 mg (28%) of (*R*)-N-{1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide. Mass Spectrum: (ESI) *m/z* 598 $(M+H)^+$.

The following compounds were prepared in a similar fashion according to the above examples.

Example	Compound Name	m/z (M+H)
1528	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one	538
1529	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-piperidin-1-ylmethyl-piperazin-2-one	552
1530	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-[(cyclopentyl-methyl-amino)-methyl]-piperazin-2-one	566

Example 1531 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one

A: (*R*)-2-(Benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (2.00 g, 3.22 mmol), triphenylphosphine (2.55 g, 9.72 mmol), and phthalimide (1.86 g, 12.6 mmol) in a mixture of THF (15 mL) and toluene (15 mL) at -70°C was added DEAD (1.45 mL, 9.66 mmol) dropwise.

After warming to ambient temperature and stirring for 16 h, chromatography on SiO_2 (5:1 Hexanes/EtOAc to 1:2 Hexanes/EtOAc) afforded 4.7 g (>100%) of (*R*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. Mass Spectrum: (ESI) *m/z* 751 $(M+H)^+$.

B: (*S*)-4-{2-Aminomethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-2-(benzhydrylidene-amino)-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (4.7 g, 3.22 mmol) in MeOH (40 mL) at 0 °C was added hydrazine monohydrate (2 mL, 41 mmol). After warming to ambient temperature and stirring for 16 h, the reaction was diluted with water and extracted with EtOAc. The EtOAc was washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 4% MeOH / CH_2Cl_2) afforded 1.13 g (57% over two steps) of (*S*)-4-{2-aminomethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-2-(benzhydrylidene-amino)-benzonitrile as an orange solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.78 (m, 2H), 7.36-7.53 (m, 4H), 7.22-7.29 (m, 4H), 7.12-7.18 (m, 2H), 6.93 (d, *J* = 3.9 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.60 (d, *J* = 1.2 Hz, 1H), 6.30 (s, 1H), 5.05 (d, *J* = 15.4 Hz, 1H), 4.00 (d, *J* = 15.4 Hz, 1H), 3.46-3.71 (m, 3H), 3.09 (d, *J* = 16.4 Hz, 1H), 2.98 (d, *J* = 11.8 Hz, 1H), 2.66-2.91 (m, 2H), 2.64-2.75 (m, 1H), 2.37-2.42 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 621 $(M+H)^+$.

C: (*S*)-2-(Benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(isopropylamino-methyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*S*)-4-{2-aminomethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-2-(benzhydrylidene-amino)-benzonitrile (1.13 g, 1.82 mmol), glacial acetic acid (104 μL, 1.82 mmol), and acetone (200 μL, 2.7 mmol) was added sodium (triacetoxy)borohydride (553 mg, 2.60 mmol). After stirring for 16 h, the reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The EtOAc was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 1.09 g (90%) of (*S*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(isopropylamino-methyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow foam. Mass Spectrum: (ESI) *m/z* 663 $(M+H)^+$.

D: (*R*)-{1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester. To a

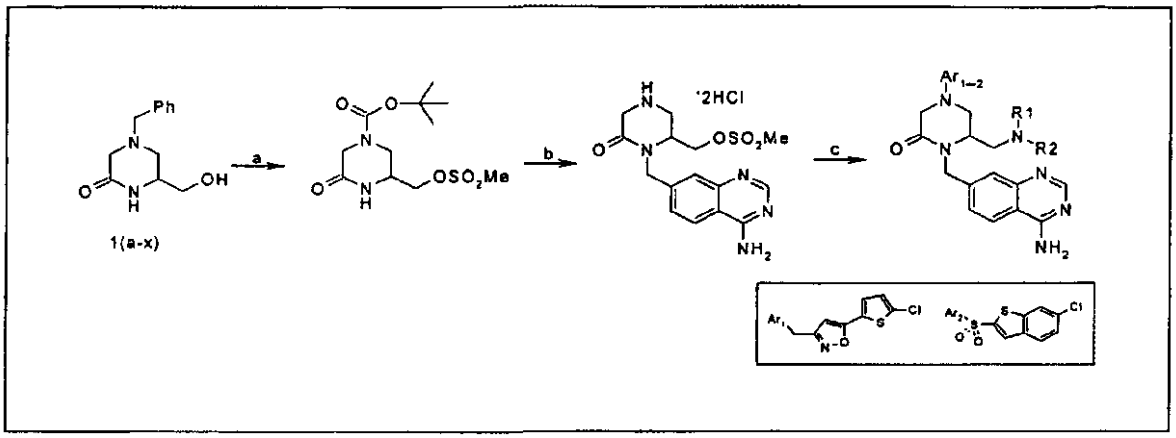
solution of (*S*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(isopropylamino-methyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (1.34 g, 2.02 mmol), Et_3N (560 μL, 4.04 mmol), and DMAP (26 mg, 0.20 mmol) in THF (15 mL) at 0°C was added Boc-anhydride (485 mg, 2.22 mmol). After warming to ambient temperature and stirring for 2 h, Boc-anhydride (144 mg, 0.660 mmol) was added. The reaction was allowed to stir for 48 h and was then diluted with water and extracted with EtOAc. The EtOAc was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 1.55 g (100%) of (*R*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.73 (m, 2H), 7.33-7.50 (m, 4H), 7.19-7.30 (m, 4H), 7.11-7.18 (m, 2H), 6.89-6.95 (m, 2H), 6.81 (s, 1H), 6.28 (s, 1H), 4.98-5.07 (m, 1H), 3.89-4.05 (m, 1H), 3.63 (s, 2H), 3.20-3.60 (m, 5H), 2.76-2.89 (m, 2H), 2.14-2.23 (m, 1H), 1.32-1.54 (m, 9H), 1.03-1.17 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 763 $(M+H)^+$.

E: (*R*)-{1-(3-Amino-4-cyano-benzyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester. To a solution of (*R*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester (1.55 g, 2.02 mmol) in a mixture of MeOH (10 mL) and THF (5 mL) at 0°C was added conc. HCl (2 drops). After stirring for 45 min conc. HCl (3 drops) was added and the reaction was allowed to warm to ambient temperature and stir for an additional 1.5 h. Chromatography on SiO_2 (CH_2Cl_2 to 10% MeOH / CH_2Cl_2) afforded 350 mg (29% over two steps) of (*R*)-{1-(3-amino-4-cyano-benzyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester as a white solid. Mass Spectrum: (ESI) *m/z* 599 $(M+H)^+$.

F: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one. A solution of (*R*)-{1-(3-amino-4-cyano-benzyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester (350 mg, 0.584 mmol), glacial acetic acid (340 μL, 5.94 mmol), and 1,3,5-triazine (492 g, 6.07 mmol) in absolute EtOH (10 mL) was heated at reflux for 16 h. The EtOH was concentrated and the residue was dissolved in CH_2Cl_2 (10 mL), cooled to 0°C and treated with TFA (4 mL). After stirring for 16 h at ambient temperature, the mixture was concentrated amd purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA). The appropriate product fractions were combined and lyophilized to afford 188 mg (50%) of the TFA salt of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-

thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (d, J = 13 Hz, 2H), 8.81 (s, 1H), 8.65 (br s, 1H), 8.50 (br s, 1H), 8.38 (d, J = 8.5 Hz, 1H), 7.53-7.63 (m, 3H), 7.29 (d, J = 4.0 Hz, 1H), 6.94 (s, 1H), 5.17 (d,J = 16.7 Hz, 1H), 4.39 (d, J = 16.7 Hz, 1H), 3.78 (AB quartet, J = 30.0, 14.4 Hz, 2H), 3.46-3.62 (m, 3H), 3.33 (t, J = 5.8 Hz, 1H), 3.09-3.25 (m, 3H), 2.72 (d,J = 10.2 Hz, 1H), 1.14-1.23 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 526 $(M+H)^+$.

Scheme 12 A mesylate scheme of the C(6)-alkylaminomethyl substituted inhibitors.



Reagents: (a) 1. Ms_2O, Et_3N, CH_2Cl_2. 2. $Pd(OH)_2$, MeOH, H_2. 3. Boc_2O, Et_3N, THF. (b) 1. NaH, 4-amino-7-bromomethylquinazoline, THF. 2. HCl, MeOH. (c) 1. Et_3N, Ar_1Br or Ar_2SO_2Cl, CH_2Cl_2. 2. Amine, DMF, K_2CO_3, 80 °C.

Example 1532 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one

A: (*R*)-Methanesulfonic acid 4-benzyl-6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-4-benzyl-6-hydroxymethyl-piperazin-2-one (2.0 g, 9.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (5.2 mL, 37 mmol), followed by methanesulfonic anhydride (3.24 g, 19 mmol). After 1 h at ambient temperature, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 2.6 g (94%) (*R*)-methanesulfonic acid 4-benzyl-6-oxo-piperazin-2-ylmethyl ester which was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-7.26 (m, 5H), 6.18 (br s, 1H), 4.32-4.16 (m, 2H), 3.8-3.7 (m, 1H), 3.61 (d, J = 12.9 Hz, 1H), 3.52 (d, J = 12.9 Hz, 1H), 3.32 (d, J = 16 Hz, 1H), 3.0 (s, 3H), 2.7-2.6 (m, 2H) ppm. Mass Spectrum: (ESI) *m/z* 299 $(M+H)^+$.

B: (*R*)-Methanesulfonic acid 6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-methanesulfonic acid 4-benzyl-6-oxo-piperazin-2-ylmethyl ester (2.9 g, 9.7 mmol) in MeOH (50

mL) was added 10% palladium hydroxide on C (1 g). The heterogenous mixture was hydrogenated at ambient temperature under a balloon of H_2 for 20 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to afford (*R*)-methanesulfonic acid 6-oxo-piperazin-2-ylmethyl ester which was used directly in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 209 $(M+H)^+$.

C: (*R*)-3-Methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. To a suspension of (*R*)-methanesulfonic acid 6-oxo-piperazin-2-ylmethyl ester and $NaHCO_3$ (2.44 g, 29 mmol) in THF/water (5:1, 20 mL) at 0 °C was added Boc-anhydride (2.75 g, 12.6 mmol). After 24 h at ambient temperature, the reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were washed with saturated NH_4Cl solution and brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (1% to 10% MeOH in CH_2Cl_2) provided 1.8 g (35%) of (*R*)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (br s, 1H), 4.3-4.1 (m, 3H), 3.94 (d, *J* = 19 Hz, 1H), 3.82-3.75 (m, 2H), 3.55 (dd, *J* = 14.6, 4.6 Hz, 1H), 3.09 (s, 3H), 1.48 (s, 9H) ppm. Mass Spectrum: (ESI)*m/z* 617 $(2M+H)^+$.

D: (*R*)-4-(4-Amino-quinazolin-7-ylmethyl)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. To a solution of (*R*)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.8 g, 5.8 mmol) in DMF (20 mL) at 0 °C was added sodium hydride (a 60% dispersion in mineral oil, 0.35 g, 8.7 mmol) followed after 15 min by 4-amino-7-bromomethyl-quinazoline (1.52 g, 6.4 mmol). After 1 h at ambient temperature, the reaction mixture was quenched with saturated NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with water (twice), dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on SiO_2 (5% to 20% MeOH in CH_2Cl_2) to provide 1.72 g (63%) of (*R*)-4-(4-amino-quinazolin-7-ylmethyl)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 466 $(M+H)^+$.

E: (*R*)-Methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-6-oxo-piperazin-2-ylmethyl ester. A solution of (*R*)-4-(4-amino-quinazolin-7-ylmethyl)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.72 g, 3.7 mmol) in MeOH (80 mL) at 0 °C was bubbled with anhydrous HCl gas for 15 min. After 6 h at ambient temperature, the reaction mixture was concentrated and triturated with MeOH and ether to provide 1.54 g of (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-6-oxo-piperazin-2-ylmethyl ester as a

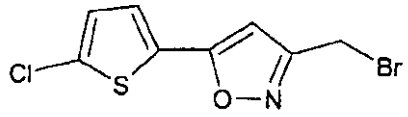
hydrochloride salt which were used in the next reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.32 (d, *J* = 4.0 Hz, 1H), 7.78 (s, 2H), 5.05 (br s, 1H), 4.56 (br s, 1H), 4.46 (br s, 1H), 4.27 (br s, 1H), 4.07 (br s, 2H), 3.76 (br s, 2H), 3.11 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 366 $(M+H)^+$.

F: (*R*)-Methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-6-oxo-piperazin-2-ylmethyl ester-HCl (0.48 g, 1.1 mmol) in DMF (3 mL) at 0 °C was added Et_3N (0.92 mL, 6.6 mmol), followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (330 mg, 1.32 mmol). After 0.5 h at ambient temperature, the reaction mixture was diluted with water to give a solid which was filtered and washed with ether. The crude (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl ester (0.7 g, 100%) was used in the following reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 7.72 (br s, 1H), 7.59 (d,*J* = 9.9 Hz, 1H), 7.51 (s, 1H), 7.32 (d, *J* = 9.9 Hz, 1H), 5.15 (d, *J* = 16 Hz, 1H), 4.45-4.30 (m, 3H), 4.07 (d, *J* = 18 Hz, 1H), 3.85-3.70 (m, 3H), 3.25 (s, 3H), 3.25-3.15 (m, 1H). Mass Spectrum: (ESI)*m/z* 596 $(M+H)^+$.

G: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one A mixture of (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl ester (100 mg, 0.17 mmol) and 2-aminoethyl methyl ether (1 ml) in DMF (2 ml) was heated to 100 °C for 24 h. The reaction mixture was concentrated and chromatographed on SiO_2 (5% to 20% MeOH in CH_2Cl_2) to provide 20 mg (20%) of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 9.77 (br. s, 2H), 8.96 (br. s, 2H), 8.81 (s, 1H), 8.39 (s, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 8.22 (s, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.65-7.58 (m, 3H), 5.14 (d, *J* = 16.8 Hz, 1H), 4.44 (d, *J* = 16.8 Hz, 1H), 4.10-3.80 (m, 5H), 3.68 (d, *J* = 16.2 Hz, 1H), 3.61 (t, *J* = 4.8 Hz, 2H), 3.50-3.20 (m, 4H), 3.32 (s, 3H) ppm. Mass Spectrum: (ESI)*m/z* 575 $(M+H)^+$.

Preparations of Methylhalides

Preparation of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole



Part A. 4-(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester.

Sodium hydride (60% dispersion in mineral oil, 2.43 g, 60.8 mmol) was added to the solution of 2-acetyl-5-chlorothiophene (4.88 g, 30.4 mmol) in 150 ml of anhydrous toluene at 0 °C under nitrogen in two portions. After the mixture was stirred at 0 °C for 10 minutes, diethyl oxalate (6.20 ml, 45.6 mmol) was added via syringe, the resulting mixture was stirred at 0 °C for half an hour, then heated to 140 °C gradually and refluxed for 1 hour. The solvents were removed under reduced pressure, 250 ml of water was added to the residue which was then washed with ethyl acetate (75 ml x 2), the aqueous portion was cooled to 0 °C and to which was added 2N HCl till PH = 2, ethyl acetate was used to extract the acidified aqueous portion (100 ml x 4), the combined organic portions were then washed with brine, dried with $MgSO_4$. Removal of the solvents afforded the desired product as a brownish solid, 7.10 g, which was used in the following reaction without further purification, 90%. ^1H NMR (CD_3OD) δ 1.36 (t, 3H, J = 7.1 Hz), 4.35 (q, 2H, J = 7.1 Hz), 6.95 (s, 1H), 7.15 (m, 1H), 7.87 (m, 1H).

Part B. 5-(5-chloro-thiophen-2-yl)-isoxazole-3-carboxylic acid ethyl ester.

The mixture of -(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester (5.40 g, 20.7 mmol) and hydroxylamine hydrochloride (5.04 g, 72.5 mmol) in 150 ml of anhydrous ethanol was refluxed for three hours. The solvents were removed under reduced pressure, 150 ml of H2O was added to the residue, followed by ammonium hydroxide (28-30 %) till PH=7. The aqueous mixture was then extracted with ethyl acetate (75ml x3), the combined organic portions were washed with brine, dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (10% of ethyl acetate/hexanes), 4.35 g of the desired product was obtained as a pale solid, 82%. ^1H NMR ($CDCl_3$) δ 1.41 (t, 3H, J = 7.1 Hz), 4.44 (q, 2H, J = 7.1 Hz), 6.71 (s, 1H), 6.95 (d, 1H, J = 4.0 Hz), 7.31 (d, 1H, J = 4.0 Hz).

Part C. [5-(5-chloro-thiophen-2-yl)-isoxazol-3-yl]-methanol.

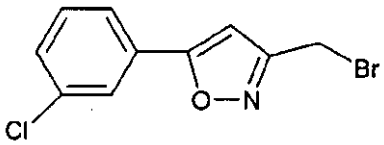
Sodium borohydride (3.20 g, 84.4 mmol) was added to the solution of 5-(5-chloro-thiophen-2-yl)-isoxazole-3-carboxylic acid ethyl ester (4.35 g, 16.9 mmol) in 80 ml of anhydrous ethanol at 0 °C, the mixture was then stirred at room temperature for 12 hours. Ethanol was removed under reduced pressure, the residue was taken up in H_2O (100ml), and NH_4Cl (aq)

was added to consume the excess $NaBH_4$. The product was extracted with ethyl acetate (75ml x 3), the combined organic portions were washed with brine, dried with $MgSO_4$, removal of the solvents afforded 3.53 g of white solid as the desired product, 97%. ^1H NMR ($CDCl_3$) δ 4.78 (s, 2H), 6.40 (s, 1H), 6.94 (d, 1H, J = 3.9 Hz), 7.27 (d, 1H, J = 3.9 Hz).

Part D. 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.

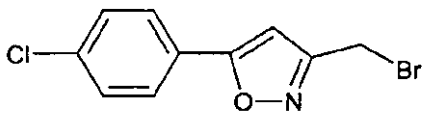
NBS (3.19 g, 17.9 mmol) was added to the mixture of 5-(5-chloro-thiophen-2-yl)-isoxazol-3-yl]-methanol (3.50 g, 16.2 mmol) and triphenyl phosphine (4.68 g, 17.9 mmol) in 80 ml of anhydrous methylene chloride at 0 °C. The mixture was then stirred at room temperature for 1 hour. The solvents were removed, the residue was purified by flash column chromatography (10 % of ethyl acetate/hexanes), 4.0 g of the product was obtained as a white solid, 89%. ^1H NMR ($CDCl_3$) δ 4.42 (s, 2H), 6.42 (s, 1H), 6.95 (d, 1H, J = 4.0 Hz), 7.28 (d, 1H, J = 4.0 Hz).

Preparation of 3-Bromomethyl-5-(3-chloro-phenyl)-isoxazole



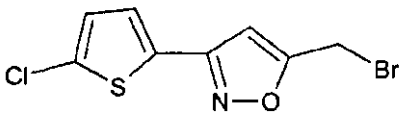
3-Bromomethyl-5-(3-chloro-phenyl)-isoxazole was prepared according to the methods described for 3-methyl-5-(5-chloro-thiophen-2-yl)-1H-pyrazole. ^1H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.64 (s, 1H), 7.41-7.43 (m, 2H), 7.64-7.67 (m, 1H), 7.77 (m, 1H).

Preparation of 3-Bromomethyl-5-(4-chlorophenyl)-isoxazole



3-Bromomethyl-5-(4-chlorophenyl)-isoxazole was prepared according to the methods described for 3-methyl-5-(5-chloro-thiophen-2-yl)-1H-pyrazole. ^1H NMR ($CDCl_3$) δ 4.45 (s, 2H), 6.60 (s, 1H), 7.44 (d, 2H, J=8.6 Hz), 7.70(d, 2H, J= 8.6 Hz).

Preparation of 5-bromomethyl-3-(5-chloro-thiophen-2-yl)-isoxazole



Method I:

Part A. 5-Chloro-thiophene-2-carbaldehyde oxime.

A mixture of 5-chloro-2-thiophene carboxaldehyde (1.36 g, 9.28 mmol) and hydroxyamine hydrochloride (0.71 g, 10.2 mmol) in 8 ml of pyridine was stirred at room temperature overnight. Pyridine was removed under reduced pressure, the residue was purified by flash column chromatography (5% -10% of ethyl acetate in methylene chloride), 1.02 g of the product was obtained as a white solid, 68%. ^{1}H NMR (CD_3OD) δ 6.94 (d, 1H, J=4.0 Hz), 7.14 (d, 1H, J=4.0 Hz), 7.60 (s, 1H), 8.81 (broad, 1H, OH).

Part B. 5-Bromomethyl-3-(5-chloro-thiophen-2-yl)-isoxazole

N-chlorosuccinimide (0.28 g, 2.10 mmol) was added to the solution of 5-Chloro-thiophene-2-carbaldehyde oxime (0.33 g, 2.04 mmol) in 10 ml of anhydrous DMF at room temperature under N_2, followed by the addition of two drops of pyridine. The mixture was stirred at r.t. for one hour, at 60 °C for 3 hours, the mixture was cooled to 0 °C and to which was added propargyl bromide (80 wt. % in toluene, 2.30 ml, 20.4 mmol), a solution of triethyl amine (0.29 ml, 2.04 mmol) in 2.5 ml of DMF was then added dropwise slowly in a period of 25 minutes . The reaction was warmed to room temperature and stirred for 18 hours, diluted with water (200 ml), extracted with ethyl acetate (50ml x 3), the combined organic portions were washed with water (100 ml x 2), brine, dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (5%-10% of ethyl acetate/hexanes), 0.28 g of the desired product was obtained as a white solid, 49%. ^{1}H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.51 (s, 1H), 6.92 (d, 1H, J = 3.9 Hz), 7.19 (d, 1H, J = 3.9 Hz).

Method II:

Part A. 3-(5-chloro-thiophen-2-yl)-isoxazole-5-carboxylic acid ethyl ester.

N-chlorosuccinimide (0.32 g, 2.41 mmol) was added to the solution of 5-Chloro-thiophene-2-carbaldehyde oxime (0.39 g, 2.41 mmol) in 10 ml of anhydrous DMF at room temperature under N_2, followed by the addition of two drops of pyridine. After stirred at 60 °C for 3 hours, the mixture was cooled to 0 °C and to which was added methyl propiolate (1.0 ml, 12.1 mmol), a solution of triethyl amine (0.34 ml, 2.41 mmol) in 2.5 ml of DMF was then added slowly in a period of 30 minutes . The reaction was warmed to room temperature and stirred for 12 hours, diluted with water (200 ml), extracted with ethyl acetate (50ml x 2), the combined organic portions were washed with water, brine, dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (3%-10% of ethyl acetate/hexanes), 0.19 g of the desired product was obtained as a white solid, 32%. ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 6.95 (d, 1H, J=3.9 Hz), 7.11 (s, 1H), 7.26 (d, 1H, J=3.9 Hz).

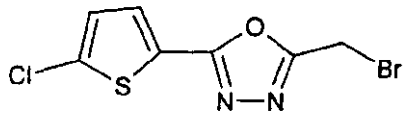
Part B. [3-(5-chloro-thiophen-2-yl)-isoxazol-5-yl]-methanol.

Sodium borohydride (0.14 g, 3.90 mmol) was added to a suspension of 3-(5-chloro-thiophen-2-yl)-isoxazole-5-carboxylic acid ethyl ester (0.19 g, 0.78 mmol) in 15 ml of anhydrous methanol at 0 °C. The mixture was then stirred at 0 °C under N_2, at room temperature for half an hour. Methanol was removed under reduced pressure, the residue was taken up in H_2O (50ml), and NH_4Cl (aq) was added until pH = 7 was obtained. The product was extracted with ethyl acetate (30 ml x 2), the combined organic portions were washed with brine, dried with $MgSO_4$, removal of the solvents afforded 0.14 g of white solid as the desired product, 83%. ^1H NMR ($CDCl_3$) δ 4.79 (s, 2H), 6.44 (s, 1H), 6.92 (d, 1H, J = 3.9 Hz), 7.19 (d, 1H, J = 3.9 Hz).

Part C. 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.

N-bromosuccinimide (0.14 g, 0.78 mmol) was added to the mixture of [3-(5-chloro-thiophen-2-yl)-isoxazol-5-yl]-methanol (0.14 g, 0.65 mmol) and triphenyl phosphine (0.21 g, 0.78 mmol) in 15 ml of anhydrous methylene chloride at 0 °C under N_2. The mixture was then stirred at room temperature for 1 hour. The solvents was removed, the residue was purified by flash column chromatography (10 % of ethyl acetate/hexanes), 0.13 g of the product was obtained as a white solid, 72%. ^1H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.51 (s, 1H), 6.92 (d, 1H, J = 3.9 Hz), 7.19 (d, 1H, J = 3.9 Hz).

Preparation of 5-(5-chlorothiophen-2-yl)-2-bromomethyl-[1,3,4]oxadiazole



Part A. 5-chloro-thiophene-2-carboxylic acid N-acetyl-hydrazide.

A 2.0 M solution of oxalyl chloride in methylene chloride (82ml) was added to a stirred solution of 5-chloro-thiophene-2-carboxylic acid (13.33 g) and DMF (0.1 ml) in methylene chloride (150 ml) at
0°C for 25 min., then warmed up to room temperature and stirred for an hour. Evaporated off methylene chloride to give an oil (the acid chloride) which was dissolved in THF (40 ml). He resulting solution was added to a stirred solution of acetyl hydrazide (6.08 g) in THF (100 ml) under N_2 at room temperature, followed by addition of K_2CO_3 (22.66 g). Stirred at room temperature for 4 hours. The THF was removed under vacuum to give a solid that was dissolved in methanol (120 ml). The precipitated solid was removed by filtration; the resulting

solution was concentrated to give the title product (17.90 g) in 100 % yield. ^{1}HNMR (CD_3OD) ppm 7.34 (d, H), 6.85 (d, H), 2.00 (s, 3H).

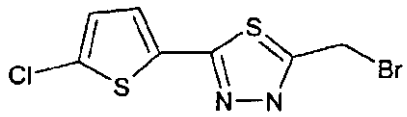
Part B. 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]oxadiazole

A mixture 5-chloro-thiophene-2-carboxylic acid N-acetyl-hydrazide (1.11 g) and P_2O_5 (18.0 g) was heated to 110°C for 20 hours. Cooling to room temperature and ice (200 g) was added to dissolve P_2O_5. The dark solution was diluted to 400 ml with water and extracted with ether (2x30 ml). The combined organic solution was washed with Brine and dried over $MgSO_4$. After concentration, 0.62 g of product was obtained in 61% yield. ^{1}HNMR ($CDCl_3$) ppm 7.45 (d,H), 6.93 (d, H), 2.56 (s, 3H).

Part C. 5-(5-chloro-thiophen-2-yl)-2-bromomethyl-[1,3,4]oxadiazole

A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]-oxadiazole (937 mg), NBS (800 mg) and benzene peroxide (330 mg) in CCl4 (100 ml) was refluxed overnight. The reaction mixture was concentrated to give a solid residue that was chromatographed through silica-gel using 5-10% ethyl acetate as an eluent. The pure product (429 mg) was obtained in 50% yield. ^{1}HNMR ($CDCl_3$) ppm 7.55 (d. H), 6.98 (d, H), 4.58 (s, 2H).

Preparation of 5-(5-chlorothiophen-2-yl)-2-bromomethyl-[1,3,4]thiadiazole



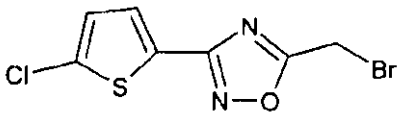
Part A. 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]thiadiazole

A solution of 5-chloro-thiophene-2-carboxylic acid N-acetyl-hydrazide (1.18 g) and Lowesson's Reagent (2.18 g) in xylene (40 ml) was stirred at 140°C for an hour. The hot solution was transfer into a chromatographic column with silica gel. After cooling, washed with hexane to remove xylene. The solid was chromatographed through silica gel using 20% ethyl acetate as an eluent. Pure product (1.18 g) was obtained in about 100% yield. ^{1}HNMR ($CDCl_3$) ppm 7.25 (d, H), 6.93 (d, H), 2.78 (s, 3H).

Part B. Preparation of 5-(5-chloro-thiophen-2-yl)-2-bromomethyl-[1,3,4] thiadiazole

A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]thiadiazole (937 mg), NBS (800 mg) and benzene peroxide (330 mg) in CCl4 (100 ml) was refluxed overnight. Concentrated to give a solid that was chromatographed through silica gel using 10% ethyl acetate as an eluent. The pure product (672 mg) was obtained in 54 % yield. ^{1}HNMR ($CDCl_3$) ppm 7.31 (d. H), 6.96 (d, H), 4.80 (s, 2H).

Preparation of 5-bromomethyl-3-(5-chloro-thiophen-2-yl)-[1,2,4]oxadiazole



Part A. 5-Chloro-thiophene-2-carbaldehyde oxime.

A mixture of 5-chloro-2-thiophene carboxaldehyde (1.36 g, 9.28 mmol) and hydroxyamine hydrochloride (0.71 g, 10.2 mmol) in 8 ml of pyridine was stirred at room temperature overnight. Pyridine was removed under reduced pressure, the residue was purified by flash column chromatography (5% -10% of ethyl acetate in methylene chloride), 1.02 g of the product was obtained as a white solid, 68%. ^{1}H NMR (CD_3OD) δ 6.94 (d, 1H, J=4.0 Hz), 7.14 (d, 1H, J=4.0 Hz), 7.60 (s, 1H), 8.81 (broad, 1H, OH).

Part B. 5-Chloro-thiophene-2-carbonitrile.

5-Chloro-thiophene-2-carbaldehyde oxime (2.20g, 13.6 mmol), in 30 ml of anhydrous acetic anhydide, was refluxed for 24 hours; the excess acetic anhydride was removed under reduced pressure. The resulting residue was taken up in 100 ml of H_2O, neutralized with ammonium hydroxide and extracted with ethyl acetate (50 ml x 3). The combined organic portions were washed with brine.. After the solvents were removed, the residue was purified by flash column chromatography (10% of ethyl acetate in hexanes); 1.50 g of the desired product was obtained as a colorless oil, 77%. ^{1}H NMR ($CDCl_3$) d, J = 4.1 Hz), 6.95 (1H, d, J = 4.0 Hz).

Part C. 5-Chloro-N-hydroxy-thiophene-2-carboxamidine.

A mixture of hydroxyamine hydrochloride (1.10 g, 15.7 mmol) and sodium hydroxide (0.63 g, 15.7 mmol) in 20 ml of ethanol and 1 ml of water was added to the solution of 5-Chloro-thiophene-2-carbonitrile (1.50 g, 10.4 mmol) in 20 ml of ethanol. The mixture was then refluxed for 12 hours. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (2% of methanol in methylene chloride); 1.65 g of the desired product was obtained as a white solid, 90%. ^{1}H NMR (CD_3OD) δ 7.52 (1H, d, J = 4.1 Hz), 7.00 - 7.01 (1H, m).

Part D. 3-(5-chloro-thiophen-2-yl)-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester.

Pyridine (0.14 ml, 1.70 mmol) was added dropwise to a mixture of 5-Chloro-N-hydroxy-thiophene-2-carboxamidine (0.15 g, 0.85 mmol) and ethyl chlorooxoacetate (0.19 ml, 1.70 mmol) in 10 ml of anhydrous chloroform. The reaction was refluxed for 16 hours; the solvents

were removed under reduced pressure. The residue was taken up in 50 ml of water and extracted with ethyl acetate (15 ml x 2); the organic portion was washed with brine and dried with MgSO4. After concentration the crude product was purified by flash column chromatography (5% of ethyl acetate in hexanes); 0.11 g of the desired product was obtained as a colorless oil, 50%. ^{1}H NMR ($CDCl_3$) δ 7.67 - 7.69 (1H, m), 6.99 (1H, d, J = 4.1 Hz), 4.56 (2H, q, J = 7.1 Hz), 1.48 (3H, t, J = 7.1 Hz).

Part E. [3-(5-chloro-thiophen-2-yl)-4,5-dihydro-[1,2,4]oxadiazol-5-yl]-methanol.

Sodium borohydride (0.080 g, 2.20 mmol) was added to the solution of 3-(5-chloro-thiophen-2-yl)-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester (0.11 g, 0.43 mmol) in 10 ml of anhydrous methanol at 0 °C. The reaction was stirred at 0 °C for 30 minutes, the solvent was removed under reduced pressure and the residue was diluted with 30 ml of water. The aqueous solution was extracted with ethyl acetate (20 ml x 2), the combined organic portions were washed with brine, dried with $MgSO_4$ and concentrated to afford the desired product as a viscous oil (0.085g, 91%). 1H NMR (CD_3OD) δ 7.25 - 7.28 (1H, m), 6.99 - 7.01 (1H, m), 5.61 - 5.62 (1H, m), 3.54 - 3.59 (2H, m).

Part F. 3-(5-Chloro-thiophen-2-yl)-[1,2,4]oxadiazol-5-yl]-methanol.

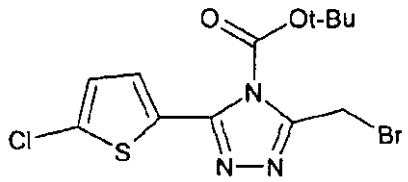
N-Chlorosuccinimide (0.052 g, 0.39 mmol) was added to the soulition of [3-(5-chloro-thiophen-2-yl)-4,5-dihydro-[1,2,4]oxadiazol-5-yl]-methanol (0.085 g, 0.39 mmol) in 4.0 ml of anhydrous DMF at 50 °C under N_2. The mixture was then stirred at 50 °C for 40 minutes, poured into 50 ml of water and extracted with ethyl acetate (15 ml x 3). The combined organic portions were washed with water, brine and dried with $MgSO_4$; removal of the solvents afforded product as a white solid (0.082 g, 96 %). 1H NMR (CD_3OD) δ 7.61 (1H, d, J = 4.0 Hz), 7.09 (1H, d, J = 3.9 Hz), 4.86 (2H, s).

Part G. 5-Bromomethyl-3-(5-chloro-thiophen-2-yl)-1,2,4-oxadiazole.

N-Bromosuccinimide (0.082 g, 0.46 mmol) was added to a mixture of the 3-(5-Chloro-thiophen-2-yl)-[1,2,4]oxadiazol-5-yl]-methanol (0.082 g, 0.38 mmol) and triphenyl phosphine (0.12 g, 0.46 mmol) in 10 ml of anhydrous methylene chloride at 0 °C under N_2. The reaction was stirred at 0 °C for 30 minutes and warmed to ambient temperature for 1 hour. The solvent was removed, the residue was purified by flash column chromatography (5% - 10% of ethyl acetate in hexanes); 0.030 g (47%) of the product was obtained as a colorless oil. Starting

material (0.036 g) was also recovered. ^{1}H NMR ($CDCl_3$) δ 7.58 (1H, d, J = 4.0 Hz), 6.97 (1H, d, J = 4.0 Hz), 4.51 (2H, s).

Preparation of 5-(5-chloro-thiophen-2-yl)-3-bromomethyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole



Part A. N, N'-(5-chloro-thiophen-2-carboxyll-acetyl-hydrazide

A solution of acetic hydrazide (1.62 g) and 1.9 M Et_3Al (25.3 ml) in toluene was stirred at room temperature for 20 min. A solution of 5-chloro-2-cyanothiophene (3.14 g) in toluene (55 ml) was added slowly at room temperature, then stirred at 85°C overnight. The reaction was cooled to room temperature, quenched with 4 drops of water, then stirred at room temperature for 20 min. Water (30 ml) was added, the solid was filtered off and washed with hot methanol (3x30 ml). The filtrate was concentrated; the solid was recrystallized from ethanol to give product as a white solid (2.88g, 61 %). ^{1}HNMR (CD_3OD) ppm 7.35 (d,H), 6.92 (d, H), 2.01 (s, 3H).

Part B. 5-(5-chloro-thiophen-2-yl)-2-methyl-4H-[1,2,4]triazole

N, N'-(5-chloro-thiophen-2-carboxyll-acetyl-hydrazide (1.80 g) was heated at 180°C for 20 min., then cooled to give product as a white solid (1.15 g, 100%). ^{1}HNMR ($CDCl_3$) ppm 7.48 (d, H), 6.96 (d, H), 4.86 (s, NH)2.46 (s, 3H).

Part C. 5-(5-chloro-thiophen-2-yl)-2-methyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole

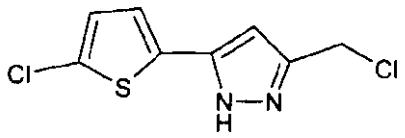
A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-4H-[1,2,4]triazole (1.09 g), $(BOC)_2O$ (1.43 g) and DMAP (0.14 g) was stirred at room temperature overnight. Evaporation of the THF gives an oil which is dissolved in methylene chloride (40 ml) and washed with 1 N HCl solution and water. After drying ($MgSO_4$) the organic layer isconcentrated to give pure product (1.64 g, 100%). ^{1}HNMR ($CDCl_3$) ppm 7.50 (d, H), 6.89 (d, H), 2.69 (s, 3H), 1.64 (s, 9H).

Part D. 5-(5-chloro-thiophen-2-yl)-3-bromomethyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole

A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole (1.16 g), NBS (1.14 g) and benzene peroxide (0.27 mg) in CCl_4 (50 ml) was refluxed overnight. Concentration gives a solid, which was chromatographed through silica gel

using 5-10% ethyl acetate as an eluent. The pure product (0.91 g) was obtained in 43% yield. ^{1}HNMR ($CDCl_3$) ppm 7.56 (d. H), 6.92 (d, H), 4.76 (s, 2H), 1.70 (s, 9H).

Preparation of 5-chloromethyl-3-(5-chloro-thiophen-2-yl)-1H-pyrazole



Part A. 4-(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester.

Sodium hydride (60% dispersion in mineral oil, 2.43 g, 60.8 mmol) was added to the solution of 2-acetyl-5-chlorothiophene (4.88 g, 30.4 mmol) in 150 ml of anhydrous toluene at 0 °C under nitrogen in two portions. After the mixture was stirred at 0 °C for 10 minutes, diethyl oxalate (6.20 ml, 45.6 mmol) was added via syringe, the resulting mixture was stirred at 0 °C for half an hour, then heated to 140 °C gradually and refluxed for 1 hour. The solvents were removed under reduced pressure, 250 ml of water was added to the residue which was then washed with ethyl acetate (75 ml x 2), the aqueous portion was cooled to 0 °C and to which was added 2N HCl till PH = 2, ethyl acetate was used to extract the acidified aqueous portion (100 ml x 4), the combined organic portions were then washed with brine, dried with $MgSO_4$. Removal of the solvents afforded the desired product as a brown solid , 7.10g, which was used in the following reaction without further purification, 90%. ^{1}H NMR (CD_3OD) δ 1.36 (t, 3H, J = 7.1 Hz), 4.35 (q, 2H, J = 7.1 Hz), 6.95 (s, 1H), 7.15 (m, 1H), 7.87 (m, 1H).

Part B. 4-(5-chloro-thiophen-2-yl)-2H-pyrazole-3-carboxylic acid ethyl ester.

Hydrazine (0.30 ml, 9.44 mmol) was added to a solution of 4-(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester (1.64 g, 6.30 mmol) in 80 ml of anhydrous ethanol at 0 °C. The mixture was warmed to room temperature, several drops of acetic acid was added and the mixture was stirred at 90 °C for 1 hour. The solvents were removed under reduced pressure, the residue was taken up in 100 ml of H_2O, and extracted with ethyl acetate (50 ml x3). The combined organic portions were washed with brine and dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (10% to 20% of ethyl acetate/hexanes); 0.53 g of the desired product was obtained as a white solid, 33%. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, J = 7.1 Hz), 4.39 (q, 2H, J = 7.1 Hz), 6.87 (d, 1H, J=3.9 Hz), 6.94 (s, 1H), 7.11 (d, 1H, J = 3.9 Hz), 11.6 (broad, 1H)

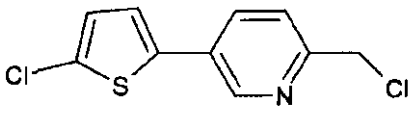
Part C. [5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-yl]-methanol.

Diisobutylaluminum hydride (1.5 M solution in toluene, 6.80 ml, 10.1mmol) was added dropwise to a solution of 4-(5-chloro-thiophen-2-yl)-2H-pyrazole-3-carboxylic acid ethyl ester (0.52 g, 2.03 mmol) in 40 ml of anhydrous tetrahydrofuran at 0 °C, under nitrogen. The mixture was stirred at 0 °C for half an hour, then at room temperature for half an hour. The reaction was quenched with methanol (0.80 ml) at -10 °C; 100 ml of 10% potassium sodium tartrate solution was added. The aqueous mixture was extracted with ethyl acetate (50 mlx3); the combined organic portions were washed with brine and dried with $MgSO_4$ and concentrated to afford 0.43 g of white solid as the desired product (99%). ^1H NMR (CD_3OD) δ 4.61 (s, 2H), 6.46 (s, 1H), 6.92 (d, 1H, J = 3.7 Hz), 7.13 (d, 1H, J = 3.9 Hz).

Part D. 5-chloromethyl-3-(5-chloro-thiophen-2-yl)-1H-pyrazole.

N-Chlorosuccinimide (0.30 g, 2.24 mmol) was added to the mixture of [5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-yl]-methanol (0.40 g, 1.86 mmol) and triphenyl phosphine (0.59 g, 2.24 mmol) in 40 ml of anhydrous tetrahydrofuran and 40 ml of anhydrous chloroform at 0 °C under nitrogen. The mixture was then stirred at 0 °C for 10 minutes and warmed to room temperature for half an hour. The solvents were removed, the residue was purified by flash column chromatography (15 % of ethyl acetate/hexanes) and 0.29 g of product was obtained as a white solid (67%). ^1H NMR ($CDCl_3$ with a small amount of CD_3OD) δ 4.58 (s, 2H), 6.42 (s, 1H), 6.84 (d, 1H, J = 3.9 Hz), 7.03 (d, 1H, J = 3.8 Hz).

Preparation of 2-Chloromethyl -5-(5-chloro-thiophen-2-yl)-pyridine hydrochloride



.HCl

Part A. 2-Methyl-5-Trifluoromethylsulfonyloxy-pyridine

2-Methyl-5-hydroxypyridine (7.4 g, 67.80 mmol) was suspended in 40 mL of pyridine. Trifluoromethanesulfonic anhydride (20 g, 70.89 mmol) was added dropwise at 5 °C. After 30 min at this temperature the resulting solution was stirred 12 hours at room temperature.The reaction mixture was diluted with 200 mL of AcOEt, washed with 1N hydrochloric acid (3 x 200 mL), brine (200 mL), dried over magnesium sulfate and concentrated. The titled compound (12.6 g, 77%) was obtained as a colorless liquid. $C_7H_6F_3O_3S$ MS $(M+H)^+ = 242$

Part B. 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine

To a solution of 2-Methyl-5-Trifluoromethylsulfonyloxy-pyridine (4.82 g, 20 mmol) in 60 mL of DMF was added 5-chlorothiophene-2-boronic acid (4 g, 24.6 mmol), tetrakis(triphenyl-

phosphine) palladium(0) (1 g, 0.86 mmol) and potassium phosphate (6.36 g, 30 mmol) under nitrogen. The mixture is heated at 100 °C for 6 hours, cooled and diluted with 200 mL of EtOAc. The EtOAc solution was washed with water (2 x 200 mL), brine (200 mL), dried over magnesium sulfate and concentrated. The resulting residue was purified by column chromatography on silica gel eluting with Cyclohexane70 %/ AcOEt 30%. The title compound (3 g, 71%) was obtained as a pale yellow solid. $C_{10}H_8NCIS$ MS $(M+H)^+$ = 210, Cl pattern

Part C. 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine-1-oxide

To a solution of 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine (1.3 g, 6.35 mmol) in 50 mL of CH_2Cl_2 at 5 °C was added portionwise 70% chloroperoxybenzoic acid (1.67g, 6.77 mmol). The resulting solution was stirred at room temperature for 2 hours and concentrated under vacuum. The resulting solid was taken-up in EtOAc (100 mL), washed with 0.5 N NaOH (2x50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate and concentratedto give the title compound (1.25 g, 71%) as a white solid. $C_{10}H_8OCINS$ MS $(M+H)^+$ = 226, Cl pattern

Part D. 5-(5-Chloro-thiophen-2-yl)-2-hydroxymethyl-pyridine

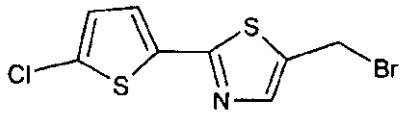
To a solution of 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine-1-oxide (1.25 g, 5.54 mmol) in 20 mL of CH_2Cl_2 was added, dropwise, trifluoroacetic anhydride (1.6 mL, 14.07 mmol). The solution was stirred 2 hours at room temperature, concentrated and dried under vacuum. The resulting solid was taken-up in 20 mL of CH_2Cl_2 and 30 mL of 2M aqueous K_2CO_3. The biphasic mixture was stirred vigorously for 6 hours at room temperature. The aqueous phase was separated and extracted twice with CH_2Cl_2. The organic phases were combined, dried over magnesium sulfate and concentrated. The resulting crude product was purified by column chromatography on silica gel eluting with EtOAc. The title compound (1 g, 80%) was obtained as a pale yellow solid.

$C_{10}H_8OCINS$ MS $(M+H)^+$ = 226, Cl pattern

Part E. 2-Chloromethyl -5-(5-chloro-thiophen-2-yl)-pyridine hydrochloride

A solution of 5-(5-Chloro-thiophen-2-yl)-2-hydroxymethyl-pyridine (550 mg, 2.44 mmol) in 20 mL of thionyl chloride was refluxed for 2 hours and concentrated under vacuum. The resulting solid was washed 3 times with Et_2O and dried under vacuum. The title compound (600 mg, 88%), obtained as a green solid, was used without further purification. $C_{10}H_7CINS$ MS $(M+H)^+$ = 244, Cl pattern.

Synthesis of 5-Bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole



Part A. 5-Chlorothiophene-2-carboxamide

To a solution of 5-chlorothiophene-2-carboxylic acid (5 g, 30.75 mmol) in 100 mL of dichloromethane were added oxalyl chloride (3.2 mL, 36.90 mmol) and 10 drops of DMF. After 2 hours at room temperature the solution was concentrated under vacuum and the residue was taken up in 100 mL of THF. A stream of NH_3 was passed through the reaction medium for 10 minutes and the suspension was stirred for 1 h 30. Water was added and the THF was evaporated under vacuum. The solid was filtered, washed with water and cyclohexane, and dried under vacuum. The titled compound (4.7 g, 95%) was obtained as a white solid.
C_5H_4OClNS

Part B. 5-Chlorothiophene-2-thiocarboxamide

5-Chlorothiophene-2-carboxamide (4.24 g, 26.2 mmol) and phosphorus pentasulfide (2.33 g, 5.25 mmol) were mixed in 80 mL of toluene and the reaction mixture was refluxed for 5 hours. After cooling the black solid was removed by filtration. The filtrate was treated with activated charcoal and filtrated again. The yellow solution was dried over magnesium sulfate and concentrat-ed. The resulting crude product was purified by column chromatography on silica gel eluting with Chloroform 95 %/ MeOH 5 %. The title compound (1.71 g, 37%) was obtained as a yellow solid.
$C_5H_4ClNS_2$

Part C. 2-(5-Chloro-thiophen-2-yl)-thiazole-5-carboxylic acid methyl ester

5-Chlorothiophene-2-thiocarboxamide (546 mg, 3.08 mmol) and methylchloroformyl acetate (663 mg at 95% pure, 4.6 mmol) were dissolved in 4.5 mL of methanol and the resulting mixture was refluxed for 3 hours, at which time additional methylchloroformylacetate (288mg at 95% pure, 2 mmol) was added. After refluxing for 20 hours the reaction mixture was concentrated under vacuum. The resulting crude product was purified by column chromatography on silica gel eluting with Cyclohexane 99 %/ EtOAc 1 %. The title compound (203 mg, 25%) was obtained as a white solid. $C_9H_6ClNO_2S_2$

Part D. 2-(5-Chloro-thiophen-2-yl)- 5-hydroxymethyl-thiazole

To a stirred suspension of 2-(5-Chloro-thiophen-2-yl)-thiazole-5-carboxylic acid methyl ester (194 mg, 0.748 mmol) in 12 mL of methanol was added, at room temperature, $NaBH_4$ (300 mg, 7.9 mmol). After 2 hours, additional $NaBH_4$ (300 mg, 7.9 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. Water was added and the methanol was evaporated under vacuum. The resulting aqueous solution was neutralized with 0.1 N HCl, and extracted with EtOAc; the organic layer was dried over magnesium sulfate and concentrated under vacuum. The title compound (173 mg, 85%) was used without further purification. $C_8H_6ClNOS_2$

Part E. 5-Bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole

To a solution of 2-(5-Chloro-thiophen-2-yl)- 5-hydroxymethyl-thiazole (90 mg, 0.39 mmol) in 5 mL of CH_2Cl_2 was added at 0 °C triphenylphosphine (122 mg, 0.467 mmol) and *N*-bromosuccinimide (83 mg, 0.467 mg). After stirring for 10 minutes at 0°C the reaction mixture was warmed to room temperature for 30 minutes. The solvent was removed under vacuum and the resulting crude product was purified by column chromatography on silica gel eluting with Cyclohexane 90 %/ AcOEt 10 % to give the title compound (31 mg, 27%). $C_8H_5BrClNS_2$

Using the methylhalides described in the preparations and the methods of the previous examples the following inhibitors were prepared:

Example 1533 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-piperazin-2-one tritrifluoroacetate

To a solution of 2-Chloromethyl -5-(5-chloro-thiophen-2-yl)-pyridine hydrochloride (600 mg, 2.13 mmol) in 25 mL of DMF was added 1-(4-Amino-quinazolin-7-ylmethyl)-piperazin-2-one (500 mg, 1.94 mmol), followed by *N*-ethyldiisopropylamine (1.5 ml, 8.61 mmol). The mixture was stirred a room temperature for 2 days, diluted with 100 mL of water. After stirring for 1 hour the yellow solid was filtered, washed thoroughly with water and dried under vacuum. The solid was purified by column chromatography on silica gel eluting with CH_2Cl_2 then 10 % MeOH - CH_2Cl_2 followed by RP-HPLC eluting in a mixture of 50% CH_3CN/H_2O (0.1% TFA). The appropriate collected fractions were lyophilized to afford the titled compound as a white solid (467 mg, 29 % yield). $C_{23}H_{21}OClN_6S$ MS $(M+H)^+$ = 465, Cl pattern. NMR (1H, DMSO) 9.82 (d, J = 17 Hz, 2H); 8.90 (d, J = 3 Hz, 1H); 8.82 (s, 1H); 8.41 (d, J = 10 Hz, 1H); 8.12 (dd, J = 2 Hz, J = 9 Hz, 1H); 7.70 (s, 1H); 7.63 (d, J = 9 Hz, 1H); 7.58 (s, 1H); 7.56 (m, 1H); 7.22 (dd, J = 1 Hz, J = 4 Hz, 1H); 4.78 (s, 2H); 4.34 (s, 2H) ; 3.82 (s, 2H); 3.50 (m, 2H); 3.48 (m, 2H).

Using the methylhalides described in the preparations and the methods of the previous examples the following inhibitors were prepared:

Example 1534 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.37 (1H, d, J = 8.6 Hz), 7.55 - 7.61 (3H, m), 7.27 - 7.29 91H, m), 6.89 (1H, s), 4.80 (1H, d, J = 16.1 Hz), 4.65 (1H, d, J = 16.0 Hz), 4.00 (1H, d, J = 14.6 Hz), 3.78 - 3.83 (4H, m), 3.36 (2H, s), 3.27 (3H, s), 3.06 - 3.10 (1H, m), 2.67 - 2.68 (1H, m). MS (Ion spray) $[M+H]^+$ of 499/501 observed, chloro pattern

Example 1535 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-propyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.74 (2H, bs), 8.81 (1H, s), 8.37 (1H, d, J = 8.5 Hz), 7.54 - 7.61 (3H, m), 7.28 - 7.29 (1H, m), 6.88 (1H, s), 4.64 - 4.76 (2H, m), 3.91 (1H, d, J = 14.4 Hz), 3.71 (1H, d, J = 14.4 Hz), 3.27 - 3.30 (2H, m), 3.13 91H, t, J = 4.7 Hz), 3.01 - 3.05 (1H, m), 2.61 - 2.65 (1H, m), 1.80 - 1.86 (2H, m), 1.39 - 1.52 (1H, m), 1.13 - 1.27 (1H, m), 0.80 - 0.85 (3H, m). MS (Ion spray) $[M+H]^+$ of 497/499 observed, chloro pattern.

Example 1536 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.59 - 7.61 (2H, m), 7.52 (1H, s), 7.29 (1H, d, J = 4.0 Hz), 6.92 (1H, s), 4.63 - 4.70 (2H, m), 3.95 (1H, d, J = 14.5 Hz), 3.76 (1H, d, J = 14.5 Hz), 3.24 - 3.32 (3H, m), 2.97 - 3.05 (1H, m), 2.60 - 2.70 (1H, m), 1.40 (3H, d, J = 6.8 Hz). MS (Ion spray) $[M+H]^+$ of 469/471 observed, chloro pattern.

Example 1537 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]- piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.81 (1H, bs), 9.77 (1H, s), 8.80 (1H, s), 8.38 (1H, d, J = 8.5 Hz), 7.59 - 7.62 (2H, m), 7.24 (1H, d, J = 3.9 Hz), 7.04 (1H, s), 4.71 (2H, s), 3.91(2H, s), 3.30 - 3.34 (4H, m), 2.82 - 2.85 (2H, m). MS (Ion spray) $[M+H]^+$ of 455/457 observed, chloro pattern.

Example 1538 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3- methoxymethyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.73 (2H, bs), 8.80 (1H, s), 8.37 (1H, d, J = 8.6 Hz), 7.55 - 7.62 (3H, m), 7.24 - 7.26 (1H, m), 7.00 (1H, s), 4.80 (1H, d, J = 16.2 Hz), 4.65 (1H, d, J = 16.0 Hz),

4.10 (1H, d, J = 15.6 Hz), 3.98 (1H, d, J = 15.6 Hz), 3.78 - 3.86 (3H, m), 3.33 (2H, s), 3.28 (3H, s), 3.10 - 3.14 (1H, m), 2.66 - 2.73 (1H, m). MS (Ion spray) $[M+H]^+$ of 499/501 observed, chloro pattern.

Example 1539 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3- methyl-piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.59 - 7.62 (2H, m), 7.51 (1H, s), 7.25 (1H, d, J = 3.9 Hz), 7.03 (1H, s), 4.69 (2H, s), 4.05 (1H, d, J = 15.6 Hz), 3.94 (1H, d, J = 15.5 Hz), 3.34 - 3.36 (1H, m), 3.20 - 3.26 (2H, m), 3.04 - 3.08 (1H, m), 2.65 - 2.71 (1H, m), 1.40 (3H, d, J = 6.8 Hz). MS (Ion spray) $[M+H]^+$ of 469/471 observed, chloro pattern

Example 1540 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]- piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.81 (1H, s), 9.77 (1H, s), 8.80 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.58 - 7.62 (2H, m), 7.26 (1H, d, J = 3.9 Hz), 7.10 (1H, d, J = 3.9 Hz), 6.62 (1H, s), 4.73 (2H, s), 3.95 (2H, s), 3.50 (2H, s), 3.38 (2H, s), 3.02 (2H, s). MS (Ion spray) $[M+H]^+$ of 454/456 observed, chloro pattern

Example 1541 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.60 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 7.25 (1H, d, J = 3.9 Hz), 7.09 (1H, d, J = 3.9 Hz), 6.61 (1H, s), 4.64 - 4.77 (2H, m), 3.98 - 4.10 (1H, m), 3.79 - 3.92(1H, m), 3.25 - 3.46 (3H, m), 3.09 - 3.20 (1H, m), 2.70 - 2.85 (1H, m), 1.47 (3H, d, J = 6.6 Hz). MS (Ion spray) $[M+H]^+$ of 468/470 observed, chloro pattern.

Example 1542 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-yimethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate)
^{1}H NMR (300 MHz, DMSO) δ 9.73 (2H, bs), 8.80 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.60 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 7.23 (1H, d, J = 3.9 Hz), 7.07 (1H, d, J = 3.9 Hz), 6.56 (1H, s), 4.81 (1H, d, J = 16.1 Hz), 4.64 (1H, d, J = 16.1 Hz), 3.65 - 4.00 (5H, m), 3.26 - 3.38 (5H, m), 3.04 - 3.16 (1H, m), 2.55 - 2.64 (1H, m). MS (Ion spray) $[M+H]^+$ of 498/500 observed, chloro pattern.

Example 1543 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.79(s, 2H), 8.80 (s, H), 8.37 (d, H), 8.04 (s, H), 7.95 (m, H), 7.47-7.68 (m, 4H), 4.57-5.94 (m, 4H), 4.40 (s, H), 4.11 (m, 2H), 3.42-3.84 (m, 4H), 3.37 (s, 3H). MS: (M+H), 493, 495.

Example 1544 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.80(s, 2H), 8.79 (s, H), 8.36 (d, H), 8.00 (s, H), 7.91 (s, H), 7.43- 7.68 (d, H), 4.75 (m, 5H), 4.05-4.83 (m, 4H), 3.10-4.02 (m, 6H). MS: (M+H), 449, 451.

Example 1545 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.81(s, 2H, NH2), 8.80 (s, H), 8.36 (d, H), 7.65 (s, H), 7.58 (d, H), 7.56 (d, 4H), 7.14 (d, H), 4.75 (s, 2H), 4.54 (s, 2H), 4.04 (s, 2H), 3.43-3.70 (m, 4H). MS: (M+H), 455, 457

Example 1546 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.79(s, 2H, NH2), 8.76 (s, H), 8.37 (d, H), 7.63 (s, H), 7.57 (d, H), 7.54 (d, H), 7.18 (d, H), 4.52-4.94 (m, 4H), 4.34 (s, 2H), 4.03 (m, 2H), 3.45-3.80 (m, 4H), 3.37 (s, 3H). . MS: (M+H), 499, 501.

Example 1547 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78(s, 2H, NH2), 8.77 (s, H), 8.35 (d, H), 8.00 (d, H), 7.61 (s, H), 7.52 (m, 3H), 4.57-5.93 (m, 4H), 4.38 (m, H), 4.10 (m, 2H), 3.45-3.84 (m, 4H), 3.39 (s, 3H). MS: (M+H), 493, 495.

Example 1548 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.76 (d, 2H, NH2), 8.75 (s, H), 8.35 (d, H), 7.64 (d, H), 7.57 (d, H), 7.55 (s, H), 7.25 (d, H), 4.43-4.80 (m, 4H), 4.72-3.84 (m, H), 3.10-3.55 (m, 4H), 1.55 (d, 3H). . MS: (M+H), 470, 472.

Example 1549 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78(d, 2H, NH2), 8.85 (s, H), 8.36 (d, H), 8.01 (s, H, NH), 7.94 (d, H), 7.63 (s, H), 7.60 (d, H), 7.54 (d, H), 4.50-4.86 (m, 4H), 4.22 (m, H), 3.40-3.84 (m, 4H), 1.68 (d, 3H). . MS: (M+H), 463, 465.

Example 1550 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.76(s, 2H, NH2), 8.76 (s, H), 8.36 (d, H), 7.65 (d, H), 7.59 (s, H), 7.57 (d, H), 7.26 (d, H), 5.74 (q, 2H), 4.35-4.55 (m, 3H), 3.00-4.00 (m, 9H including s, 3H). MS: (M+H), 500, 502.

Example 1551 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78(d, 2H, NH2), 8.79 (s, H), 8.35 (s, H), 7.66 (d, H), 7.63 (s, H), 7.56 (d, H), 7.29 (d, H), 4.72 (s, 2H), 4.56 (s, 2H), 3.85 (s, 2H), 3.32-3.52 (d, 4H) . MS: (M+H), 456, 458.

Example 1552 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.80(d, 2H, NH2), 8.78 (s, H), 8.37 (d, H), 8.00 (d, 2H), 7.66 (s, H), 7.60 (d, H), 7.56 (d, 2H), 4.78 (s, 2H), 4.60 (s, 2H), 4.10 (s, 2H), 3.45-3.72 (m, 4H), MS: (M+H), 449, 451.

Example 1553 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]thiadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.80 (d, 2H, NH2), 8.79 (s, H), 8.36 (d, H), 7.72 (d, H), 7.64 (s, H), 7.60 (d, H), 7.22 (d, H), 4.53-5.87 (m, 4H), 4.80-4.96 (m, 2H), 3.31-3.64 (m, 4H) . MS: (M+H), 472, 474.

Example 1554 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.77 (s, 2H, NH2), 8.79 (s, H), 8.37 (d, H), 7.66 (d, H), 7.60 (d, H), 7.58 (s, H), 7.22 (d, H), 4.52-4.87 (m, 5H), 3.94-4.00 m, 9H). MS: (M+H), 516, 518

Example 1555 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78 (d, 2H, NH2), 8.81 (s, H), 8.37 (d, H), 7.68(d, H), 7.60 (d, H), 7.68 (s, H), 7.21 (d, H), 4.50-4.85 (m, 5H), 3.10-3.90 (m, 4H)., 1.52 (d, 3H). MS: (M+H), 486, 488.

Example 1556 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-propyl-piperazin-2-one ditrifluorocetate.
1HNMR: (DMSO-d6) 9.74 (s, 2H, NH2), 8.79 (s, H), 8.36 (d, H), 7.62 (d, H), 7.57 (d,H), 7.55 (s, H), 7.16 (d, H), 4.58-4.83 (m, 3H), 4.40 (q, 2H), 2.80-3.53 (m, 4H), 1.67-2.00 (m, 2H), 1.15-1.60 (m, 2H), 0.85 (t, 3H). MS: (M+H), 514, 516.

Example 1557 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-ethyl-piperazin-2-one ditrifluorocetate.
1HNMR: (DMSO-d6) 9.85 (s, 2H, NH2), 8.80 (s, H), 8.38 (d, H), 7.66 (d, H), 7.64 (d, H), 7.56 (s, H), 7.17 (d, H), 4.75 (m, 3H), 4.35 (q, 2H), 2.80-3.45 (m, 4H), 1.80-1.12 (m, 2H), 0.88 (t, 3H). MS: (M+H), 500, 502.

Example 1558 1-4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.75 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.55 - 7.63 (3H, m), 7.29 (1H, d, J = 4.0 Hz), 6.92 (1H, s), 4.71 (2H, s), 3.74 (2H, s), 3.18 - 3.29 (4H, m), 2.76 - 2.78 (2H, m). MS (Ion spray) $[M+H]^+$ of 455/457 observed, chloro pattern.

Example 1559 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-pyridin-5-yl-methyl]-piperazin-2-one tritrifluoroacetate
Part A. 2-Bromo-5-pyridinecarboxaldehyde
To a solution of 2,5-dibromopyridine (1g, 4.22 mmol) in 10 mL of THF was added dropwise at -78 °C *n*-BuLi (1.7 mL, 2.5 N solution in hexane, 4.25 mmol). After 15 minutes at this temperature DMF (0.49 mL, 6.33 mmol) was added and the reaction mixture was stirred for 15 minutes. Methanol was added and the solution was diluted with AcOEt, washed with water, brine, dried over magnesium sulfate and concentrated. The resulting crude product was purified by column chromatography on silica gel eluting with heptane90 %/ AcOEt 10% then heptane 85%/AcOEt 15%. The title compound (146 mg, 18%) was obtained as a yellow solid. C_5H_4OBrN MS $(M+H)^+$ = 185, Br pattern
Part B. 2-(5-Chloro-thiophen-2-yl)-5-pyridinecarboxaldehyde

To a solution of 2-Bromo-5-pyridinecarboxaldehyde (140 mg, 0.756 mmol) in 5 mL of DME was added 5-chlorothiophene-2-boronic acid (131 mg, 0.806 mmol), tetrakis(triphenyl-phosphine) palladium(0) (47 mg, 0.041 mmol) and Na_2CO_3 (0.7 mL of 2 M aqueous solution) under nitrogen. The mixture was refluxed for 5 hours, concentrated under vacuum, taken-up in AcOEt. The solution was washed with water, brine, dried over magnesium sulfate and concentrated. The resulting crude product was purified by column chromatography on silica gel eluting with heptane 95 %/ AcOEt 5% then heptane 90%/AcOEt 10%. The title compound (137 mg, 81%) was obtained as a yellow solid. $C_{10}H_6OClNS$ MS $(M+H)^+$ = 224, Cl pattern

Part C. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-pyridin-5-ylmethyl]-piperazin-2-one tritrifluoroacetate

To 1-(4-Amino-quinazolin-7-ylmethyl)-piperazin-2-one (20 mg, 0.078 mmol) in 5 mL of acetonitrile is added 2-(5-Chloro-thiophen-2-yl)-5-pyridinecarboxaldehyde (17 mg, 0.078 mmol), sodiumtriacetoxyborohydride (33 mg, 0.156 mmol) and 2mL of AcOH. The mixture was stirred at room temperature overnight, then diluted with EtOAc, washed with a saturated aqueous $NaHCO_3$ solution, brine, died over magnesium sulfate and concentrated. The product was purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions were lyophilized to afford the titled compound as a white solid (2 mg, 3 % yield). $C_{23}H_{21}OClN_6S$ MS $(M+H)^+$ = 465, Cl pattern

Example 1560 4-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

To a solution of 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.33g, 1.0 mmol) and Et_3N (0.34 mL, 2.4 mmol) in MeCN (40 mL) was added a solution of 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in MeCN (10 mL). The solution was stirred at r.t. overnight and concentrated to dryness. The residue was then treated with 20% TFA/DCM (40 mL) overnight. The solution was concentrated. The residue was purified by RP HPLC to give the product as a white solid (0.23 g, 0.35 mmol). ^1H NMR (DMSO) δ 14.6 (br, 1H), 12.7 (s, 1H), 9.14 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.61 (d, 1H), 7.33 (d, 1H), 6.93 (s, 1H), 6.87 (s, 1H), 4.75 (s, 2H), 3.75 (s, 2H), 3.36 (t, 2H), 3.23 (s, 2H), 2.75 (t, 2H). MS M+1: 428, 430.

Example 1561 4-[5-(5-Chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-

[1,2,4]triazole-4-carboxylic acid tert-butyl ester. ^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.68 (s, 1H), 9.20 (s, 1H), 8.36 (d, 1H), 7.88 (d, 1H), 7.48 (d, 1H), 7.20 (d, 1H), 6.89 (s, 1H), 4.74 (s, 2H), 3.90 (s, 2H), 3.38 (m, 4H), 2.81 (t, 2H). MS M+1: 428, 430.

Example 1562 [5-(5-Chloro-thiophen-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 2-bromomethyl-5-(5-chloro-thiophen-2-yl)-[1,3,4]oxadiazole. ^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.67 (s, 1H), 9.19 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.69 (d, 1H), 7.32 (d, 1H), 6.88 (s, 1H), 4.75 (s, 2H), 4.01 (s, 2H), 3.35 (s, 2H), 3.14 (m, 4H), 2.85 (t, 2H). MS M+1: 429, 431.

Example 1563 4-[5-(5-Chloro-thiophen-2-yl)-oxazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 2-Bromomethyl-5-(5-chloro-thiophen-2-yl)-oxazole. ^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.7 (s, 1H), 9.16 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.49 (s, 1H), 7.30 (d, 1H), 7.20 (d, 1H), 6.87 (s, 1H), 4.74 (s, 2H), 3.79 (s, 2H), 3.30 (t, 2H), 3.25 (s, 2H), 2.89 (t, 2H). MS M+1: 428, 430.

Example 1564 4-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 2-bromomethyl-5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazole. ^{1}H NMR (DMSO) δ 14.5 (br, 1H), 12.7 (s, 1H), 9.18 (s, 1H), 8.37 (d, 1H), 7.87 (d, 1H), 7.69 (d, 1H), 7.26 (d, 1H), 6.87 (s, 1H), 4.75 (s, 2H), 4.05 (s, 2H), 3.33 (t, 2H), 3.14 (s, 2H), 2.80 (t, 2H). MS M+1: 445, 447.

Example 1565 4-[5-(5-Chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 5-chloromethyl-3-(5-chloro-thiophen-2-yl)-1H-pyrazole. ^{1}H NMR (CD_3OD) δ 8.71 (s, 1H), 8.10 (d, 1H), 7.37 (d, 1H), 7.13 (d, 1H), 6.93 (d, 1H), 6.55 (s, 1H), 6.48 (s, 1H), 4.75 (s, 2H), 3.69 (s, 2H), 3.37 (t, 2H), 3.24 (s, 2H), 2.72 (t, 2H). MS M+1: 427, 429.

Example 1566 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

Part A. 2-(3-Oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

To a solution of piperazin-2-one (2.5 g, 25 mmol) and DIEA (5.2 mL, 30 mmol) in MeCN (50 mL) was added slowly propargyl bromide (4.5 g, 80% in toluene). The solution was stirred at r.t. overnight. The white solid was filtered off and the filtrate was concentrated to residue. The above residue was mixed with (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (6.4 g, 20 mmol), $Pd(PPh_3)_4Cl_2$ (0.70 g, 1 mmol), CuI (0.12 g, 0.6 mmol), Et_3N (14 mL, 100 mmol) in DMF (100 mL). The mixture was heated at 100 °C for 1.5 h, then cooled to 50 °C. DBU (7.5 mL, 50 mmol) was added. The mixture was stirred at 50 °C for another 1.5 h before being concentrated to residue. The residue was treated with activated carbon in CH_2Cl_2 and washed with H_2O. Crude product from CH_2Cl_2 layer was purified by flash column eluting with 5-6% MeOH/CH_2Cl_2 to give off-white foam (1.1 g, 3.3 mmol). ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.20 (d, 1H), 7.86 (d, 1H), 6.64 (s, 1H), 6.02 (s, 1H), 3.98 (s, 2H), 3.38 (m, 2H), 2.77 (t, 2H). MS M+1: 331.

Part B. 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate.

A solution of 2-(3-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.066 g, 0.20 mmol) in THF (5 mL) was treated NaH (0.010 g, 60%, 0,24 mmol) for 15 min. Bu_4NI was added and the mixture was stirred for another 15 min. 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole (0.056 g, 0.20 mmol) was then added. The mixture was stirred at r.t. for 4 h and concentrated to residue. The residue was then treated with 20% TFA/DCM (4 mL) for 4h and concentrated again. The residue was purified by RP HPLC to give the title compound as a white solid (0.0033 g, 0.005 mmol). ^1H NMR (DMSO) δ 14.5 (br, 1H), 12.8 (s, 1H), 9.20 (s, 1H), 8.37 (d, 1H), 7.84 (d, 1H), 7.62 (d, 1H), 7.28 (d, 1H), 6.94 (s, 1H), 6.80 (s, 1H), 4.57 (s, 2H), 3.86 (s, 2H), 3.3 (m, 2H), 3.19 (s, 2H), 2.74 (m, 2H). MS M+1: 428, 430.

Example 1567 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A 2-Carbomethoxy-6-chlorobenzo[b]thiophene.

To a solution of 4-chloro-2-nitrobenzaldehyde (18 g, 97 mmol) in DMF (100 mL) was added powdered K_2CO_3 (16 g, 116 mmol) followed by methylthioglycolate (8.7 mL, 97 mmol). The mixture was heated to 75 °C for 2 h then cooled to RT and poured into water (2L) The resulting yellow precipitate was collected and dried to yield the title compound (21 g, 93 mmol). Note

that the product can be recrystallized from EtOH/water. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.03 (s, 1H), 7.85 (s, 1H), 7.80 (d, 1H), 7.39 (d, 1H), 3.95 (s, 3H).

B. 2-Carboxy-6-chlorobenzo[b]thiophene.

5N NaOH (50 mL) was added to a solution of 2-carbomethoxy-6-chlorobenzo[b]thiophene (12.57 g, 55.45 mmol) in MeOH (30 mL) and then heated to 80 °C for 4 h. The reaction mixture was then cooled and made acidic to pH ~3 with concentrated HCl. The resulting precipitate was washed with water then dried under vacuum at 50 °C with P_2O_5 to yield the title compound (11.52 g, 54.18 mmol). ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.21 (s, 1H), 8.11 (s, 1H), 8.00 (d, 1H), 7.50 (d, 1H).

C. 6-Chlorobenzo[b]thiophene.

Copper (5.58 g, 87.9 mmol) was added to a solution of 2-carboxy-6-chlorobenzo[b]thiophene (17.8 g, 83.7 mmol) in quinoline (70 mL) and heated to 180 °C for 1.5 hr. The reaction mixture was then cooled to RT and poured into 500 g of ice. After the ice melted, the mixture was filtered through Celite and the aqueous filtrate acidified with conc. HCl. The aqueous solution was extracted with Et_2O (x3) and the combined ethereal layers were washed with 2N HCl and then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting crude product was chromatographic using 50% EtOAc/hexanes to give the title compound (12.48 g, 74.30 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.88 (s, 1H), 7.72 (d, 1H), 7.43 (d, 1H), 7.35 (dd, 1H), 7.31 (dd, 1H).

D. 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.

To a solution of 6-chlorobenzo[b]thiophene (12.5 g, 74.4 mmol) in 250 mL of THF at -78°C was added n-BuLi (29.7 mL of a 2.5M solution in hexanes, 74.4 mmol). After 1h, SO_2 was added dropwise to the solution via a dry-ice condenser. After addition over a one hour period, the solution was stirred for 1 hr then allowed to warm to ambient temperature overnight. The reaction mixture was concentrated and the residue suspended in hexanes (500 mL) and cooled to 0°C. To the solution was added SO_2Cl_2 (7.2 mL, 89.3 mmol) and the resulting suspension was brought to room temperature and stirred for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc. The organic solution was washed with saturated $NaHCO_3$ (aq.) and saturated NaCl (aq.). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product can be purified by column chromatography eluting with hexanes to yield the title compound as a white solid (18.3 g, 70.3 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.11 (s, 1H), 7.88 (m, 2H), 7.50 (m, 1H).

E. 3-Iodopyridin-4ylamine.

A solution of potassium iodide (19.48 g, 117.4 mmol) and iodine (18.37 g, 72.3 mmol) in water (77 mL) was added dropwise via an addition funnel to a refluxing solution of 4-

aminopyridine (9.21 g, 97.8 mmol) and sodium carbonate (6.12 g, 57.7 mmol) in water (35 mL). Upon complete addition the mixture was stirred for 2 hours at reflux then cooled to room temperature and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium thiosulfate solution (3x) and brine then dried over $MgSO_4$, filtered and concentrated to give the title product (8.37 g, 38.0 mmol) and a trace of the di-iodo compound as an yellow/orange solid. This material was used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.10 (d, 1H), 6.55 (d, 1H), 4.60 (bs, 2H).

F. (3-Iodopyridin-4-yl)-carbamic acid tert-butyl ester.

Di-tert-butyl dicarbonate (20.7 g, 94.8 mmol) was added to a solution of 3-iodopyridin-4-ylamine (19.0 g, 86.4 mmol) in THF (86 mL). The resulting solution was stirred for 2 h at room temperature then concentrated. The residue was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography eluting with 1% EtOAc/CH_2Cl_2 to give the title product and a small amount of the BOC-protected di-iodo compound. Trituration of the mixture with ether/hexane removed the undesired compound leaving the title product in solution. Filtration of the solid and concentration of the filtrate yielded the title product (18.95 g, 59.2 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.05 (bs, 1H), 1.55 (s, 9H).

Alternatively (3-iodopyridin-4-yl)-carbamic acid tert-butyl ester can be made as follows:

G. Pyridin-4-yl-carbamic acid tert-butyl ester.

Di-tert-butyl dicarbonate (43.3 g, 0.20 mmol) was added portionwise to a solution of 4-aminopyridine (18.68 g, 0.20 mol) in THF (300 mL) at room temperature. After 3h, the reaction mixture was concentrated in vacuo and the residue was purified by chromatography using EtOAc as the eluent to yield a white solid as the title compound (38.7 g, 0.20 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, 2H), 7.40 (d, 2H), 6.65 (bs, 1H), 1.5 (s, 9H).

H. (3-Iodopyridin-4-yl)-carbamic acid tert-butyl ester.

nBuLi (255.2 mL of a 2.5M solution in hexanes, 0.64 mol) was added to a solution of xxx (38.7 g, 0.20 mol) and TMEDA (95 mL, 0.64 mol) in THF (400 mL) at -78 °C. After addition the reaction mixture was warmed to -20 °C and stirred for 1.5 h. The mixture was then cooled again to -78 °C and a solution of I_2 (81 g, 0.32 mol) in THF (100 mL) was added dropwise to the reaction vessel. After addition was complete, the resulting solution was brought to room temperature and stirred for 1 h. The reaction mixture was treated with water and then poured into EtOAc. The organic layer was washed with water, saturated sodium thiosulfate (x2) and brine then dried over $MgSO_4$, filtered and concentrated. The crude solid was purified by chromatography using 20% EtOAc/hexanes as the eluent to afford the title compound (58 g,

0.18 mol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.05 (bs, 1H), 1.55 (s, 9H).

I. 4-[(Methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester.

Charged 4-oxazolidine aldehyde (75 g, 0.33 mol), glycine methylester hydrochloride (166.25 g. 1.32 mol) and anhydrous methanol (915 mL) to a 2 L 3-necked flask under nitrogen and cooled to 5 °C in an ice water bath. After 30 min a 1M solution of $NaBH_3CN$ in THF (381 ml, 0.38 mol) was added via addition funnel over 10 min. The temperature of the reaction rose to 8 °C during this addition. The reaction was allowed to warm to 23 °C. After 3 h at 23 °C TLC (2 : 1, heptane : EtOAc) showed the reaction to be complete. The solvent was removed under reduced pressure to obtain an oily white solid. MTBE (500 mL) and saturated aqueous sodium bicarbonate was added to the solid and stirred until all solids had dissolved. The phases were allowed to separate and the MTBE layer removed. The aqeous phase was extracted with another 200 mL of MTBE. The organic phases were combined washed with water (100 mL), dried over $MgSO_4$ and evaporated under reduced pressure to obtain the title compound as a light yellow oil (90 g, 0.30 mol). MS (ESI) m/z 303 (M^+ + 1, 100); ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 2H), 3.75 (m, 1H), 3.70 (s, 3H), 3.45 (s, 2H), 2.7 (m, 2H), 1.5 (m, 15H).

J. 4-[(Benzyloxycarbonyl-methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester.

Charged 4-[(methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (88 g, 0.29 mol), dichloromethane (1.1 L) and triethylamine (38.3 g, 0.38 mol) to a 2 L 3-necked flask under nitrogen. Cooled the solution to 5 °C and added benzylchloro-formate dropwise via an addition funnel. The addition took 30 min and the temperature of the reaction rose to 10 °C. The reaction was run for 1.5 hours at 2-5 °C and 2 h at 20 °C before TLC (2:1, heptane:EtOAc) showed the reaction to be complete. Once complete aqueous NH_4Cl (300 mL) was added to the mixture and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain a cloudy yellow oil. MTBE (100 mL) was added to this oil and the mixture was filtered through a bed of celite. Removal of the solvent under reduced pressure afforded the title compound as a clear yellow oil (128.5 g, 0.29 mol). MS (ESI) m/z 437 (M^+ + 1, 60), 459 (M^+ + Na, 40); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.15 (d, 2H), 4.00 (m, 5H), 3.75 (d, 2H), 3.65 (d, 2H), 3.25 (m, 1H), 1.5 (m, 15H).

K. [(2-Amino-3-hydroxy-propyl)-benzyloxycarbonyl-amino]-acetic acid methyl ester hydrochloride.

Charged methanol (1.2 L) to a 2 L 3-necked flask. Bubbled anhydrous HCl into the methanol until the temperature stabilized at 55 °C. Cooled the solution to 20 °C and added 4-[(benzyloxy-

carbonyl-methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (125 g, 0.28 mol). The solution was stirred at 20-23 °C for 15 h. Distilled off 0.9-1 L of solvent under reduced pressure at 25-30 °C. Solids started to precipitate out of the solution upon cooling so 1 L of MTBE was added, the mixture was cooled to 5 °C and filtered to obtain an off white solid. This material was placed in a vacuum oven to dry at 45 °C and 21 in. Hg vacuum. The title compound was obtained as an off white solid (79.3 g, 0.24 mol) after drying. MS (ESI) m/z 297 (M^+ + 1, 100). ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 3H), 7.30 (m, 5H), 5.15 (d, 2H), 4.40 (s, 1H), 4.15 (m, 2H), 3.95 (m, 1H), 3.70 (m, 5H), 3.50 (s, 2H).

L. 3-(R)-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid benzyl ester.

Charged methanol (790 ml), [(2-amino-3-hydroxy-propyl)-benzyloxycarbonyl-amino]-acetic acid methyl ester (79 g, 0.24 mol), water (79 mL) and K_2CO_3 (99.5 g, 0.72 mol) to a 1 L 3-necked flask. The mixture was stirred at high speed with a mechanical stirrer for 6 h until TLC (2 : 1, heptane : EtOAc) showed the reaction to be complete. Once completed the reaction was diluted with water (600 mL) and extracted with dichloromethane (3 X 800 mL). The combined dichloromethane layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the title compound as a viscous amber oil (60 g, 0.23 mol). MS (ESI) m/z 265 (M^+ + 1, 70), 306 (M^+ + CH_3CN, 90); ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H), 7.30 (s, 5H), 5.15 (s, 2H), 4.4 (s, 1H), 4.15 (dd, 2H), 3.85 (m, 2H), 3.55 (m, 3H), 3.40 (m, 1H).

M. 3-(R)-(tert-Butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester.

3-(R)-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid benzyl ester (17.6 g, 66.7 mmol), imidazole (5.9 g, 86.7 mmol) and *tert*-butyldimethylsilyl chloride (8.2 g, 54.4 mmol) in CH_2Cl_2 (450 mL) were stirred at room temperature for 2 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo* and purified by chromatography eluting with 2% MeOH/CH_2Cl_2 to yield a colorless oil as the title compound (20.6 g, 54.4 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 5H), 6.40 (bs, 1H), 5.13 (s, 2H), 4.30 (d, 1H), 4.01 (d, 1H), 3.78-3.95 (m, 1H), 3.53-3.71 (m, 2H), 3.49 (m, 1H), 3.22 (m, 1H), 0.93 (s, 9H), 0.1 (s, 6H). MS

N. 3-(R)-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-(R)-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester (20.6 g, 54.5 mmol) in DMF/THF (50 mL/250 mL) at 0 °C was slowly added NaH (2.29 g, 57.2 mmol). After stirring for 10 min, propargyl bromide (6 mL, 54.5 mmol) was added and the resulting solution stirred for 1 h. The reaction mixture was then warmed to room temperature and after 2 h the reaction was quenched with water and poured into EtOAc. The organic layer was washed with water (x2) and brine then dried over $MgSO_4$, filtered and concentrated. The resulting crude material was chromatographed using 30% EtOAc/hexanes

as the eluent to yield the title product (18.2 g, 43.7 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 1H), 5.20 (s, 2H), 4.78 (d, 1H), 4.28-4.45 (m, 2H), 3.90-4.01 (m, 2H), 3.63-3.78 (m, 3H), 3.30 (dd, 1H), 2.28 (m, 1H), 0.90 (s, 9H), 0.05 (s, 6H). MS

O. 3-(R)-Hydroxymethyl-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-(R)-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester (18.2 g, 43.7 mmol) in THF (300 mL) was added AcOH (2.77 mL, 48.1 mmol) followed by dropwise addition of nBu_4NF (48.1 mL of a 1M solution in THF, 48.1 mmol). After 3 h, the reaction mixture was treated with water and poured into EtOAc. The organic layer was washed with water and brine then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by chromatography using 5% MeOH/CH_2Cl_2 to yield an oil as the title product (12.5 g, 41.4 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 5H), 5.18 (bs, 2H), 4.30-4.61 (m, 3H), 3.85-4.01 (m, 2H), 3.70-3.89(m, 2H), 3.50-3.60 (bd, 1H), 3.20-3.40 (bd, 1H), 2.61 (bs, 1H), 2.28 (m, 1H). ESI MS [M+H]+= 303.

P. 3-(R)-Methoxymethyl-5-oxo-4-propyl-2-ynyl-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-(R)-hydroxymethyl-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester (10g, 33.1 mmol) in THF/DMF (300 mL/80 mL) at 0 °C was added NaH (1.39g, 34.8 mmol). After 5 min, MeI (2.27 mL, 36.4 mmol) was added and the reaction mixture was stirred for 20 min and then warmed to room temperature. The solution was stirred for 2 hr then treated with water and poured into EtOAc. The organic layer was washed with water and brine then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by chromatography using 30% EtOAc/hexanes to yield a colorless oil as the title product (7.5 g, 23.7 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 5H), 5.18 (s, 2H), 4.75 (d, 1H), 4.41 (m, 1H), 4.28 (d, 1H), 3.75-3.95 (m, 3H), 3.51 (bs, 2H), 3.20-3.48 (m, 4H), 2.22 (m, 1H). ESI MS [M+H]+= 317.

Q. 2-(4-Benzyloxycarbonyl-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester.

3-(R)-methoxymethyl-5-oxo-4-propyl-2-ynyl-piperazine-1-carboxylic acid benzyl ester (7.2 g, 22.8 mmol), (3-iodopyridin-4-yl)-carbamic acid tert-butyl ester (7.3 g, 22.8 mmol), CuI (0.13 g, 0.68 mmol), $Pd(PPh_3)_2Cl_2$ (0.80 g, 1.14 mmol) and Et_3N (12.7 mL, 91.1 mmol) in DMF (100 mL) were heated at 100 °C for 3 h then cooled to 50 °C. DBU (6.8 mL, 45.6 mmol) was then added and the resulting mixture was stirred for 1 h. The reaction mixture was then cooled to room temperature and poured into EtOAc. The organic layer was washed with water (x2) and brine then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by 100% EtOAc or 2% MeOH/CH_2Cl_2 to afford the title compound (9.0 g, 17.7 mmol) as a foamy pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.42 (d, 1H), 7.90 (d, 1H), 7.31-7.39 (m,

5H), 6.38 (s, 1H), 5.04 (AB, 2H), 5.21 (bs, 2H), 4.30 (AB multiplet, 2H), 4.42 (d, 1H), 3.20-3.68 (m, 5H), 1.71 (s, 9H). ESI MS [M+H]+= 509.

R. 2-(2-(R)-Methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester.

A solution of 2-(4-benzyloxycarbonyl-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (9.0 g, 17.7 mmol) in 5% HCO_2H/MeOH (100 mL) was added to wet Pd black (10 g, 94.0 mmol) under Ar. After 30 min during which vigorous bubbling occurs, the mixture was filtered through Celite and the filtrate neutralized with saturated $NaHCO_3$. The volume of the filtrate was reduced in vacuo and the resulting solution was extracted with CH_2Cl_2. The combined organic layers were washed with brine then dried over $MgSO_4$, filtered and concentrated to yield the title product (5.94 g, 15.9 mmol) as a foamy pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.41 (d, 1H), 7.88 (d, 1H), 6.45 (s, 1H), 5.02 (AB, 2H), 3.71 (dd, 1H), 3.64 (d, 2H), 3.50-3.58 (m, 2H), 3.30 (dd, 1H), 3.34 (s, 3H), 3.20 (dd, 1H), 1.71 (s, 9H). HRMS measured 375.2013, calcd 375.2027. ESI MS [M+H]+= 375.

S. 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester.

2-(2-(R)-Methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester (5.94 g, 15.9 mmol), 6-chlorobenzo[b]thiophene-2-sulfonyl chloride (4.24 g, 15.9 mmol) and Et_3N (2.4 mL, 17.2 mmol) were stirred in CH_3CN (120 mL) at room temperature for 5 h. The reaction mixture was concentrated to dryness then absorbed onto silica gel with CH_2Cl_2 and chromatographed using EtOAc as the eluent to yield a white solid (6.4 g, 10.6 mmol) as the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.41 (d, 1H), 7.82-7.91 (m, 4H), 7.50 (dd, 1H), 6.25 (s, 1H), 5.01 (AB, 2H), 4.19 (AB, 2H), 3.62-3.72 (m, 4H), 3.38 (s, 3H), 3.02 (d, 1H), 1.70 (s, 9H). ESI MS [M+H]+= 605, 607, Cl pattern.

T. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

HCl(g) was bubbled into EtOAc (300 mL) at 0 °C for 20 min to saturate the solution. 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester (5.5 g, 9.2 mmol) was then added and the suspension was stirred for 1 h at 0 °C then brought to room temperature. Additional HCl(g) was bubbled into the slurry during which time the reaction flask became warm. MeOH (60 mL) was subsequently added and the solution became clear. After 1 h, analytical RP-HPLC indicated still a significant amount of starting material so HCl(g) was bubbled through the solution for 30 min at room temperature. The reaction mixture was stirred for 10 h then N_2 was bubbled through the solution for 30 min. The mixture was concentrated to dryness and the

resulting crude material was purified by RP-HPLC (Metachem monochrom 10 micron C-18 column) eluting with a gradient of 20-70% CH_3CN/H_2O (HCl, pH=2.8) over 18 min at 70 mL/min and collecting the fractions eluting at ca. 45% CH_3CN/H_2O (HCl, pH=2.8). The appropriate fractions were lypholized to yield the title product as the hydrochloride salt. ^1H NMR ($CDCl_3$, 300 MHz) δ 11.82 (s, 1H), 8.89 (d, 1H), 8.15 (m, 1H), 7.80-7.85 (m, 3H), 7.77 (d, 1H), 7.41 (d, 1H), 6.75 (s, 1H), 4.90 (AB, 2H), 4.01 (AB, 2H), 3.91 (d, 1H), 3.62-3.78 (m, 3H), 3.34 (s, 3H), 3.13 (d, 1H). EI MS, $[M+H]^+$=505, 507, Cl pattern. HRMS measured 505.0730, calcd 505.0765. Anal. ($C_{22}H_{21}N_4O_4S_2Cl.HCl.1.5H_2O$) Calcd: C, 46.53; H, 4.44; N, 9.87. Found: C, 46.28; H, 4.43; N, 9.45. >99% ee (Chiralpak AD eluting with 100% EtOH).

Example 1568 4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo [3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

A. 6-Chlorothieno[2,3,b]pyridine-2-sulfonyl chloride

6-Chlorothieno[2,3,b]pyridine (J. Het. Chem. (1976), 13, 1197) was converted to the title compound by the method Described in Example 1, Part C: ^1H NMR ($CDCl_3$, 300MHz) δ 8.20 (d, 1H), 8.16 (s, 1H), 7.53 (d, 1H). Mass Spec, M+ 267, 269, 271 two Cl pattern.

B. 4-(6-Chlorothieno[2,3,b]pyridine-2-sulfonyl-(R)-6-methoxymethyl-1-(butylcarboxypyrollo-[3,2,c]pyridine-2-ylmethyl)-piperizin-2-one

2-(2-(R)-Methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert butyl ester (500 mg), 6-chlorothieno[2,3,b]pyridine-2-sulfonyl chloride (360 mg) and 19 ml triethylamine in 50 ml acetonitrile was stirred at room temp overnight. The solution was concentrated, partitioned between ethylacetate and 10% Sodium Bicarbonate. The organic solution was washed with water, dried over sodium sulfate, and chromatographed with 2 % methanol / ethylacetate to give 780 mg of the title compound. Mass Spec M+H=606.2, 608.2 (Cl). ^1H NMR CDCl3 8.7 (s,1H), 8.4 (d, 1H), 8.1 (d, 1H), 7.85 (d, 1H), 7.8 (s,1H), 7.5 (d, 1H), 6.25 (s, 1H), 5.4 (d, 1H), 4.8 (d, 1H), 4.3 (d, 1H), 4.1 (d, 1H), 3.6-3.7 (m, 4H), 3.4 (s,3H), 3.05 (d, 1H), 1.7 (s, 9H).

C. 4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo [3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

4-(6-chlorothieno[2,3,b]pyridine-2-sulfonyl-(R)-6-methoxymethyl-1-(butylcarboxypyrollo-[3,2,c]pyridine-2-ylmethyl)-piperizin-2-one (700 mg) in 50 ml 40% trifluoroacetic acid in methylenechloride was stirred at room temp for 2 hours, concentrated and purified by HPLC to give 560 mg of the title compound. Mass Spec M+H=506.2, 508.2 (Cl); 1H NMR CD3OD 8.9 (s, 1H), 8.4 (d, 1H), 8.3 (d, 1H), 8.0 (d, 1H), 7.8, (d, 1H), 7.6 (d, 1H), 6.9 (s, 1H), 5.1 (d, 1H), 4.7 (d, 1H), 4.2 (d, 1H), 3.9 (d, 1H), 3.5-3.8 (m, 4H), 3.3 (s,3H),3.2 (d,1H), HPLC > 98A%.

The following 6-substituted ketopiperazine compounds are prepared using synthetic procedures described above.

Example	Name	*m/z* [M+H]
1569	4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	488, 490 Cl pattern
1570	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	503, 505 Cl pattern
1571	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	479, 481 Cl pattern
1572	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one	503, 505 Cl pattern
1573	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)- propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one	479, 481 Cl pattern

The following ketopiperazines are prepared similar to methods described above.

Example	Name	*m/z* [M+H]
1574	4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	444, 446 Cl pattern
1575	4-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	428, 430 Cl pattern
1576	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483 Cl pattern
1577	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one	464, 466 Cl pattern
1578	1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one	464, 466 Cl pattern

The following compounds are prepared using methods described above with 3-methyl-4-aminopyridine (prepared according to Recueil 1951, *70*, 571-579) as the starting material.

Example	Name	*m/z* [M+H]
1579	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	475, 477 Cl pattern
1580	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	451, 453 Cl pattern

Inhibition of Factor Xa

The compounds described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme in the coagulation cascade, controlling the activity of Factor Xa. Both the activity of free Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula 1. The inhibition of the Factor Xa activity is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective inhibition of the Factor Xa activity is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the activity of Factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

Accumulated experimental evidence has also reflected that prothrombin activation is only one of the biological activities of Factor Xa. EPR-1 (effector cell protease receptor-1,

recognizing Factor Xa), is believed to mediate several of the vascular wall interactions by Factor Xa. It has been shown to be expressed on human umbilical vein endothelial cells, rat smooth muscle cells and platelets(CR McKenzie, et al., Arterioscler Thromb Vasc Biol 16 1285-91 (1996); also F Bono, et al., J Cell Physiol 172 36-43 (1997), AC Nicholson, et al., J Biol Chem 271 28407-13 (1996),J.M. Herbert, et al., J Clin Invest 101993-1000 (1998)). This protease-receptor interaction could mediate not only prothrombinase-catalyzed thrombin generation, but also diverse cellular functions such as cell proliferation, release of PDGF and DNA syntheses. The mitogenic effect of Factor Xa has been reported to be dependent on Factor Xa enzymatic activity (F Bono, et al., J Cell Physiol 172 36-43 (1997), J.M. Herbert, et al., J Clin Invest 101 993-1000 (1998)). TAP for example inhibited the mitogenesis of human and rat cultured vascular smooth muscle cells (F Bono, et al., J Cell Physiol 172 36-43 (1997)). In a study of the rabbit carotid artery air-drying injury model, increased EPR-1 expression is detected after vascular injury. Animals treated with the specific Factor Xa inhibitor, DX-9065a, exhibited less neointimal proliferation. The important regulatory role of Factor Xa in the coagulation process coupled with its mitogenic effects points to Factor Xa's involvement in the formation of thrombin at the luminal surface of the vessel wall and contribution to the atherothrombotic process and abnormal proliferation of vascular cells resulting in restenosis or angiogenesis.

These compounds may be used alone or in combination with other diagnostic, anticoagulant, antiplatelet or fibrinolytic agents. For example adjunctive administration of inhibitors of the activity of Factor Xa with standard heparin, low molecular weight heparin(s), synthetic pentasaccharides, direct thrombin inhibitors (e.g. hirudin, Agratroban (Novastan®), aspirin, fibrinogen receptor antagonists, statins / fibrates streptokinase, urokinase and/or tissue plasminogen activator. The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates including humans. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any inhibitor of Factor Xa activity can be added to or contacted with any medium containing or suspected of containing Factor Xa and in which it is desired that blood coagulation be inhibited.

In addition to their use in anticoagulant therapy, Factor Xa inhibitors may find utility in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis,

cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF and DNA syntheses. Inhibition of Factor Xa will effectively block thrombin generation and therefore neutralize any physiologic effects of thrombin on various cell types.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, a physiological condition which can be ameliorated by the administration of an inhibitor of the Factor Xa activity, for example conditions as hereinbefore described, which comprises the administration to the patient of a therapeutically effective amount of compound of formula I or formula II, or a *composition containing a compound of formula I or formula II,. "Effective amount" is meant to* describe an amount of compound of the present invention effective in inhibiting the activity of Factor Xa and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I or formula II in association with a pharmaceutically acceptable carrier or coating.

The pharmaceutical compositions can be administered in a suitable formulation to humans and animals by topical or systemic administration, including oral, inhalational, rectal, nasal, buccal, sublingual, vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), intracisternal and intraperitoneal. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice.

For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I or formula II.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70,

more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature which tests results are believed to correlate to pharmacological activity in humans and other mammals. The following pharmacological test results are typical characteristics of compounds of the present invention.

Enzyme Assays:

The ability of the compounds in the present invention to act as inhibitors of factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasmin and activated protein C is evaluated by determining the concentration of inhibitor which resulted in a 50% loss in enzyme activity (IC50) using purified enzymes.

All enzyme assays are carried out at room temperature in 96-well microtiter plates using a final enzyme concentration of 1 nM. The concentrations of factor Xa and thrombin are determined by active site titration and the concentrations of all other enzymes are based on the protein concentration supplied by the manufacturer. Compounds according to the invention are dissolved in DMSO, diluted with their respective buffers and assayed at a maximal final DMSO concentration of 1.25%. Compound dilutions are added to wells containing buffer and enzyme and pre-equilibrated for between 5 and 30 minutes. The enzyme reactions are initiated by the addition of substrate and the color developed from the hydrolysis of the peptide-p-nitroanilide substrates is monitored continuously for 5 minutes at 405 nm on a Vmax microplate reader (Molecular Devices). Under these conditions, less than 10% of the substrate is utilized in all assays. The initial velocities measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the control velocity (IC50). The apparent Ki values are then

determined according to the Cheng-Prusoff equation (IC50 = Ki [1+[S]/Km]) assuming competitive inhibition kinetics.

An additional in vitro assay may be used to evaluate the potency of compounds according to the invention in normal human plasma. The activated partial thromboplastin time is a plasma-based clotting assay that relies on the in situ generation of factor Xa, its assembly into the prothrombinase complex and the subsequent generation of thrombin and fibrin which ultimately yields the formation of a clot as the assay endpoint. This assay is currently used clinically to monitor the ex vivo effects of the commonly used anticoagulant drug heparin as well as direct acting antithrombin agents undergoing clinical evaluation. Therefore, activity in this in vitro assay is considered as a surrogate marker for in vivo anticoagulant activity.

Human Plasma Based Clotting Assay:

Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A volume of 100 ml of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing 100 ml of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and placed in the instrument. Following a 3 minute warming period the instrument automatically adds 100 ml of activated cephaloplastin reagent (Actin, Dade) followed by 100 ml of 0.035 M $CaCl_2$ to initiate the clotting reaction. Clot formation is determined spectrophotometrically and measured in seconds. Compound potency is quantitated as the concentration required to double a control clotting time measured with human plasma in the absence of the compound according to the invention.

A compound according to the invention may also be evaluated for their in vivo antithrombotic efficacy in two well established animal experimental models of acute vascular thrombosis. A rabbit model of jugular vein thrombosis and a rat model of carotid artery thrombosis are used to demonstrate the antithrombotic activity of these compounds in distinct animal model paradigms of human venous thrombosis and arterial thrombosis, respectively.

Experimental Plazma Protein Binding Assay

Compounds are dissolved into DMSO to prepare a 10 mM stock. Serial dilutions of compounds are made in a buffer containing 0.05M Tris, 0.15M NaCl, 0.1% PEG-8000, PH 7.5. Human FXa and the substrate, Spectrozyme FXa, are prepared in the aforementioned buffer containing human Albumin and fibrinogen at 3.45 mg/ml and 2.3 mg/ml, respectively. The FXa assay is carried out at room temperature in the 96-well microtiter plates with a final enzyme

concentration and substrate concentration of 1nM and 200 μM, respectively. Compound dilutions are added to the wells containing buffer and FXa and preincubated for 30 minutes. The enzyme reactions are initiated by the addition of substrate, Spectrozyme FXa, and the color developed from the release of p-nitroanilide from each chromogenic substrate is monitored continuously for 5 minutes at 405 nm on a Thermomax microtiter plate reader(Molecular Devices, Sunnyvale, CA.). In the final reaction mixture, the concentration of albumin and fibeinogen is 3mg/ml and 2 mg/ml, respectively.Under the experimental conditions, less than 10% of the substrate is consumed in all assays. The initial velocities measured are used to determine the amount of inhibitor required to diminish 50% of the control velocity and defined as IC_{50} of the inhibitor. Assuming the kinetic mechanisms are competitive inhibition, the apparent Ki values are then calculated according to the Cheng-Prusoff equation , $Ki = IC_{50}/(1 + [S]/Km)$

Experimental In Vivo Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI 1-161) in Experimental Venous Thrombosis-a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen and U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994). The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) in vivo generated at a site of injury and partial stasis in the jugular vein.

Male and female New Zealand white rabbits weighing 1.5-2 kg are anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of 1 ml/kg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 ml/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just proximal to the common jugular vein. A 1 cm segment of the vein is isolated with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp. This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled

with 0.5 ml of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The vascular clamps are then removed, restoring blood flow through this portion of the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as the primary end point. Animals are maintained for an additional thirty minutes to obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and continued through the period of clot formation and maturation. Three blood samples (3 ml ea.) are obtained for evaluation of hemostatic parameters: one just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to vehicle treated control animals.

Experimental In Vivo Rat Arterial Thrombosis Model:

The antithrombotic efficacy of factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery $FeCl_2$-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model, R.J. Broersma, L.W. Kutcher and E.F. Heminger. Thrombosis Research 64, 405-412 (1991). This model is widely used to evaluate the antithrombotic potential of a variety of agents including heparin and the direct acting thrombin inhibitors.

Sprague Dawley rats weighing 375-450 g are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is

made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4-0 silk sutures are placed around the vessel to facilitate instrumentation. An electromagnetic flow probe (0.95-1.0 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of parafilm is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 mm strip of filter paper previously saturated in 35% $FeCl_2$ is placed on top of the vessel downstream from the probe for ten minutes and then removed. The $FeCl_2$ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the $FeCl_2$-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained, the artery is ligated proximal and distal to the area of injury and the vessel is excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 ml of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to $FeCl_2$ application. The time between $FeCl_2$ application and the time at which carotid blood flow reached zero is recorded as time to occlusion (TTO). For vessels that did not occlude within 60 minutes, TTO is assigned a value of 60 minutes. Five minutes after application of $FeCl_2$, a second blood sample is drawn (B2). After 10 minutes of $FeCl_2$ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some instances a compound according to the invention may be administered orally. Rats are restrained manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 ml/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then performed according to the protocol described above.

Experimental Canine intravenous and intragastric dosing experiments.

Beagle dogs (9-13 kg) of either sex are used to evaluate the pharmacodynamic effect of compounds of this invention after intravenous and intragastric dosing. Blood samples for these experiments are obtained via venipuncture of the cephalic vein. After discarding the first 0.5 ml of blood drawn, the control sample of 4.5 ml of blood is drawn into chilled plastic syringes containing 0.5 ml of trisodium citrate. After drug administration, 0.9 ml of blood is obtained at each time point (after discarding the first 0.5 ml of blood) by drawing the sample directly into chilled plastic syringes containing 0.1 ml trisodium citrate.

For the intravenous experiments, compounds are administered in the cephalic vein in the forelimb contralateral to that used for blood sampling. Compounds are dissolved in saline (0.5 ml/kg body weight) and administered as an i.v. bolus. Post-dosing blood samples are obtained at specific time points after dosing.

For the intragastric experiments, Compounds (in 0.5% methyl cellulose and 1 % polysorbate-80, 1 ml/kg dosing volume) are administered via an intragastric feeding tube. A pre-dosing control blood sample is obtained as above and post-dosing samples are obtained at specific time points after dosing.

Coagulation times. Platelet-poor plasma is used for determination of activated partial thromboplastin time (APTT) and prothrombin time (PT), which are measured using a Microsample Coagulation Analyzer (MCA210, Bio Data Corp, Horsham, PA) and Dade® reagents (Thromboplastin-C Plus and Actin® FS Activated PTT reagent, Baxter Diagnostics, Inc., Deerfield, IL).

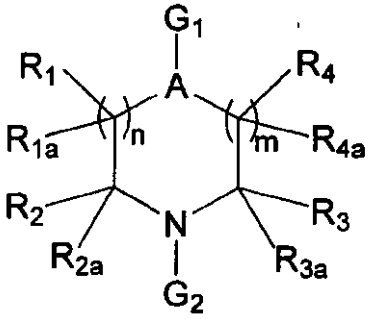
Ex vivo inhibition of Factor Xa. Factor-Xa inhibitory activity is analyzed by chromogenic methods using reagents (bovine factor Xa and spectrozyme Xa) supplied by American Diagnostica (Greenwich, CT). The rate of change of optical density (Vmax, 405 nm) is measured using a SPECTRAmax microtiter plate spectrophotometer and Softmax Pro software (Molecular Devices Corp., Sunnyvale, CA). Inhibition of Xa activity is determined as follows: percent inhibition of Xa activity = 1-(Vmax of sample with inhibitor/Vmax of the pre-drug control sample) X 100.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects of the invention and obtain the ends and advantages mentioned, as well as those inherent therein. The compounds, compositions and methods described herein are presented as representative of the preferred embodiments, or intended to be exemplary and not intended as limitations on the scope of the present invention.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

Claims:

1. A compound of formula I



I

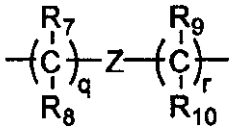
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein

G_1 and G_2 are L_1- Cy_1 or L_2- Cy_2, provided that when R_1 and R_{1a} or R_4 and R_{4a} taken together form O or S, then G_1 is L_2- Cy_2 and G_2 is L_1-Cy_1, or when R_2 and R_{2a} or R_3 and R_{3a} taken together form O or S, then G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

Cy_1 and Cy_2 are independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

L_1 is absent, O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, -C(O)Y-C(X)Y-, -C(X)YC(O)-, -C(O)NR_5-S(O)p-, or -C(O)C(O)NR_5S(O)p-;

L_2 is absent or a group of formula



;

L_3 and L_5 are independently absent, optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene;

L_4 is optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene;

Q and Q' are independently absent, O, S, NR_5, -S(O)p-, -S(O)pNR_5- or -C(X)Y-;

A is CH or N;

R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a}, R_3 and R_{3a}, or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_3 and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

m and n are independently 0, 1 or 2, provided that m and n are not both 0 and further provided that when R_1 and R_{1a} taken together form O or S, n is 1, and when R_4 and R_{4a} taken together form O or S, m is 1;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH2)v$-, $R_6O2C(CH2)x$-, $Y_1Y_2NC(O)(CH2)x$-, or $Y_1Y_2N(CH2)v$-;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y_1 and Y_2 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y_1 and Y_2 taken together with the N through which Y_1 and Y_2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when any of R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α-substituted to an N, O or S in Z;

X is O or S; Y is absent or is selected from O, S and NR_5;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, -C(O)-, S(O)p, NR_5, -NR_5C(O)- and -C(O)NR_5-;

x is 1, 2, 3 or 4; v is 2, 3 or 4;

p is 1 or 2; and q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0,

provided that when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5- and R_3 and R_{3a} taken together form O or S, then R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen;

or when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5- and R_3 and R_{3a} taken together form O or S, then R_4 and R_{4a} taken together form O or S;

or when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5- and R_3 and R_{3a} taken together form O or S, then Cy_1 is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol and Cy_2 is amino-quinazolin or pyrrolo-pyridin;

or when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5- then R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_3 and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;.

or when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, then R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently Y_1Y_2NC(O)- and Y_1 and Y_2 are independently hydrogen, optionally substituted alkoxy or optionally substituted aryloxy, but Y_1 and Y_2 are not simultaneously hydrogen,

or when L_1 is O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, then Z is –C(O)-.

2. A compound according to claim 1 wherein Cy_2 is optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylcycloalkyl, fused arylheteroclyl, optionally substituted fused arylheterocyclenyl, or optionally substituted aryl.

3. A compound according to claim 1 wherein L_1 is absent, optionally substituted alkylene, optionally substituted alkenylene, $-C(O)NR_5-$, $-S(O)p-$, $-C(O)-$, $-C(O)Y-C(X)Y-$, $-C(O)O-$, $C(O)NR_5-S(O)p-$, $-C(O)-C(O)NR_5S(O)p-$, $-S(O)pNR_5-$, -C(O)-alkylene-O-, -C(O)-alkenylene-O-, -S(O)p-alkenylene-, -S(O)p-alkylene-, -C(O)-alkylene-C(O)-, -C(O)-alkylene-S(O)p-, -S(O)p-alkylene-C(O)-, -C(O)-alkylene, -C(O)-alkenylene-, - alkylene-$C(O)NR_5-$, methylene, -S(O)p-alkenylene-,$-C(O)C(O)NR_5$ or -C(O)CH(OH)-alkylene-.

4. A compound according to claim 1 wherein Cy_1 is optionally substituted aryl, heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycolalkenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl.

5. A compound according to claim 1 wherein R_4 is alkoxyalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxycarbonylalkyl, hydroxyalkyl, acylalkyl, acylaminoalkyl or carbamoylalkyl; and R_{4a} is hydrogen and. wherein R_2 alkoxyalkyl, alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or heterocyclylalkyloxycarbonyl, and R_{2a} is hydrogen.

6. A compound according to claim 1 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene, sulfonyl, alkylenesulfonyl or alkylene;

Cy_1 is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroarylcycloalkyl, fused thiaheteroarylcycloalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl, thiophen-isoxazolyl, thieno-pyridineyl, benzo-thiophen, indolyl, morholinyl, aminopyridine-

benzyl, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin, phenyl-triazol optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, bipyridinyl, pyridin-benzyl, thiophenyl, thiophen-benzyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl;

R_3 and R_{3a} taken together form O or S;

R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen, or carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

R_1 and R_{1a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted

aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

or R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group, or R_4 and R_{4a} taken together form O or S;

and m and n are each 1.

7. A compound according to claim 6 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 is sulfonyl or alkylenesulfonyl;

L_2 is absent, methylene, ethylene or alkylene;

Cy_1 is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroarylcycloalkyl, fused thiaheteroarylcycloalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl, thiophen-isoxazolyl, thieno-pyridineyl, benzo-thiophen, indolyl, morholinyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused

azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl;

R_3 and R_{3a} taken together form O or S;

R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen;

R_1, R_{1a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

or the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

and m and n are each 1.

8. A compound according to claim 6 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene or alkylene;

Cy_1 is thiophen-isoxazolyl, aminopyridine-benzyl, benzo-thiophen, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is bipyridinyl, amino-quinazolin, pyridin-benzyl, thiophenyl, thiophen-benzyl, pyrrolo-pyridin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused

arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

R_3 and R_{3a} taken together form O or S; and

R_4 and R_{4a} taken together form O or S;

R_1, R_{1a}, R_2, R_{2a}, are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

and m and n are each 1.

9. A compound according to claim 6 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene or alkylene;

Cy_1 is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol;

Cy_2 is amino-quinazolin or pyrrolo-pyridin;

R_3 and R_{3a} taken together form O or S;

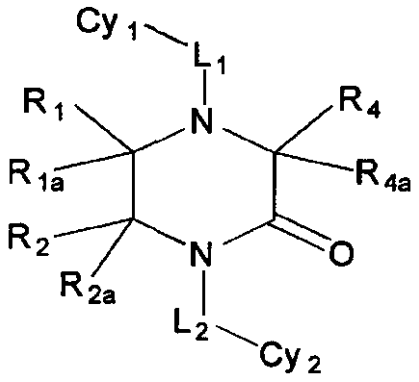
R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through

which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; and m and n are each 1.

10. A compound according to claims 1, 6, 7, 8 and 9 wherein Cy_2 is optionally substituted with one or more groups selected from amino, carbamoyl, acylamino, heteroaryl, heterocyclenyl, heterocyclyl, alkyl, amidino, alkyloxycarbonyl, hydroxy, alkoxy, aryl, isourea, guanidino, acylhydrazino, acyl, cyano, carboxy, sulfamoyl, or halo.

11. A compound according to claims 1, 6, 7, 8 and 9 wherein Cy_1 is optionally substituted with one or more groups selected from amino, halo, hydroxyl, aryl, heteroaryl, amidino, alkyl, acylamino, carbamoyl, cyano, alkoxy, nitro, carbamate, sulfamyl.

12. A compound according to claim 1 having the formula II

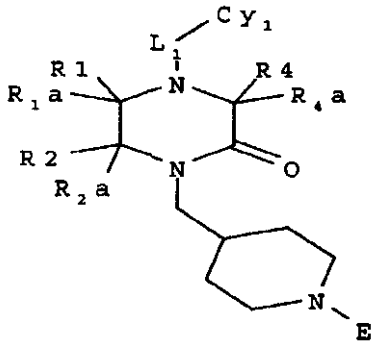


II

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof,
wherein R_1, R_{1a}, R_2, R_{2a}, R_4, R_{4a}, Cy_1, Cy_2, L_1, and L_2 are as defined in formula I.

13. A compound according to claim 12 wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

14. A compound according to claim 1 having the formula IIa



IIa

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof,

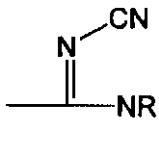
wherein

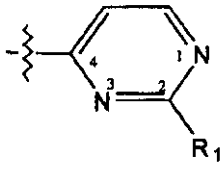
R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a} or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

Cy_1 are independently selected from isoxazolyl, thiophenyl, thiophenyl-isoxazolyl, obtionally substituted by halogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

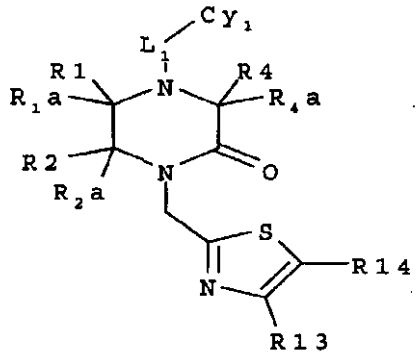
L_1 is absent, methylene, O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, -C(O)Y-C(X)Y-,

-C(X)YC(O)-, -C(C)NR_5-S(O)p-, or -C(O)C(O)NR_5S(O)p-; p is 1 or 2, and

E is alkoxycarbonyl, carbamoyl, acyl, alkyl, pyridinyl, amidino;  wherein R_{12} and $R_{12'}$ are independently selected from hydrogen or optionally substituted lower alkyl; or

 wherein R_{15} is selected from halogen, alkoxy, alkylthio and Y_1Y_2N-, wherein Y_1 and Y_2 are independently, hydrogen, alkyl and aralkyl.

15. A compound according to claim 1 having the formula IIb



IIb

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a} or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

Cy_1 are independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused

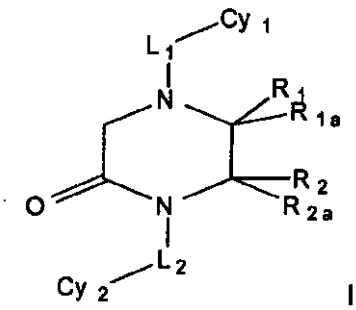
arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

L_1 is absent, O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, -C(O)Y-C(X)Y-, -C(X)YC(O)-,

-C(C)NR_5-S(O)p-, or -C(O)C(O)NR_5S(O)p-; and

R_{13} and R_{14} are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxycarbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, heterocyclenyl group, aryl group or heteroaryl group.

16. A compound according to claim 1 having the formula IIc



IIc

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein:

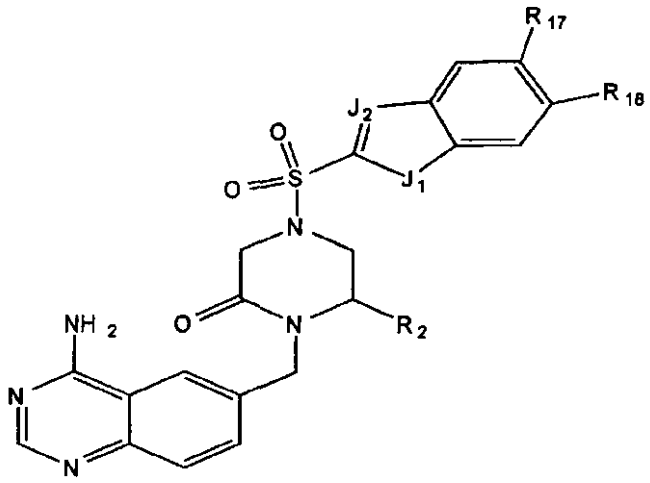
Cy_1 is thiaheteroaryl, benzothiopheneyl or azaheteroaryl, which are unsubstituted or substituted by halogen,

L_1 is -$S(O)_2$-, -$S(O)_2$-alkylene-, -$S(O)_2$-alkyenlene- or -$S(O)_2$-alkynylene-;

R_1, R_{1a}, R_2, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxycarbonyl, or carbamoyl; L_2 is methylene; and

Cy_2 is azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl.

17. A compound according to claim 1 having the formula IId



IId

wherein R_{17} and R_{18} are independently hydrogen or halogen;

J_1 is S or NH;

J_2 is CH or N; and

R_2 is hydrogen, alkyl, carboxyl, alkoxycarbonyl, or carbamoyl.

18. A compound according to claim 12 wherein L_1 and L_2 independently are methylene, ethylene, propylene or butenylene; R_1, R_{1a}, R_2, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxycarbonyl, or carbamoyl; Cy_1 is heteroaryl, thiaheteroaryl, biheteroaryl, thiophenyl, isoxazolyl, isoxazolyl-thiophenyl or azaheteroaryl, which are unsubstituted or substituted by halogen; Cy_2 is azaheteroaryl, quinazolin, amino-quinazolin or 4-aminoquinazolin.

19. A compound according to claim 1 selected from the group consisting of

5-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester,

6-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester,

3-(5-Chloro-thiophen-2-yl)-3-oxo-propionic acid tert-butyl ester,

Methyl-6-Chloro-benzofurancarboxylate,

2-Cyclopentyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one,

5-Methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester,

4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine,

(*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester,

6-Isopropyl-piperazin-2-one,

9-(4-Aminoquinazolin-7-ylmethyl)-6,9-diaza-spiro[4,5]decan-10-one,

(+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one,

(+/-)-cis-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one,,
(+/-)-trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one,
(+/-)-trans-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one,
4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R/S)1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-octahydro-quinoxalin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-piperazin-2-one
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-piperazin-2-one,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid tert-butyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-sulfonic acid (4-chloro-phenyl)-amide,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-imidazol-1-yl-ethyl ester,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-morpholin-4-yl-ethyl ester,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid pyrrolidin-2-ylmethyl ester,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-methylamino-ethyl ester,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one,

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-imidazo[1,2-a]pyridin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-(S)-3-propyl-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo(S)--2-propyl-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-ylmethyl)-3(S)-propyl-piperazin-2-one,

9-(4-Amino-quinazolin-7-ylmethyl)-6-[3-(5-chloro-thiophen-2-yl)-allyl]-6,9-diaza-spiro[4.5]decan-10-one,

(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one,

(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-isobutyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3(S)-isobutyl-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-benzamidine,

(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one,

(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one,

(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-octahydro-quinoxalin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-N-methyl-acetamide,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3(S)-isobutyl-piperazin-2-one,

(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-(4-pyrimidin-4-yl-benzyl)-piperazin-2-one,

4-[4-(2-Amino-pyrimidin-4-yl)-benzyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

3-Amino-5-[4-(4-amino-quinazolin-7-ylmethyl)-2(S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-thiophene-2-carbonitrile,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzonitrile,

3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzamidine,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,

1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione,

1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-2-fluoro-propane-1,3,dione,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfinyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfonyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-dimethylaminomethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo-[b]thiophene-2-carbonyl)-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chlorobenzo[b]-thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one ,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-on,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one,
3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidine,
3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidin,
4-[3-(4-Amino-cyclohexyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one trifluoroacetate,
1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(3-chloro-phenyl)-propane-1,3-dione,
4-[(5-Amino-pyridin-2-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-(S)-3-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(R)-methoxymethyl-piperazin-2-one,
3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine,
3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-imidazol-1-yl-benzoyl)-3(S)-propyl-piperazin-2-one,
(6-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-yl)-carbamic acid tert-butyl ester,
(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one,
(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one,
(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-octahydro-quinoxalin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-6-oxo-1,6-dihydro-pyridin-3-yl)-acryloyl]-(S)-3-propyl-piperazin-2-one ,

1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(4-hydroxy-phenyl)-propane-1,3-dione,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetic acid methyl ester

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

4-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzenesulfonamide,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-pyridin-2-yl)-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-propyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carbonyl]-benzamidine,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(piperidin-3-yloxy)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-4-hydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one,

(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-hydroxy-naphthalene-2-carbonyl)-3-propyl-piperazin-2-one,

(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-hydroxy-1H-indole-2-carbonyl)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-(S)-propyl-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,4-dihydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-6-methyl-pyridin-2-yl)-acetamide,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide,

4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-butyl-piperazin-2-one

1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione,

4-[3-(3-Amino-4-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,

4-[3-(3-Amino-5-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-benzenesulfinyl)-acetyl]-(3-S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfinyl)-acetyl]-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-hydroxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one,
4-[(6-Amino-pyrimidin-4-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfonyl)-acetyl]-piperazin-2-one,
1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(4-chloro-phenyl)-propane-1,3-dione
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylsulfanyl)-acetyl]-piperazin-2-one,
4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-3-hydroxy-acryloyl]-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-dimethylamino-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,
3-(S)-6-(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-hydroxymethyl-3-methoxymethyl-piperazin-2-one,
4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-isobutyl-piperazin-2-one,
4-[3-(2-Amino-pyrimidin-5-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,
4-[3-(3-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,
4-[3-(4-Amino-3-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-amino-thiazol-4-yl)-acetyl]-(S)-3-propyl-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethyl ester,

4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-isobutyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-hydroxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide,

(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide,

(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-hydroxy-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methylcarbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-carbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

(4aRS,8aRS)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-octahydro-quinoxaline-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methylsulfanyl-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-furan-2-yl)-amide,

(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide,

N-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carbonyl]-4-chloro-benzenesulfonamide,

1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-propyl-piperazin-2-one,

1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-4-oxy-3-propyl-piperazin-2-one,

1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methoxymethyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

(S)-4-(4-Aminoquinolin-7-ylmethyl)-2-methoxylmethyl-3-oxo-2-piperazine-1-carboxylic acid (5-chlorothiophen-2-yl)-amide,

1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-1-carboxylic acid phenylamide,

1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

1-(S)-4-(4-Amino-cinnolin-7-ylmethyl)-2-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

1-(S)-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one,

1-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid methyl ester,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid methyl ester,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid amide,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-
(-)-carboxylic acid amide,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(7-Methoxy-naphthalene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(Benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[2-(4-Chloro-phenyl)-1H-indol-3-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[2,2']Bithiophenyl-5-ylmethyl-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

7-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one,

7-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-(S)-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one,

7-{4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-2H-isoquinolin-1-one,

7-[4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl]-2H-isoquinolin-1-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3-methyl-3H-quinazolin-4-one,

6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3H-quinazolin-4-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-propionyl]-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(3-imidazol-1-yl-benzyl)-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methylamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-4-yl-thiazol-2-ylmethyl)-piperazin-2-one hydrobromide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide,

{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid methyl ester,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl este,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methyl ester,

1-(4-tert-Butyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(5-chloro-thiophen-2-yl)-thiazol-2-ylmethyl]-piperazin-2-one,

1-[4-(4-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-[4-(3-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-methyl-thiazol-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one,

1-(5-Acetyl-4-methyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-*methyl-butyric acid ethyl ester*,

1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-phenyl-thiazol-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester,
2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzoic acid,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(2-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-2-yl-thiazol-2-ylmethyl)-piperazin-2-one,
2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzamide,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[4,5-c]pyridin-6-one,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl ester,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one,
(R)-3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide,

(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide,
(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid ethyl ester,
(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid dimethylamide,
(S)-(2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazol-4-yl)-acetic acid methyl ester,
(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime,
1-(4-Amino-benzothiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(morpholine-4-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(piperazine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid N',N'-dimethyl-hydrazine,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid (2-hydroxy-ethyl)-methyl-amide,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(3-hydroxy-pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,
2-(4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methoxy-methyl-amide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropyl-methyl-amide,

({2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carbonyl}-methyl-amino)-acetic acid ethyl ester,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methylamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropylamide,

{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetamide,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-methyl-acetamide,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-isopropyl-acetamide,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N,N-dimethyl-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid amide,

2-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-acetamide,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one,

(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one,

(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one,

(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,

4-[(4-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-pyrimidin-2-yl)-methyl-amino]-butyric acid,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethoxy)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,

Example 1270 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-{2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl}-piperidin-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethylsulfanyl)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrimidin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrazin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-carboxylic acid,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylmethyl)-piperazin-2-one,

O-Phenyl-1-cyano-3-{4-[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl} isourea,

Preparation of N,N Dimethyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine,

Preparation of N-Methyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine,

Preparation of N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-cyanoguanidine,

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N',N'-dimethyl-cyanoguanidine,

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-methyl-cyanoguanidine

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-(2-hydroxyethyl)-N'-methyl-cyanoguanidine,

Preparation of 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one,

and 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[(2-hydroxy-ethyl)-methyl-1-amino]-cyclohexylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-(4-cis-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester,

4-(4-trans-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-cis-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-trans-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one,

4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one,
4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one,
4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one,
4-[(5-Chlorothiophen-2-yloxy)-acetyl]-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione,
1-(3-carbamimidoyl-benzyl)-4-(4-carbamimidoyl-benzyl)-2,3 dioxopiperizine,
Bis-1,4-(3-carbamimidoyl-benzyl)-2,3-dioxopiperizine,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione,
1-[3-(3-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(4-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-(6-chloro-benzo[b]thiophen-2-yl-methyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(thieno[3,2-b]pyridin-2-ylmethyl)-piperazine-2,3-dione,

1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-2-yl-benzyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-2-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-4-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-cyclohexymethyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-cyclohexylmethyl)-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-ethyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-propyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-butyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-isopropyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-isobutyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methoxymethyl-piperazine-2,3-dione,
4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid,
4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl ester,
4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid amide or

4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl amide
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

20. A compound according to claim 1 selected from the group consisting of
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
2-Amino-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-(r)-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(R/S)1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)-1-(4-Amino-6-chloro-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(R/S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,

(R/S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-on,e

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-bromo-5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-pyrrolidin-1-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-morpholin-4-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-dimethylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one,
(S)-4-[4-(6-Chloro-1H-benzoimidazole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
(S)-4-[4-(5-Chloro-1H-indole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
(S)-4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
(S)-4-[4-(6-Chloro-1H-indole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
(6S)-2-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one,
(6S)-6-Aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-

one,

(6S)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-acetamide

4-(3-Acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid,

(2S)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-methanesulfonamide,

(2S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-carbamic acid methyl ester,

(2S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-carbamic acid isopropyl ester,

(2S)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-phenyl-urea,

(2S)-5-Bromo-thiophene-2-sulfonic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide,

(2S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-urea,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,

(2S)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-ethyl-urea,

(2S)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-formamide,

(2S)-Furan-2-carboxylic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide,

(S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-fluoro-1H-indol-2-ylmethyl)-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(isopropylamino-methyl)-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one,
(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one,
(2R)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-isopropoxy ethylamino)-methyl]-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-piperidin-1-ylmethyl-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-[(cyclopentyl-methyl-amino)-methyl]-piperazin-2-one,
(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-ethoxymethyl-piperazin-2-one or
(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-6-benzyloxymethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

21. A compound according to claim 1 selected from the group consisting of
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid tert-butyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-{[(2-dimethyl-amino-ethyl)-methyl-amino]-methyl}-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,
(2R)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[([1,3]dioxolan-2-ylmethyl-methyl-amino)-methyl]-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one or
(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

22. A compound according to claim 1 selected from the group consisting of 1-[4-(2-Chloro-pyrimidin-4-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione, 1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione, 1-[4-(5-Chloro-thiophen-2-yl)-benzyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione, 1-(4-Amino-quinolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione, 1-[1-(2-Chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-3-yl-benzyl)-piperazine-2,3-dione, 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione, 1-[4-(6-Amino-pyridin-3-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-[4-(1-oxy-pyridin-3-yl)-benzyl]-piperazine-2,3-dione, 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione or 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazine-2,3-dione or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

23. A compound according to claim 1 selected from the group consisting of

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester;

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)--oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester;

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)--oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl amide;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(S)-[1-(4-Amino-quinazolin-7-ylmethyl0-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl] acetic acid;

(S)-[1-(4-Amino-quinazolin-7-ylmethyl0-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl] acetic acid tert-butyl ester;

(+/-)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropylaminomethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one;

N,N-Dimethhyl-N4{[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl]} cyanoguanidine;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one;

3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester;

(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one;

(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropyl-methyl-amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methoxy-methyl-amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one;

(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide;

1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one; and

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one;

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

24. A compound according to claim 1 selected from the group consisting of 1-4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-propyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]- piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3-methoxymethyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3- methyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate),

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-yl-methyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-yl-methyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-yl-methyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]thiadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-propyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-ethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-piperazin-2-one tritrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-pyridin-5-yl-methyl]-piperazin-2-one tritrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

[5-(5-Chloro-thiophen-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(5-Chloro-thiophen-2-yl)-oxazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate or

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

25. A compound according to claim 6 selected from the group consisting of 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo [3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one,

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)- propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one,

4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one or

4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

26. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

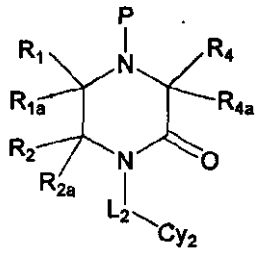
27. A method for treating a patient suffering from a physiological condition capable of being modulated by inhibiting activity of Factor Xa comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 1.

28. A method for treating a patient suffering from a physiological condition capable of being modulated by directly inhibiting activity of both Factor Xa and Factor IIa comprising administering to said patient a pharmaceutically effective amount of a compound according to claims 21 and 23.

29. A method for treating a patient suffering from a physiological condition capable of being modulated by directly inhibiting activity of both Factor Xa and Factor IIa comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 16.

30. A method for treating a patient suffering from a physiological condition capable of being modulated by directly inhibiting activity of both Factor Xa and Factor IIa comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 17.

31. A compound of formula III

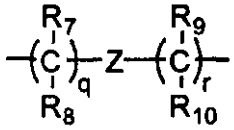


III

wherein P is H or a nitrogen protecting group;

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a} or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_1 and R_{1a} taken together with the carbon atom through wrich they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through wrich they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

L_2 is absent or a group of formula



Cy_2 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH_2)v$-, $R_6O_2C(CH_2)x$-, $Y_1Y_2NC(O)(CH_2)x$-, or $Y_1Y_2N(CH_2)v$-;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y_1 and Y_2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y_1 and Y_2 taken together with the N through which Y_1 and Y_2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α-substituted to a N, O or S in Z;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, S(O)p, -C(O)-, NR_5, $-NR_5C(O)$- and $-C(O)NR_5$-;

x is 1, 2, 3 or 4;

v is 2, 3 or 4; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0,

provided that when R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl then L_2 is absent, or when

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently $Y_1Y_2NC(O)$- then Y_1 and Y_2 are independently hydrogen, optionally substituted alkoxy or optionally substituted aryloxy, but Y_1 and Y_2 are not simultaneously hydrogen, or when

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl then Z is –C(O)-.

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[54] 发明名称 取代的氧代氮杂杂环基化合物

[57] 摘要

本发明涉及抑制因子 Xa 的氧代氮杂杂环化合物，涉及既抑制因子 Xa 又抑制因子 IIa 的氧代氮杂杂环化合物，涉及含有这些化合物的药物组合物，涉及用于制备这些化合物的中间体，涉及直接抑制因子 Xa 的方法以及同时直接抑制因子 Xa 和因子 IIa 的方法。

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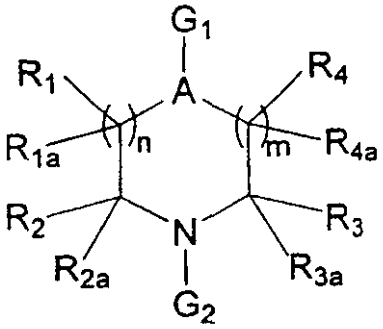
1. 式I的化合物



I

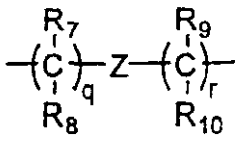
或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中

G_1和G_2是L_1-Cy_1或L_2-Cy_2，条件是当R_1和R_{1a}或R_4和R_{4a}一起形成O或S时，则G_1是L_2-Cy_2而G_2是L_1-Cy_1，或当R_2和R_{2a}或R_3和R_{3a}一起形成O或S时，则G_1是L_1-Cy_1而G_2是L_2-Cy_2；

Cy_1和Cy_2独立地选自任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基和任选地被取代的稠合的杂芳基杂环烯基；

L_1是不存在、O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$、$-C(O)Y-C(X)Y-$、$-C(X)YC(O)-$、$-C(O)NR_5-S(O)_p-$或$-C(O)C(O)NR_5S(O)_p-$；

L_2不存在或是下式的基团



L_3和L_5不存在或独立地是任选地被取代的亚烷基、任选地被取代的亚烯基或任选地被取代的亚炔基；L_4是任选地被取代的亚烷基、任选地被取代的亚烯基或任选地被取代的亚炔基；

Q和Q'独立地不存在、O、S、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$或$-C(X)Y-$；

A是CH或N；

R_1、R_{1a}、R_2、R_{2a}、R_3、R_{3a}、R_4和R_{4a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基，或者R_1和R_{1a}，R_2和R_{2a}，R_3和R_{3a}，或R_4和R_{4a}一起形成O或S；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_3和R_4与R_3和R_4所连接的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或者R_{3a}和R_{4a}不存在而R_3和R_4与R_3和R_4所连接的碳原子一起形成芳基或杂芳基；或一个或多个R_1和R_{1a}对与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_3和R_{3a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

m和n独立地是0、1或2，其条件是m和n 不都是0且另一个条件是当R_1和R_{1a}一起形成O或S时，n是1，而当R_4和R_{4a}一起形成O或S时，m是1；

R_5是氢原子、任选地被取代的烷基、任选地被取代的芳烷基、任选地被取代的杂芳烷基、$R_6O(CH_2)_v-$、$R_6O_2C(CH_2)_x-$、$Y_1Y_2NC(O)(CH_2)_x-$或$Y_1Y_2N(CH_2)_v-$；

R_6是氢原子、任选地被取代的烷基、任选地被取代的芳烷基或任选地被取代的杂芳烷基；

Y_1和Y_2独立地是氢原子、任选地被取代的烷基、任选地被取代的烷氧基、任选地被取代的芳氧基、任选地被取代的芳基、任选地被取代的芳烷基或任选地被取代的杂芳烷基，或Y_1和Y_2与Y_1和Y_2所连接的氮原

子一起形成单环杂环基；

R_7、R_8、R_9和R_{10}独立地选自氢原子、羟基、烷氧基、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的芳烷基和任选地被取代的杂芳烷基，其条件是R_7和R_8中只有一个或者R_9和R_{10}中只有一个是羟基或烷氧基，且另一个条件是当R_7、R_8、R_9和R_{10}中任何一个是羟基或烷氧基时，则此羟基或烷氧基对Z中的N、O或S而言不是α-取代的；

X是O或S；Y不存在或选自O、S和NR_5；

Z不存在或选自任选地被取代的低级亚烯基、任选地被取代的低级亚炔基、O、-C(O)-、$S(O)_p$、NR_5、$-NR_5C(O)-$和$-C(O)NR_5-$；

x是1、2、 3或4；v是2、3或4；

p是1或2；而q和r独立地是0、1、2或3，其条件是q和r 不都是0，

且条件是当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、-C(X)Y-或$-L_3-Q-L_4-Q'-L_5-$且R_3和R_3一起形成O或S时，则R_2和R_{2a}独立地选自氢原子、烷基、氨基烷基、烷基氨基烷基、烷氧基、烷氧基烷基、烷氧基氨基烷基、环烷基烷基氨基、苄氧基烷基、异丙基、氨基甲基、甲氧基乙基氨基甲基、哌嗪基、吡咯烷基、乙氧基甲基、苄氧基甲基、甲氧基甲基、异丁基、异丙基氨基或异丙基氨基甲基，其条件是R_2和R_{2a}不都是氢原子；

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、-C(X)Y-或$-L_3-Q-L_4-Q'-L_5-$而R_3和R_{3a}一起形成O或S时，则R_4和R_{4a}一起形成O或S；

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、-C(X)Y-或$-L_3-Q-L_4-Q'-L_5-$且R_3和R_{3a}一起形成O或S时，则Cy_1是噻吩-异噁唑、噻吩-吡唑、噻吩-噁二唑、噻吩-噻二唑、噻吩-三唑、噻吩-吡啶或苯基-三唑而Cy_2是氨基喹唑啉或吡咯并-吡啶；

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、-C(X)Y-或$-L_3-Q-L_4-Q'-L_5-$，则R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_3和R_4 与R_3和R_4所连接的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一

起形成芳基或杂芳基；或R_{3a}和R_{4a}不存在且R_3和R_4与R_3和R_4所连接的碳原子一起形成芳基或杂芳基；或一个或多个R_1和R_{1a}对与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_3和R_{3a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$时，则R_1、R_{1a}、R_2、R_{2a}、R_3、R_{3a}、R_4和R_{4a}独立地是$Y_1Y_2NC(O)-$而Y_1和Y_2独立地是氢原子、任选地被取代的烷氧基或任选地被取代的芳氧基，但Y_1和Y_2不同时是氢原子，

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$时，则Z是$-C(O)$。

2. 权利要求1所述的化合物，其中Cy_2任选地被取代的杂芳基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的稠合的杂芳基杂环基、任选地被取代的稠合的杂芳基杂环烯基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基环烷基、稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基或任选地被取代的芳基。

3. 权利要求1所述的化合物，其中L_1是不存在、任选地被取代的亚烷基、任选地被取代的亚烯基、$-C(O)NR_5-$、$-S(O)_p-$、$-C(O)-$、$-C(O)Y-C(X)Y-$、$-C(O)O-$、$C(O)NR_5-S(O)_p-$、$-C(O)-C(O)NR_5S(O)_p-$、$-S(O)_pNR_5-$、$-C(O)-$亚烷基$-O-$、$-C(O)-$亚烯基$-O-$、$-S(O)_p-$亚烯基$-$、$-S(O)_p-$亚烷基$-$、$-C(O)-$亚烷基$-C(O)-$、$-C(O)-$亚烷基$-S(O)_p-$、$-S(O)_p-$亚烷基$-C(O)-$、$-C(O)-$亚烷基、$-C(O)-$亚烯基$-$、$-$亚烷基$-C(O)NR_5-$、亚甲基、$-S(O)_p$亚烯基$-$、$-C(O)C(O)NR_5$或$-C(O)CH(OH)-$亚烷基$-$。

4. 权利要求1所述的化合物，其中Cy_1是任选地被取代的芳基、杂芳基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的环烷基、任选地被取代的环链烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合

的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基。

5. 权利要求1所述的化合物，其中R_4是烷氧基烷基、烷硫基烷基、烷基亚磺酰基烷基、烷基磺酰基烷基、烷氧羰基烷基、羟基烷基、酰基烷基、酰基氨基烷基或氨基甲酰基烷基；而R_{4a}是氢原子，且其中R_2烷氧基烷基、烷氧羰基烷基、羧基烷基、羟基烷基或杂环基烷氧羰基，而R_{2a}是氢原子。

6. 权利要求1所述的化合物，其中

A是N；

G_1是L_1-Cy_1而G_2是L_2-Cy_2；

L_1和L_2独立地是不存在、亚甲基、亚乙基、磺酰基、亚烷基磺酰基或亚烷基；

Cy_1是硫杂杂芳基、硫杂杂环基、硫杂杂环烯基、稠合的硫杂杂芳基环烷基、稠合的硫杂杂芳基环烯基、稠合的杂芳基硫杂环烷基或稠合的杂芳基硫杂环烯基、噻吩-异噁唑基、噻吩并-吡啶基、苯并噻吩基、吲哚基、吗啉基、氨基吡啶苄基、嘧啶-苄基、氨基喹唑啉、嘧啶-哌啶基、噻吩-吡唑、噻吩-噁二唑、噻吩-噻二唑、噻吩-三唑、噻吩-吡啶、任选地被取代的芳基的苯基-三唑、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基；

Cy_2是氨基-喹唑啉、二苯亚甲基-氨基、吡咯并-吡啶、联吡啶基、吡啶-苄基、噻吩基、噻吩-苄基、任选地被取代的芳基、任选地被取

代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基、任选地被取代的稠合的杂芳基杂环烯基、氮杂杂芳基、氮杂环基、氮杂环烯基、稠合的氮杂杂芳基环烷基、稠合的氮杂杂芳基环烯基、稠合的杂芳基氮杂环烷基或稠合的杂芳基氮杂环烯基；

R_3和R_{3a}一起形成O或S；

R_2和R_{2a} 独立地选自氢原子、烷基、氨基烷基、烷基氨基烷基、烷氧基、烷氧基烷基、烷氧基氨基烷基、环烷基烷基氨基、苄氧基烷基、异丙基、氨基甲基、甲氧基乙基氨基甲基、哌嗪基、吡咯烷基、乙氧基甲基、苄氧基甲基、甲氧基甲基、异丁基、异丙基氨基或异丙基氨基甲基，其条件是R_2和R_{2a}不都是氢原子，或羧基、烷氧羰基、$Y_1Y_2NC(O)-$，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

R_1和R_{1a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；

或R_1和R_{1a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

R_4和R_{4a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳

基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基，或R_4和R_{4a}一起形成O或S；

而m和n各是1。

7. 权利要求6所述的化合物，其中

A是N；

G_1是L_1-Cy_1而G_2是L_2-Cy_2；

L_1是磺酰基或亚烷基磺酰基；

L_2是不存在、亚甲基、亚乙基或亚烷基；

Cy_1是硫杂杂芳基、硫杂杂环基、硫杂杂环烯基、稠合的硫杂杂芳基环烷基、稠合的硫杂杂芳基环烯基、稠合的杂芳基硫杂环烷基或稠合的杂芳基硫杂环烯基、噻吩-异噁唑基、噻吩并-吡啶基、苯并噻吩基、吲哚基、吗啉基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基；

Cy_2是氨基-喹唑啉、二苯亚甲基-氨基、吡咯并-吡啶、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基、任选地被取代的稠合的杂芳基杂环烯基、氮杂杂芳基、氮杂环基、氮杂环烯基、稠合的氮杂杂芳基环烷基、稠合的氮杂杂芳基环烯基、稠合的杂芳基氮杂环烷基或稠合的杂芳基氮杂环烯基；

R_3和R_{3a}一起形成O或S；

R_2和R_{2a}独立地选自氢原子、烷基、氨基烷基、烷基氨基烷基、烷氧基、烷氧基烷基、烷氧基氨基烷基、环烷基烷基氨基、苄氧基烷基、异丙基、氨基甲基、甲氧基乙基氨基甲基、哌嗪基、吡咯烷基、乙氧基甲基、苄氧基甲基、甲氧基甲基、异丁基、异丙基氨基或异丙基氨基甲基，其条件是R_2和R_{2a}不都是氢原子；

R_1、R_{1a}、R_4和R_{4a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；

或R_1和R_{1a}与它们连接的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

而m和n各是1。

8. 权利要求6所述的化合物，其中

A是N；

G_1是L_1-Cy_1而G_2是L_2-Cy_2；

L_1和L_2独立地是不存在、亚甲基、亚乙基或亚烷基；

Cy_1是噻吩-异噁唑基、氨基吡啶-苄基、苯并噻吩基、嘧啶-苄基、氨基喹唑啉、嘧啶-哌啶基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基；

Cy_2是联吡啶基、氨基-喹唑啉、吡啶-苄基、噻吩基、噻吩-苄基、吡咯并-吡啶、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、

任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基；

R_3和R_{3a}一起形成O或S；且

R_4和R_{4a}一起形成O或S；

R_1、R_{1a}、R_2、R_{2a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或一对或多对R_1和R_{1a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

而m和n各是1。

9. 权利要求6所述的化合物，其中

A是N；

G_1是 L_1-Cy_1而G_2是L_2-Cy_2；

L_1和L_2独立地是不存在、亚甲基、亚乙基或亚烷基；

Cy_1是噻吩-异噁唑、噻吩-吡唑、噻吩-噁二唑、噻吩-噻二唑、噻吩三唑、噻吩-吡啶或苯基-三唑；

Cy_2是氨基-喹唑啉或吡咯并-吡啶；

R_3和R_{3a}一起形成O或S；

R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与

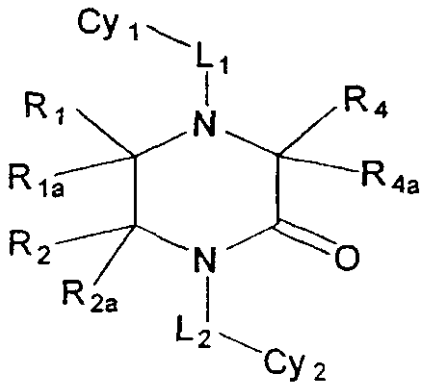
连接R_1和R_2的碳原子一起形成芳基或杂芳基；或一对或多对R_1和R_{1a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；

而m和n各是1。

10. 权利要求1、6、7、8和9所述的化合物，其中Cy_2任选地被选自如下的一个或多个基团取代：氨基、氨基甲酰基、酰基氨基、杂芳基、杂环烯基、杂环基、烷基、脒基、烷氧羰基、羟基、烷氧基、芳基、异脲、胍基、酰肼基、酰基、氰基、羧基、氨磺酰基或卤素。

11. 权利要求1、6、7、8和9所述的化合物，其中Cy_1任选地被选自如下的一个或多个基团取代：氨基、卤素、羟基、芳基、杂芳基、脒基、烷基、酰基氨基、氨基甲酰基、氰基、烷氧基、硝基、氨基甲酸酯、氨磺酰基。

12. 权利要求1所述的化合物，其特征是具有式II的化合物

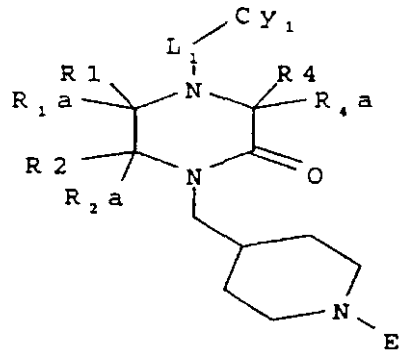


II

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中R_1、R_{1a}、R_2、R_{2a}、R_4、R_{4a}、Cy_1、Cy_2、L_1和L_2如式I所定义。

13. 权利要求12所述的化合物，其中Cy_2含有至少一个氮原子且当Cy_2是任选地被取代的芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的稠合的苯基环烷基或任选地被取代的稠合的苯基环烯基时，则所述氮原子是碱性氮原子。

14. 权利要求1所述的化合物，其特征是式IIa的化合物

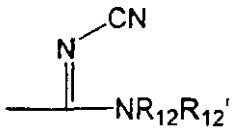


IIa

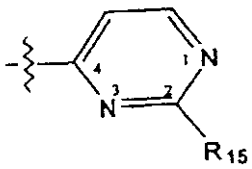
或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a}独立地选自氢原子、烷基、烷氧基烷基、氨基烷基、氨基烷基烷氧基、羧基、烷氧羰基、$Y_1Y_2NC(O)$-、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基，或R_1和R_{1a}、R_2和R_{2a}或R_4和R_{4a}一起形成O或S；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或一对或多对R_1和R_{1a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；Cy_1独立地选自异噁唑基、噻吩基、噻吩基-异噁唑基，其任选地被卤素取代、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合芳基环烷基、任选地被取代的稠合芳基环烯基、任选地被取代的稠合芳基杂环基、任选地被取代的稠合芳基杂环烯基、任选地被取代的稠合杂芳基环烷基、任选地被取代的的稠合杂芳基环烯基、任选地被取代的稠合杂芳基杂环基和任选地被取代的稠合杂芳基杂环烯基；

L_1是不存在、亚甲基、O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$、$-C(O)Y-C(X)Y-$、$-C(X)YC(O)-$、$-C(C)NR_5-S(O)_p-$或$-C(O)C(O)NR_5S(O)_p-$；p是1或2，且

E是烷氧羰基、氨基甲酰基、酰基、烷基、吡啶基、脒基；

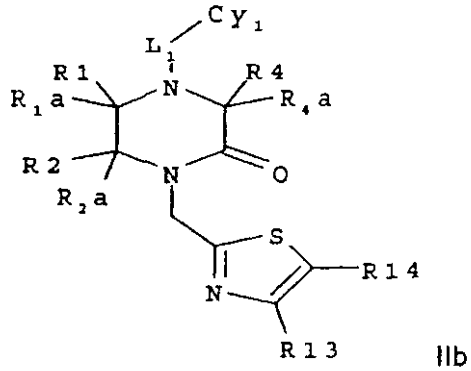


其中R_{12}和$R_{12'}$独立地选自氢原子或任选地被取代的低级烷基；或



其中R_{15}选自卤素、烷氧基、烷硫基和Y_1Y_2N-，其中Y_1和Y_2独立地是氢原子、烷基和芳烷基。

15. 权利要求1所述的化合物，其具有式IIb的结构



IIb

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中

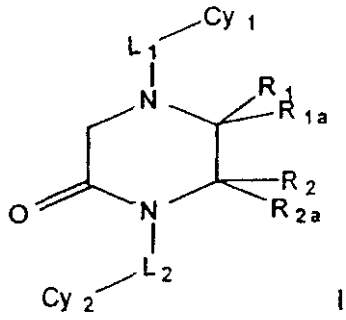
R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基，或R_1和R_{1a}、R_2和R_{2a}或R_4和R_{4a}一起形成O或S；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或一对或多对R_1和R_{1a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；

Cy_1独立地选自任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基和任选地被取代的稠合的杂芳基杂环烯基；

L_1是不存在、O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$、$-C(O)Y-C(X)Y-$、$-C(X)YC(O)-$、$-C(C)NR_5-S(O)_p-$或$-C(O)C(O)NR_5S(O)_p-$；而

R_{13}和R_{14}独立地是氢原子、低级烷基、芳基、杂芳基、氨基、酰基氨基烷基、烷氧羰基烷基、氨基甲酰基烷基或烷氧基烷基；或R_{13}和R_{14}与连接R_{13}和R_{14}的碳原子一起形成环烷基、环烯基、杂环基、杂环烯基、芳基或杂芳基。

16. 权利要求1所述的化合物，其具有式IIc



IIc

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中：

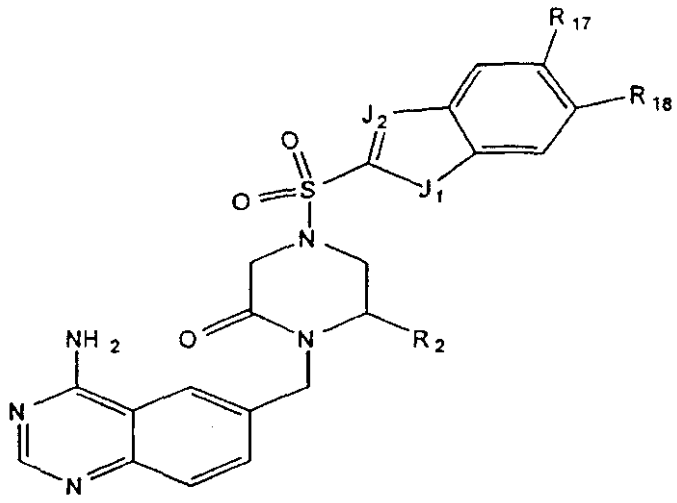
Cy_1是硫杂杂芳基、苯并噻吩基或氮杂杂芳基，其未被取代或被卤素取代，

L_1是$-S(O)_2-$、$-S(O)_2-$亚烷基-、$-S(O)_2-$亚烯基-或$-S(O)_2-$亚炔基-；R_1、R_{1a}、R_2、R_{2a}独立地是氢原子、烷基、烷氧基烷基、氨基烷基、氨基烷基烷氧基、羧基、烷氧羰基或氨基甲酰基；L_2是亚甲基；而

Cy_2是氮杂杂芳基、氮杂环基、氮杂环烯基、稠合的氮杂杂芳基环

烷基、稠合的氮杂杂芳基环烯基、稠合的杂芳基氮杂环烷基或稠合的杂芳基氮杂环烯基。

17. 权利要求1所述的化合物，其具有式IId



IId

其中R_{17}和R_{18}独立地是氢原子或卤素；

J_1是S或NH；

J_2是CH或N；且

R_2是氢原子、烷基、羧基、烷氧羰基或氨基甲酰基。

18. 权利要求12所述的化合物，其中L_1和L_2独立地是亚甲基、亚乙基、亚丙基或亚丁基；R_1、R_{1a}、R_2、R_{2a}独立地是氢原子、烷基、烷氧基烷基、氨基烷基、氨基烷基烷氧基、羧基、烷氧羰基或氨基甲酰基；Cy_1杂芳基、硫杂杂芳基、联杂芳基、噻吩基、异噁唑基、异噁唑基-噻吩基或氮杂杂芳基，其未被取代或被卤素取代；Cy_2是氮杂杂芳基、喹唑啉、氨基-喹唑啉或4-氨基喹唑啉。

19. 权利要求1所述的化合物，其选自：

5-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯，

6-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯，

3-(5-氯-噻吩-2-基)-3-氧代-丙酸叔丁基酯，

甲基-6-氯-苯并呋喃甲酸酯，

2-环戊基-3-氧代-哌嗪-1-甲酸苄酯，

(+/-)-顺式-4-苄氧基羰基-十氢喹喔啉-2-酮,

5-甲基-3-氧代-2-丙基-哌嗪-1-甲酸叔丁酯,

4-[4-氨基-喹唑啉-7-基甲基]-5-甲基-3-氧代-2-丙基-哌嗪,

(R)-3-甲氧基甲基-5-氧代-哌嗪-1-甲酸烯丙基酯,

6-异丙基-哌嗪-2-酮,

9-(4-氨基喹唑啉-7-基甲基)-6,9-二氮杂-螺[4,5]癸-10-酮,

(+/-)-顺式-4-苄氧基羰基-十氢喹喔啉-2-酮,

(+/-)-顺式-1-(4-氨基-喹唑啉-7-基甲基)-十氢喹喔啉-2-酮,

(+/-)-反式-4-苄氧基羰基-十氢喹喔啉-2-酮,

(+/-)-反式-1-(4-氨基-喹唑啉-7-基甲基)-十氢喹喔啉-2-酮,

4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(R/S)1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-氧代-哌嗪-2-甲酸乙酯,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-八氢-喹喔啉-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-哌嗪-2-酮,

[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-(S)-基]-乙酸,

[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-(S)-基]-乙酸叔丁基酯,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸(2-吡咯烷基-1-基-乙基)-酰胺,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代哌嗪-2-甲酸2-吡咯烷基-1-基-乙基酯,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(s)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-磺酸(4氯-苯基)-酰胺,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸2-咪唑-1-基-乙基酯,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸2-吗啉-4-基-乙基酯,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸吡咯烷基-2-基甲基酯,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-

磺酰基)-6-氧代-哌嗪-2-甲酸2-甲基氨基-乙基酯,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(2-氯-咪唑并[1,2-a]吡啶-7-基甲基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3(S)-(2-甲硫基-乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-噻吩并[2,3-b]吡啶-2-基甲基)-(S)-3-丙基-哌嗪-2-酮,

2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代(S)-2-丙基-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-基甲基)-3(S)-丙基-哌嗪-2-酮,

9-(4-氨基-喹唑啉-7-基甲基)-6-[3-(5-氯-噻吩-2-基)-烯丙基]-6,9-二氮杂-螺[4.5]癸烷-10-酮,

(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-八氢-喹喔啉-2-酮,

(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-八氢-喹喔啉-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3(S)-异丁基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-

3(S)-异丁基-哌嗪-2-酮,

3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基甲基]-苯甲腈,

(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-八氢-喹喔啉-2-酮,

(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-八氢-喹喔啉-2-酮,

(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-八氢-喹喔啉-2-酮,

2-[4-(4-氨基-喹唑啉-7-基甲基)-1-(7-氯-异喹啉-3-基甲基)-3-氧代-哌嗪基-2-(S)-基]-N-甲基-乙酰胺,

2-[4-(4-氨基-喹唑啉-7-基甲基)-1-(7-氯-异喹啉-3-基甲基)-3-氧代-哌嗪基-2-(S)-基]-乙酰胺,

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-3-氧代-哌嗪基-2-(S)-基}-乙酰胺,

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-3-氧代-哌嗪基-2-(S)-基}-N-甲基-乙酰胺,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3(S)-异丁基-哌嗪-2-酮,

(s)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-甲氧基甲基哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(4-氨基-噻吩并[3,2-d]嘧啶-6-基甲基)-3(S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-4-(4-嘧啶-4-基-苄基)-哌嗪-2-酮,

4-[4-(2-氨基-嘧啶-4-基)-苄基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮,

3-氨基-5-[4-(4-氨基-喹唑啉-7-基甲基)-2(S)-甲氧基甲基-3-氧代-哌嗪-1-基甲基]-噻吩-2-甲腈,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮,

3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-苯甲腈,

3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代丙烯基}-苯甲脒,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-羟基-苯基)-丙烯酰基]-(3S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-丙烯酰基]-(3S)-丙基-哌嗪-2-酮,

1-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(5-氯-噻吩-2-基)-丙烷-1,3-二酮,

1-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(5-氯-噻吩-2-基)-2-氟-丙烷-1,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(S)-(2-甲亚磺酰基-乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(S)-(2-甲磺酰基-乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-二甲基氨基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并-[b]噻吩-2-羰基)-(3S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-2-甲基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-丙基哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-羰基)-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-羰基)-

3(S)-(2-甲硫基乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯苯并[b]-噻吩-2-羰基)-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并[b]-噻吩-2-羰基)-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]-噻吩-2-羰基)-(S)-6-甲基(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并呋喃-2-羰基)-3(S)-丙基-哌嗪-2-酮,

3-{2-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-基]-2-氧代乙基}-苯甲腈,

3-{2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-2-氧代-乙基}-苯甲腈,

4-[3-(4-氨基-环己基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-羰基)-3(S)-丙基-哌嗪-2-酮三氟乙酸酯,

1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(3-氯-苯基)-丙烷-1,3-二酮,

4-[(5-氨基-吡啶-2-基氧基)-乙酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(S)-3-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(R)-甲氧基甲基-哌嗪-2-酮,

3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-3-氧代-丙基}-苯甲腈,

3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代丙基}-苯甲腈,

1-(4-氨基-喹唑啉-7-基甲基)-4-(4-咪唑-1-基-苯甲酰基)-3(S)-丙基-哌嗪-2-酮,

(6-{2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-甲氧基甲基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-吡啶-3-基)-氨基甲酸叔丁酯,

(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]八氢-喹喔啉-2-酮,

(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-八氢-喹喔啉-2-酮,

(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-八氢-喹喔啉-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-6-氧代-1,6-二氢-吡啶-3-基)-丙烯酰基]-(S)-3-丙基-哌嗪-2-酮,

1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(4-羟基-苯基)-丙烷-1,3-二酮,

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-氧代-哌嗪基-2(S)-基}-乙酰胺,

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-氧代-哌嗪基-2(S)-基}-乙酰胺,

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-氧代-哌嗪基-2(S)-基}-乙酰胺,

{4-(4-氨基-喹唑啉-7-基甲基)-1-[(5-氯-噻吩-2-基氧基)-乙酰

基]-3-氧代-哌嗪基-2-(S)-基}-乙酸甲基酯，

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-氧代-哌嗪基-2-(S)-基}-N-甲基-乙酰胺，

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-氧代-哌嗪基-2(S)-基}-N-甲基-乙酰胺，

2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-氧代-哌嗪基-2(S)-基}-N-甲基-乙酰胺，

4-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代丙烯基}-苯磺酰胺，

N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代丙基}-吡啶-2-基)-乙酰胺，

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氨基-[1,3,4]噻二唑-2-基硫基)-乙酰基]-(S)-3-丙基-哌嗪-2-酮，

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氨基-[1,3,4]噻二唑-2-基硫基)-乙酰基]-(S)-3甲氧基甲基-哌嗪-2-酮，

3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-羰基]-苯甲腈，

1-(4-氨基-喹唑啉-7-基甲基)-4-[(吡啶基-3-基氧基)-乙酰基]-哌嗪-2-酮，

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-4-羟基-苯基)-(E)-丙烯酰基]-(3S)-甲氧基甲基-哌嗪-2-酮，

(3S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-羟基-萘-2-羰基)-3-丙基-哌嗪-2-酮，

(3S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-羟基-1H-吲哚-2-羰基)-3-丙基-哌嗪-2-酮，

1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-羟基-苯氧基)-乙酰基]-(3S)-甲氧基甲基哌嗪-2-酮，

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-羟基-苯基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮，

N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-(S)-丙基-哌嗪-1-基]-3-氧代-丙烯基}-吡啶-2-基)-乙酰胺,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-嘧吩-2-基氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-嘧吩-2-基氧基)-乙酰基]-3,6-双-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-嘧吩-2-基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(S)-2-丙基-哌嗪-1-基]-N-(5-氯-嘧吩-2-基)-2-氧代-乙酰胺,

2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-N-(5-氯-嘧吩-2-基)-2-氧代-乙酰胺,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-嘧吩-3-基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-嘧吩-2-基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-甲氧基甲基-3-氧代-哌嗪-1-基]-N-(5-氯-嘧吩-2-基)-2-氧代-乙酰胺,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-嘧吩-2-基氧基)-乙酰基]-6-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3,4-二羟基-苯基)-(E)-丙烯酰基]-(3S)-甲氧基甲基-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙酰基]-1-(4-氨基-喹唑啉-7-基甲

基)-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-(S)-羟基甲基-哌嗪-2-酮,

N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-丁基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-6-甲基-吡啶-2-基)-乙酰胺,

N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-丁基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-吡啶-2-基)-乙酰胺,

4-[3-(6-氨基-2-甲基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-丁基-哌嗪-2-酮,

1-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-3-(5-氯-噻吩-2-基)-丙烷-1,3-二酮,

4-[3-(3-氨基-4-氯-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮,

4-[3-(3-氨基-5-氯-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯亚磺酰基)-乙酰基]-(3-S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-羟基-苯氧基)-乙酰基]-(3S)-甲氧基甲基哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯基硫基)-乙酰基]-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯亚磺酰基)-乙酰基]-(3S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-羟基-苯基)-(E)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-羟基-苯基)-(E)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-羟基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-羟基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3,6-双甲氧基甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-甲氧基甲基-哌嗪-2-酮,

4-[(6-氨基-嘧啶-4-基氧基)-乙酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯磺酰基)-乙酰基]-哌嗪-2-酮,

1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-3-(4-氯-苯基)-丙烷-1,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯基硫基)-乙酰基]-哌嗪-2-酮,

4-[3-(6-氨基-2-甲基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-3-羟基-丙烯酰基]-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-二甲基氨基-苯基)-丙烯酰基]-3(S)-丙基-哌嗪-2-酮,

3-(S)-6-(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-羟基甲基-3-甲氧基甲基-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基

甲基)-3(S)-异丁基-哌嗪-2-酮,

4-[3-(2-氨基-嘧啶-5-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-羟基-苯基)-丙烯酰基]-(3S)-丙基哌嗪-2-酮,

4-[3-(3-氨基-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮,

4-[3-(4-氨基-3-氯-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡嗪-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡嗪-2-基氧基)-乙酰基]-3(S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-异丁基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-异丁基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(2-氨基-噻唑-4-基)-乙酰基]-3(S)-丙基-哌嗪-2-酮,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸乙酯,

4-[3-(4-氨基-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(3,4-二氯-噻吩-2-基氧基)-乙酰基]-3(S)-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[(3,4-二氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮,

4-(4-氨基-喹唑啉-7-基甲基)-(S)-5-甲基-3-氧代-(S)-2-丙基-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-(S)-5-甲基-3-氧代-(S)-2-丙基-哌嗪-1-甲酸(5-氯-噻吩-2-基)酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-2(S)-异丁基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-羟基甲基-3-氧代-哌嗪-1-甲酸(4氯-苯基)-酰胺,

(2S)-4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-甲酸(5-溴噻唑-2-基)-酰胺,

(2S)-4-(4-氨基-喹唑啉-7-基甲基)-2-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-氯-噻唑-2-基)-酰胺,

(2S)-4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-甲酸(5-氯-噻唑-2-基)-酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4羟基-苯基)-酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲基氨基甲酰基甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-氨基甲酰基甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

(4aRS,8aRS)-4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-八氢-喹喔啉-1-甲酸(4-氯-苯基)-酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-2(S)-(2-甲硫基-乙基)-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-

1-甲酸(5氯-呋喃-2-基)-酰胺,

(2S)-4-(4-氨基-喹唑啉-7-基甲基)-2-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-溴-噻唑-2-基)-酰胺,

N-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(S)-2-丙基-哌嗪-1-羰基]-4-氯-苯磺酰胺,

1-(S)-4-(4-氨基-喹啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

1-(S)-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-丙基-哌嗪-2-酮,

1-(S)-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-4-氧基-3-丙基-哌嗪-2-酮,

1-(S)-4-(4-氨基-喹啉-7-基甲基)-2-甲氧基甲基-3-氧代-2-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

(S)-4-(4-氨基喹啉-7-基甲基)-2-甲氧基1甲基-3-氧代-2-哌嗪-1-甲酸(5氯噻吩-2-基)-酰胺,

1-(S)-4-(4-氨基-喹啉-7-基甲基)-2-甲基-3-氧代-2-哌嗪-1-甲酸苯基酰胺,

1-(S)-4-(4-氨基-喹啉-7-基甲基)-2-甲基-3-氧代-2-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

1-(S)-4-(4-氨基-噌啉-7-基甲基)-2-甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺,

1-(S)-(4-氨基-噌啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-甲基-哌嗪-2-酮,

1-(4-氨基-噌啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-甲基-哌嗪-2-酮,

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-(+)-甲酸甲基酯,

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(-)-甲酸甲基酯,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-(+)-甲酸酰胺,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2(-)-甲酸酰胺,

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-羟基甲基-1-(1-甲基-1H-吡咯并[3,2c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-羟基甲基-1-(1-甲基-1H-吡咯并[3,2c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(5-氯-1H-吲哚-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-(7-甲氧基-萘-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[4-(5-氯-噻吩-2-基)-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-苄基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-3-(S)-丙基-1-(1H-

吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[5-(5-氯-嘧吩-2-基)-吡啶-2-基甲基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶2-基甲基)-哌嗪-2-酮,

4-[2-(4-氯-苯基)-1H-吲哚-3-基甲基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[6-(5-氯-嘧吩-2-基)-吡啶-2-基甲基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶2-基甲基)-哌嗪-2-酮,

4-[4-(5-氯-嘧吩-2-基)-苄基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-[6-(5-氯-嘧吩-2-基)-吡啶-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(5-氯-[2,3']联噻吩基-5'-基甲基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(5'-氯-[2,2']联噻吩基-5-基甲基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[2,2']联噻吩基-5-基甲基-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(5-氯-[2,3']联噻吩基-5'-基甲基)-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[6-(5-氯-嘧吩-2-基)-吡啶-2-基甲基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[3-(5-氯-嘧吩-2-基)-4-氟-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[5-(3-氯-苯基)-呋喃-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[4-(5-氯-嘧吩-2-基)-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[3-(5-氯-嘧吩-2-基)-4-氟-苄基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[4-(5-氯-噻吩-2-基)-苄基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-[5-(3-氯-苯基)-呋喃-2-基甲基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-(5-氯-1H-吲哚-2-基甲基)-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(5'-氯-[2,2']联噻吩基-5-基甲基)-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-[4-(5-氯-噻吩-2-基)-苄基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

1-(4-氨基-2-甲基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮,

7-{4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-2-氧代-(S)-3-丙基-哌嗪-1-基甲基}-3H-喹唑啉-4-酮,

7-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-2-氧代-(S)-3-丙基-哌嗪-1-基甲基1-3H喹唑啉-4-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-烯丙基]-(S)-3-乙基-1-(4-羟基-喹啉-7-基甲基)-哌嗪-2-酮,

7-{4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-2H异喹啉-1-酮,

7-[4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基]-2H异喹啉-1-酮,

4-(5-氯-1H-吲哚-2-基甲基)-1-[4-(6-氧代-1,6-二氢-吡啶-3-

基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-(5-氯-1H-吲哚-2-基甲基)-3-(S)-甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]哌嗪-2-酮,

6-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-3甲基-3H-喹唑啉-4-酮,

6-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-3H喹唑啉-4-酮,

4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮,

4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮,

4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-甲基-哌嗪-2-酮,

4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2-酮,

4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲氧基甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)苄基]-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙酰基]-3-(S)-甲氧基甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮,

(S)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-甲氧基甲基-1-[4-(6-甲氧基-吡啶-3-基)苄基]-哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-异丁基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-(3-咪唑-1-基-苄基)-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-异丁基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-3(S)-异丁基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮,

4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[(5-氯-噻吩-3-基氧基)-乙酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮,

4-[(5-氯-噻吩-3-基氧基)-乙酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基哌嗪-2-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4-甲基-噻唑-5-甲酸甲基酰胺,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4-甲基-噻唑-5羧酸二甲基酰胺,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-吡啶-4-基-噻唑-2-基甲

基)-哌嗪-2-酮氢溴酸盐,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸酰胺,

{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸甲基酯,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸乙酯,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4-甲基-噻唑-5-甲酸甲基酯,

1-(4-叔丁基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(5-氯-噻吩-2-基)-噻唑-2-基甲基]-哌嗪-2-酮,

1-[4-(4-溴-苯基)-噻唑-2-基甲基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮,

1-[4-(3-溴-苯基)-噻唑-2-基甲基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-甲基-噻唑-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-吡啶-3-基-噻唑-2-基甲基)-哌嗪-2-酮,

1-(5-乙酰基-4-甲基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮,

3-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-3-甲基-丁酸 乙基酯,

1-(4-金刚烷-1-基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮,

1-(4-金刚烷-1-基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-苯基-噻唑-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(4-羟基=-苯基)-噻唑-2-基甲基]哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(4-羟基-苯基)-噻唑-2-基甲基]哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4,5,6,7-四氢-苯并噻唑-2-基甲基)哌嗪-2-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸乙酯,

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-苯甲酸,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(2-羟基-苯基)-噻唑-2-基甲基]哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-吡啶-2-基-噻唑-2-基甲基)-哌嗪-2-酮,

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-苯甲酰胺,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4,5,6,7-四氢-噻唑并[5,4-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(5-甲基-4,5,6,7-四氢-噻唑并[5,4-c]吡啶2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4,5,6,7-四氢-噻唑并[4,5-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(5-甲基-4,5,6,7-四氢-噻唑并[4,5-c]吡啶2-基甲基)-哌嗪-2-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-

4,7-二氢-5H-噻唑并[4,5-c]吡啶-6-酮,

(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸酰胺,

(R)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮,

(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸乙酯,

(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-4-甲基-噻唑-5-甲酸二甲基酰胺,

(R)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(4-吡啶-3-基-噻唑-2-基甲基)-哌嗪-2-酮,

(R)-3-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-基}-3-甲基-丁酸乙基酯,

(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸,

(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺,

(S)-2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-(3S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-4,5,6,7-四氢-苯并噻唑-4-甲酸酰胺,

(S)-2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-(3S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}噻唑-4-甲酸乙酯,

(S)-2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基)-噻唑-4-甲酸二甲基酰胺,

(S)-(2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-噻唑-4-基)-乙酸甲基酯,

(S)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-1-(4,5,6,7-四氢苯并噻唑-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-羟基-4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮肟,

1-(4-氨基-苯并噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-5,6,7,8-四氢-噻唑并[4,5-c]氮杂环庚三烯4-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(吡咯烷-1-羰基)-噻唑-2-基甲基]-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(吗啉-4-羰基)-噻唑-2-基甲基]-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(哌嗪-1-羰基)-噻唑-2-基甲基]-哌嗪-2-酮,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸N',N'-二甲基-肼,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸(2-羟基-乙基)-甲基-酰胺,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(3-羟基-吡咯烷-1-羰基)-噻唑-2-基甲基]-哌嗪-2-酮,

2-(4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸甲氧基-甲基-酰胺,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸异丙基-甲基-酰胺,

({2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-羰基}-甲基-氨基)-乙酸乙基酯,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酰胺,

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-

噻唑-4-甲酸甲基酰胺，

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸异丙基酰胺，

{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸，

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酰胺，

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-N-甲基-乙酰胺，

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-N-异丙基-乙酰胺，

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-N,N二甲基-乙酰胺，

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,7-二氢-5H-噻唑并[5,4-c]吡啶-6-酮，

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-哌啶基-4-基甲基-哌嗪-2-酮，

4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-哌啶-1-甲酸酰胺，

2-{4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-哌啶基-1-基}乙酰胺，

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-(2-氯-嘧啶-4-基)-哌啶基-4-基甲基]-哌嗪-2-酮，

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-哌嗪-2-酮，

(R)-4-(5-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-哌嗪-2-酮，

(R)-4-(6-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-哌嗪-2-酮，

(R)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-哌嗪-2-酮,

(R)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-甲基-哌嗪-2-酮,

(R)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-甲氧基甲基-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-氧代-哌嗪-2-甲酸甲基酯,

(R)-4-(5-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-甲基-哌嗪-2-酮,

(R)-4-(5-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-甲氧基甲基-哌嗪-2-酮,

4-(5-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-氧代-哌嗪-2-甲酸甲基酯,

(R)-4-(6-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-甲基-哌嗪-2-酮,

(R)-4-(6-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-甲氧基甲基-哌嗪-2-酮,

4-(6-氯-1H-吲哚-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-氧代-哌嗪-2-甲酸甲基酯,

(R)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-甲基-哌嗪-2-酮,

(R)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基4-基甲基]-6-甲氧基甲基-哌嗪-2-酮,

4-(6-氯-1H-苯并咪唑-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)-哌啶基-4-基甲基]-6-氧代-哌嗪-2-甲酸甲基酯,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-{1-[2-(2-羟基-乙基氨基)-嘧啶-4-基]哌啶基-4-基甲基}-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-{1-[2-(4-二甲基氨基-丁基

氨基)-嘧啶-4-基]哌啶基-4-基甲基}-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-{1-[2-(3-咪唑-1-基-丙基氨基)-嘧啶-4-基]-哌啶基-4-基甲基}-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-[2-(3-吗啉-4-基-丙基氨基)-嘧啶-4-基]-哌啶基-4-基甲基}-哌嗪-2-酮,

4-[(4-{4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-哌啶基-1-基}-嘧啶-2-基)-甲基-氨基]-丁酸,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-{1-[2-(2-二甲基氨基-乙氧基)-嘧啶-4-基]哌啶基-4-基甲基}-哌嗪-2-酮,

实施例1270 4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1-[2-[2-(2-氧代-咪唑烷-1-基)乙基氨基]-嘧啶-4-基}-哌啶基-4-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-{1-[2-(2-二甲基氨基-乙基硫基)-嘧啶-4-基]-哌啶基-4-基甲基}-哌嗪-2-酮,

4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-3,4,5,6-四氢-2H-[1,2']联吡啶基-5'-甲酸,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1-嘧啶-2-基-哌啶基-4-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1-吡嗪-2-基-哌啶基-4-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(3,4,5,6-四氢-2H-[1,2']联吡啶基-4-基甲基)哌嗪-2-酮,

4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-3,4,5,6-四氢2H-[1,2']联吡啶基-3'-甲酸,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(6'-甲氧基-3,4,5,6-四氢-2H-[1,2']联吡啶基-4-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-磺酰基)-1-(6-'甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶基-4-基甲基)-哌嗪-2-酮,

O-苯基-1-氰基-3-{4-[(氯苯并[b]噻吩-2-磺酰基)-2-(酮基)哌

嗪-1-基]甲基哌啶基}异脲,

制备N,N-二甲基-2-{4-[6-(氯苯并[b]噻吩-2-磺酰基)-2-(酮基)哌嗪-1-基]甲基哌啶-1-基]}氧基甲脒,

制备N-甲基-2-{4-[6-(氯苯并[b]噻吩-2-磺酰基)-2-(酮基)哌嗪-1-基]甲基哌啶-1-基]}氧基甲脒,

制备N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-氧基胍,

N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-N',N'-二甲基-氧基胍,

N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-N'-甲基-氧基胍,

N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-N'-(2-羟基乙基)-N'-甲基-氧基胍,

制备4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-(4-吗啉-4-基-环己基甲基)-哌嗪-2-酮,

和4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-(4-吗啉-4-基-环己基甲基)-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-{4-[(2-羟基-乙基)-甲基-1-氨基]环己基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-[4-[2-(R,S)-(1-甲基吡咯烷基-2-基)-乙基氨基]-环己基甲基}-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-{4-[2-(R,S)-(1-甲基吡咯烷基-2-基)-乙基氨基]-环己基甲基}-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-[4-(2-吡啶-2-基-乙基氨基)-环己基甲基]-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-[4-(2-吡啶-2-基-乙基氨基)-环己基甲基]-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-顺式-[4-(2-二甲基氨基-乙基氨基)-环己基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-[4-(2-二甲基氨基-乙基氨基)环己基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-(4-顺式-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-哌嗪-1-甲酸乙酯,

4-(4-反式-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-哌嗪-1-甲酸乙酯,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-顺式-([4-(4-羟基-哌啶基-1-基)-环己基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-([4-(4-羟基-哌啶基-1-基)-环己基甲基]3-(S)-甲氧基甲基-哌嗪-2-酮,

1-顺式-(4-氮杂环庚烷-1-基-环己基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

1-反式-(4-氮杂环庚烷-1-基-环己基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-{4-[(吡啶-2-基甲基)氨基]-环己基甲基}-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-{4-[(吡啶-2-基甲基)氨基]-环己基甲基}-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-(4-苯基氨基-环己基甲基)-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-(4-苯基氨基环己基甲基)-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-顺式-{4-[2-(2-羟基-乙氧基)-乙基氨基]环己基甲基}-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-{4-[2-(2-羟基-乙氧基)-乙基氨基]环己基甲基}-3-(S)-甲氧基甲基-哌嗪-2-酮,

4-[(5-氯噻吩-2-基氧基)-乙酰基]-1-[(2-{[N,N-二甲基氨基乙

基]-氨基}-嘧啶-5-基)甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-烯丙基]-哌嗪-2,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基-甲基)-哌嗪-2,3-二酮,

1-(4-氨基-喹啉-7-基甲基)-4-(3-(4-氯-苯基)-烯丙基]-哌嗪-2,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩基-5-基甲基)-哌嗪-2,3-酮,

1-(3-亚氨基氨基甲酰基-苄基)-4-(4-亚氨基氨基甲酰基-苄基)-2,3-二氧代哌嗪,

双-1,4-(3-亚氨基氨基甲酰基-苄基)-2,3-二氧代哌嗪,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-烯丙基]-哌嗪-2,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮,

1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基-甲基)-哌嗪-2,3-二酮,

1-(4-氨基-喹啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩基-5-基甲基)-哌嗪-2,3-二酮,

1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮,

1-[3-(3-氯-苯基)-烯丙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮,

1-[3-(4-氯-苯基)-烯丙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮,

1-(6-氯-苯并[b]噻吩-2-基-甲基)-4-(1H-吡咯并[3,2-c]吡啶-

2-基甲基)-哌嗪2,3-二酮,

1-(5'-氯-[2,2']联噻吩基-5-基甲基)-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(1H-吡咯并[2,3-c]吡啶-2-基甲基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(噻吩并[3,2-b]吡啶-2-基甲基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-2-基-苄基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(1-羟基-吡啶-2-基)-苄基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-4-基-苄基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(1-羟基-吡啶-4-基)-苄基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(2-二甲基氨基-嘧啶-4-基)-苄基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-{2-[(2-二甲基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-苄基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(2-二甲基氨基-嘧啶-4-基)-环己基甲基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-{2-[(2-二甲基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-环己基甲基)-哌嗪-2,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-甲基-哌嗪-2,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-乙基-哌嗪-2,3-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-丙基-哌嗪-2,3-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-丁基-哌嗪-2,3-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-异丙基-哌嗪-2,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-异丁基-哌嗪-2,3-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-甲氧基甲基-哌嗪-2,3-二酮,

4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2羧酸,

4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2-甲酸甲基酯,

4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2羧酸酰胺, 或

4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2-甲酸甲基酰胺,

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

20. 权利要求1所述的化合物, 其选自:

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸(2-吡咯烷基-1-基-乙基)-酰胺,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-(S)-基]-乙酸,

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

2-氨基-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-(r)-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(R/S)1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-氧代-哌嗪-2-甲酸乙酯,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺

酰基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-6-氯-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲基-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮,

(R/S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酯,

(R/S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酯,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(3-溴-5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(3,5-二氯-1H-吲哚-2-基甲基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-吡咯烷基-1-基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-吗啉-4-基甲基-1H-吲哚-2-基甲基)哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-甲基氨基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-二甲基氨基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮,

(S)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈,

(S)-4-[4-(5-氯-1H-吲哚-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈,

(S)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈,

(S)-4-[4-(6-氯-1H-吲哚-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-异丁基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-甲氧基甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-异丁基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-6-甲氧基甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基

甲基)-6-甲氧基甲基-哌嗪-2-酮,

(6S)-2-(1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-异吲哚-1,3-二酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-6-异丁基哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-吗啉-4-基甲基-哌嗪-2-酮,

(6S)-6-氨基甲基-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)哌嗪-2-酮,

(6S)-N-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-乙酰胺,

4-(3-乙酰基-5-氯-1H-吲哚-2-基甲基)-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-吡咯烷基-1-基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸,

(2S)-N-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-甲磺酰胺,

(2S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-氨基甲酸甲基酯,

(2S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-氨基甲酸异丙基酯,

(2S)-1-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-3-苯基-脲,

(2S)-5-溴-噻吩-2-磺酸[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-酰胺,

(2S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-脲,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-(异丙基氨基-甲基)-哌嗪-2-酮,

(2S)-1-(1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-3-乙基-脲,

(2S)-N-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-甲酰胺,

(2S)-呋喃-2-甲酸[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基甲基]-酰胺,

(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基-2-基]-乙酸,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-甲基-1H-吲哚-2-基甲基)-3-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-氟-1H-吲哚-2-基甲基)-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(3,5-二氯-1H-吲哚-2-基甲基)-3-甲氧基甲基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-(异丙基氨基-甲基)-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-(异丙基氨基-甲基)-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-吡咯烷基-1-基甲基-哌嗪-2-酮,

(6R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-甲氧基甲基-哌嗪-2-酮,

(2R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪基-2-基甲基}-N-(2-异丙氧基-乙基)-甲酰胺,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[(2-异丙氧基 乙基氨基)-甲基]-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-哌啶基-1-基甲基-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-[(环戊基-甲基-氨基)-甲基]-哌嗪-2-酮,

(6R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-乙氧基甲基-哌嗪-2-酮, 或

(6R)-1-(4-氨基-喹唑啉-7-基甲基)-6-苄氧基甲基-4-[5-(5-氯-噻吩-2-基)异噁唑-3-基甲基]-哌嗪-2-酮, 或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

21. 权利要求1所述的化合物, 其选自:

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代哌嗪-2-甲酸2-吡咯烷基-1-基-乙基酯,

[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-(S)-基]-乙酸叔丁基酯,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6(异丙基氨基-甲基)-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺

酰基)-6-异丁基-哌嗪-2-酮,

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-甲基-哌嗪-1-基甲基)-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-{[(2-二甲基-氨基-乙基)-甲基-氨基]-甲基}-哌嗪-2-酮,

(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-吡咯烷基-1-基甲基-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-(异丙基氨基-甲基)-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-(异丙基氨基-甲基)-哌嗪-2-酮,

(2R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪基-2-基甲基}-N-(2-异丙氧基-乙基)-甲脒,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6[([1,3]二氧杂环戊烷-2-基甲基-甲基-氨基)-甲基]-哌嗪-2-酮,

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-吡咯烷基-1-基-哌啶基-1-基甲基)-哌嗪-2-酮, 或

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[(2甲氧基-乙基氨基)-甲基]-哌嗪-2-酮, 或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

22. 权利要求1的化合物, 其选自:

1-[4-(2-氯-嘧啶-4-基)-苄基]-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[4-(5-氯-噻吩-2-基)-苄基]-哌嗪-2,3-二酮,

1-[4-(5-氯-噻吩-2-基)-苄基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-酮,

1-(4-氨基-喹啉-7-基甲基)-4-[4-(5-氯-噻吩-2-基)-苄基]-哌嗪-2,3-二酮,

1-[1-(2-氯-嘧啶-4-基)-哌啶基-4-基甲基]-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-5-(S)-异丙基-4-(3,4,5,6-四氢-2H-[1,4']联吡啶基-4-基甲基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(3,4,5,6-四氢-2H-[1,4']联吡啶基-4-基甲基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-3-基-苄基)-哌嗪-2,3-二酮,

1-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-4-(4-吡啶-4-基-苄基)-哌嗪-2,3-二酮,

1-[4-(6-氨基-吡啶-3-基)-苄基]-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(1-氧基-吡啶-3-基)-苄基]-哌嗪-2,3-二酮,

1-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-5-(S)-异丙基-4-(3,4,5,6-四氢-2H-[1,4']联吡啶基-4-基甲基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-5-(S)-异丙基-4-(4-嘧啶-4-基-苄基)-哌嗪-2,3-二酮,

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-嘧啶-4-基-苄基)-哌嗪-2,3-二酮, 或

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-哌嗪2,3-二酮, 或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

23. 权利要求1所述的化合物, 其选自:

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-

磺酰基)-6-氧代-哌嗪-2-甲酸;

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酯;

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸乙酯;

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-氧代-哌嗪-2-甲酸2-吡咯烷基-1-基-乙基酯;

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-氧代哌嗪-2-甲酸2-吡咯烷基-1-基-乙基酰胺;

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酯;

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酯;

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酯;

(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-基]乙酸;

(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-基]乙酸叔丁基酯;

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基-哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基-哌嗪-2-酮;

酰基)-6-异丙基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基氨基甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

基)-6-甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲基-哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮;

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮;

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(3,4,5,6-四氢-2H-[1,2']联吡啶基-4-基甲基)-哌嗪-2-酮;

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-(2-二甲基氨基-嘧啶-4-基)哌啶基-4-基甲基]-哌嗪-2-酮;

N,N-二甲基-N4{[(氯苯并[b]噻吩-2-磺酰基)-2-(酮基)哌嗪-1-基]甲基哌啶基]}氨基胍;

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-{1-[2-(2-羟基-乙基氨基)-嘧啶-4-基]-哌啶基-4-基甲基}-哌嗪-2-酮;

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[1-嘧啶-4-基)-哌啶基-4-基甲基]-哌嗪-2-酮;

3-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-3-甲基-丁酸乙基酯;

(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸酰胺;

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸乙酯;

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮;

(R)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(4-吡啶-3-基噻唑-2-基甲基)-哌嗪-2-酮;

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-羟基-4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮;

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸异丙基-甲基-酰胺;

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,5,6,7四氢-苯并噻唑-4-甲酸酰胺;

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮肟;

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-

噻唑-4-甲酸甲氧基-甲基-酰胺；

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢5H-苯并噻唑-4-酮；

(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺；

1-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-甲酸甲基酯；

1-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-甲酸甲基酯；

1-(6-氯-苯并[b]噻吩-2-磺酰基)-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-甲酸甲基酯；

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-羟基甲基-1-(1-甲基-1H-吡咯并[3,2c]吡啶-2-基甲基)-哌嗪-2-酮；

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-甲酸甲基酯；

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶2-基甲基)-哌嗪-2-酮；和

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮；

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

24. 权利要求1所述的化合物，其选自：

1-(4-氨基喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-3-(S)丙基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-

3-基甲基]-3-(S)-甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-3-甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]-3-(S)-甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐)，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(3-氯-苯基)-4H-[1,2,4]三唑-3-基甲基]-(s)-3甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(3-氯-苯基)-4H-[1,2,4]三唑-3-基-甲基]-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(4-氯-苯基)-4H-[1,2,4]三唑-3-基-甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基-[1,3,4]噁二唑-2-基甲基]-(s)-3-甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-(s)3-甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-

[1,2,4]三唑-3-基甲基]-(s)3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基-[1,3,4]噁二唑-2-基甲基]哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(4-氯-苯基)-4H-[1,2,4]三唑-3-基-甲基]-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基-[1,3,4]噻二唑-2-基甲基]哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-甲基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-丙基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-乙基-哌嗪-2-酮二-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-哌嗪-2-酮三-三氟乙酸盐，

1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-吡啶-5-基-甲基]-哌嗪-2-酮三-三氟乙酸盐，

4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐，

4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐，

[5-(5-氯-噻吩-2-基)-[1,3,4]噁二唑-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮，

4-[5-(5-氯-噻吩-2-基)-噁唑-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮二-三氟乙酸盐，

4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-2-基甲基]-1-(1H-吡

咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐,

4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮二-三氟乙酸盐,或

1-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮二-三氟乙酸盐或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

25. 权利要求6的化合物,其选自:

4-(6-氯苯并[b]噻吩-2-磺酰基)-6-(R)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-(6-氯-噻吩并[2,3-b]吡啶-2-磺酰基)-6-(R)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶2-基甲基)-哌嗪-2-酮,

4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(S)-异丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-(S)-异丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-(5-氯-1H-吲哚-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮,

4-[4-(5-氯-噻吩-2-基)-苄基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-苄基]-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-4-[4-(5-氯-噻吩-2-基)-苄基]-哌嗪-2-酮，

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(7-甲基-1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮，或

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-(7-甲基-1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮，

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

26. 药物组合物，其中含有药学有效量的权利要求1所述的化合物以及药用载体。

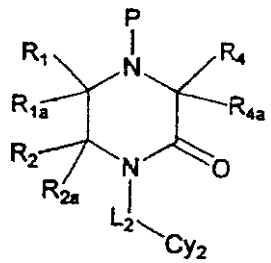
27. 对能通过抑制因子Xa活性调节的生理机能病症患者的治疗方法，其中包括给所述患者使用药学有效量的权利要求1所述的化合物。

28. 对能通过直接抑制因子Xa和因子IIa调节的生理机能病症患者的治疗方法，其中包括给所述患者使用药学有效量的权利要求21和23所述的化合物。

29. 对能通过直接抑制因子Xa和因子IIa调节的生理机能病症患者的治疗方法，其中包括给所述患者使用药学有效量的权利要求16所述的化合物。

30. 对能通过直接抑制因子Xa和因子IIa调节的生理机能病症患者的治疗方法，其中包括给所述患者使用药学有效量的权利要求17所述的化合物。

31. 式III的化合物

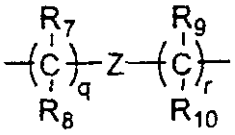


III

其中P是H或氮原子保护基；

R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基，或R_1和R_{1a}、R_2和R_{2a}或R_4和R_{4a}一起形成O或S；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或者R_1和R_{1a}与它们连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与它们连接的碳原子一起形成3至7元环烷基或环烯基；

L_2不存在或是下式基团



Cy_2选自任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基和任选地被取代的稠合的杂芳基杂环烯基；

R_5是氢原子、任选地被取代的烷基、任选地被取代的芳烷基、任选地被取代的杂芳烷基、$R_6O(CH_2)_v-$、$R_6O_2C(CH_2)_x-$、$Y_1Y_2NC(O)(CH_2)_x-$或$Y_1Y_2N(CH_2)_v-$；

R_6是氢原子、任选地被取代的烷基、任选地被取代的芳烷基或任选地被取代的杂芳烷基；

Y_1和Y_2独立地是氢原子、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基或任选地被取代的杂芳烷基，或Y_1和Y_2与Y_1和Y_2所连接的氮原子一起形成单环杂环基；

R_7、R_8、R_9和R_{10}独立地选自氢原子、羟基、烷氧基、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的芳烷基和任选地被取代的杂芳烷基，其条件是R_7和R_8中只有一个或R_9和R_{10}中只有一个是羟基或烷氧基，且另一个条件是当R_7、R_8、R_9和R_{10}是羟基或烷氧基时，则此羟基或烷氧基对于Z中的N、O或S而言不是α-取代的；

Z不存在或选自任选地被取代的低级亚烯基、任选地被取代的低级亚炔基、O、$S(O)_p$、-C(O)-、NR_5、$-NR_5C(O)-$和$-C(O)NR_5-$；

x是1、2、 3或4；

v是2、3或4；而

q和r独立地是0、1、2或3，其条件是q和r 不都是0，

条件是当R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基时，最则L_2不存在，

或当R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a}独立地是$Y_1Y_2NC(O)-$时，则Y_1和Y_2独立地是氢原子、任选地被取代的烷氧基或任选地被取代的芳氧基，但Y_1和Y_2不同时是氢原子，

或当R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基时，则Z是C(O)-。

取代的氧代氮杂杂环基化合物

发明领域

本发明涉及抑制因子Xa的氧代氮杂杂环基化合物，涉及含有这些化合物的药物组合物，涉及用于制备这些化合物的中间体并涉及抑制因子Xa的方法。本发明还涉及既抑制因子Xa又抑制因子IIa(凝血酶)的化合物，涉及含有这些化合物的药物组合物，涉及用于制备这些化合物的中间体以及同时直接抑制因子Xa和因子IIa(凝血酶)的方法。

发明背景

因子Xa和在凝血激酶复合物(因子Xa、因子Va、钙离子和磷脂)中装配的因子Xa激活凝血酶原(因子II)产生凝血酶(因子IIa)。因子Xa颇策略地位于凝血系统的外源和内源路径的交叉点。因此，因子Xa的抑制剂抑制凝血酶的形成，并因此用于预防或治疗与哺乳动物凝血有关的疾病。

静脉和动脉脉管系统的多种血栓形成病症的治疗和预防需要抗凝血药疗法。在动脉系统中，异常的血栓形成主要与冠状动脉、脑动脉和外周动脉有关。与这些血管栓塞性阻塞有关的疾病主要包括急性心肌梗塞(AMI)、不稳定性心绞痛、血栓栓塞、与溶解血栓治疗以及经皮冠状动脉成形术(PTCA)、短暂性缺血发作、中风、间歇性跛行和冠状动脉搭桥术(CABG)或外周动脉的搭桥术有关的急性血管闭塞。慢性抗凝血药治疗还可能有益于防止PTCA和CABG后常常发生的动脉腔渐窄(再狭窄)，并有益于维持长期血液透析患者的血管入口开放。对于静脉血管，腹部、膝部和臀部手术后在远端的静脉中常常发生病理性血栓形成(深部静脉血栓栓塞，DVT)。DVT还使患者预先有肺血栓栓塞的较高危险性。系统性、弥漫性血管内凝血(DIC)一般发生在脓毒性休克、某些病毒感染和癌症期间的两种血管系统中。此病症的特征是凝

血因子及其血浆抑制剂的快速消耗，导致在若干器官系统的微血管中威胁生命血块的形成。

除了在抗凝血药治疗中的用途，因子Xa抑制剂用于治疗和预防其它疾病，在这些疾病中凝血酶的产生已被推断为起生理作用。例如，已有人提出凝血酶对慢性和变性疾病如关节炎、癌症、动脉粥样硬化和早老性痴呆的发病率和死亡率有关，这是凭借其通过细胞表面凝血酶受体的特异性裂解和激活来调节多种不同细胞类型、致有丝分裂作用、不同的细胞功能如细胞增殖(例如，血管细胞的异常增殖导致再狭窄或血管生成)、释放PDGF和DNA合成的能力。抑制因子Xa会有效地阻断凝血酶的产生并因此中和凝血酶对多种细胞类型的任何生理作用。

上述代表性指征包括一些，但不是所有的应用因子Xa抑制剂治疗的可能的临床情形。

氧代氮杂杂环基因子Xa抑制剂公开于国际专利申请PCT/US98/07158，出版于1998年10月22日；PCT/US98/07159，出版于1998年10月22日；PCT/US98/07160，出版于1998年10月22日；PCT/US98/07161，出版于1998年10月22日；和PCT/US96/09290，出版于1996年12月19日。氧代氮杂杂环基纤维蛋白原拮抗剂公开于国际专利申请PCT/US92/09467，出版于1993年5月13日。

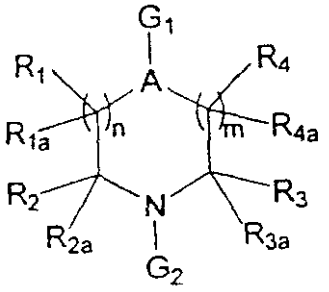
生化或物理紊乱引起的血管损伤，导致凝血系统的激活，最后产生凝血酶。凝血酶通过催化纤维蛋白原转变为纤维蛋白、通过激活凝血因子XIII(其使该血栓稳定)并通过激活血小板促进血栓形成。凝血酶通过对凝血级联的正反馈(激活凝血因子V和VIII)进一步促进血栓生长，导致凝血酶的爆发性生成。在栓塞性血管病患者的血栓中凝血酶存在并激活。凝血酶抑制防止了凝血酶已由凝血酶原激活后的凝血酶作用。凝血酶的抑制剂抑制纤维蛋白原向纤维蛋白的裂解、因子XIIIa的激活、血小板的激活以及向凝血级联发出的产生更多凝血酶的凝血酶反馈。于是，用直接的凝血酶抑制剂抑制凝血酶活性，将有利于预防或治疗与哺乳动物凝血有关的紊乱。

本文描述的因子Xa和因子IIa的联合抑制剂抑制凝血酶活性(通过

IIa抑制)和凝血酶产生(通过因子Xa抑制)。因此，这些制剂抑制可能存在的任何凝血酶，且还抑制凝血酶的进一步产生。具有此双重功能的其它制剂包括肝素和低分子量肝素(LMWHs)，它们在血栓疾病中具有示范性效果。但是，肝素和LMWHs直接通过辅因子、抗凝血酶-III(ATIII)、抑制Xa和IIa起作用。而此肝素/ATIII复合物太大，无法抑制血栓结合的Xa和IIa，因此，限制了其效果。如本文中所述的因子Xa和因子IIa的直接抑制剂，能抑制溶解性和结合血栓的Xa和IIa，因此较目前使用的Xa/IIa抑制剂而言，提供了重要的治疗优点。

发明概述

本发明涉及式I的化合物



I

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中

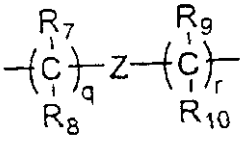
G_1和G_2是L_1-Cy_1或L_2-Cy_2，条件是当R_1和R_{1a}或R_4和R_{4a}一起形成O或S时，则G_1是L_2-Cy_2而G_2是L_1-Cy_1，或当R_2和R_{2a}或R_3和R_{3a}一起形成O或S时，则G_1是L_1-Cy_1而G_2是L_2-Cy_2；

Cy_1和Cy_2独立地选自任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被

取代的稠合的杂芳基杂环基和任选地被取代的稠合的杂芳基杂环烯基；

L_1是不存在、O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$、$-C(O)Y-C(X)Y-$、$-C(X)YC(O)-$、$-C(O)NR_5-S(O)_p-$或$-C(O)C(O)NR_5S(O)_p-$；

L_2不存在或是下式的基团



；

L_3和L_5不存在或独立地是任选地被取代的亚烷基、任选地被取代的亚烯基或任选地被取代的亚炔基；L_4是任选地被取代的亚烷基、任选地被取代的亚烯基或任选地被取代的亚炔基；

Q和Q'独立地不存在、O、S、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$或$-C(X)Y-$；

A是CH或N；

R_1、R_{1a}、R_2、R_{2a}、R_3、R_{3a}、R_4和R_{4a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基，或者R_1和R_{1a}，R_2和R_{2a}，R_3和R_{3a}，或R_4和R_{4a}一起形成O或S；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_3和R_4与R_3和R_4所连接的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或者R_{3a}和R_{4a}不存在而R_3和R_4与R_3和R_4所连接的碳原子一起形成芳基或杂芳基；或一个或多个R_1和R_{1a}对与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_3和R_{3a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

m和n独立地是0、1或2，其条件是m和n不都是0且另一个条件是当R_1和R_{1a}一起形成O或S时，n是1，而当R_4和R_{4a}一起形成O或S时，m是1；

R_5是氢原子、任选地被取代的烷基、任选地被取代的芳烷基、任选地被取代的杂芳烷基、$R_6O(CH_2)_v-$、$R_6O_2C(CH_2)_x-$、$Y_1Y_2NC(O)(CH_2)_x-$或$Y_1Y_2N(CH_2)_v-$；

R_6是氢原子、任选地被取代的烷基、任选地被取代的芳烷基或任选地被取代的杂芳烷基；

Y_1和Y_2独立地是氢原子、任选地被取代的烷基、任选地被取代的烷氧基、任选地被取代的芳氧基、任选地被取代的芳基、任选地被取代的芳烷基或任选地被取代的杂芳烷基，或Y_1和Y_2与Y_1和Y_2所连接的氮原子一起形成单环杂环基；

R_7、R_8、R_9和R_{10}独立地选自氢原子、羟基、烷氧基、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的芳烷基和任选地被取代的杂芳烷基，其条件是R_7和R_8中只有一个或者R_9和R_{10}中只有一个是羟基或烷氧基，且另一个条件是当R_7、R_8、R_9和R_{10}中任何一个是羟基或烷氧基时，则此羟基或烷氧基对Z中的N、O或S而言不是α-取代的；

X是O或S；

Y不存在或选自O、S和NR_5；

Z不存在或选自任选地被取代的低级亚烯基、任选地被取代的低级亚炔基、O、$-C(O)-$、$S(O)_p$、NR_5、$-NR_5C(O)-$和$-C(O)NR_5-$；

x是1、2、 3或4；

v是2、3或4；

p是1或2；而

q和r独立地是0、1、2或3，其条件是q和r 不都是0，

且条件是当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$且R_3和R_3一起形成O或S时，则R_2和R_{2a}独立地选自氢原子、烷基、氨基烷基、烷基氨基烷基、烷氧基、烷氧基烷基、烷氧基氨基烷基、环烷基烷基氨基、苄氧基烷基、异丙基、氨基甲基、甲氧基乙基氨基甲基、哌嗪基、吡咯烷基、乙氧基甲基、苄氧基甲基、甲氧基甲基、异丁基、异丙基氨基或异丙基氨基甲基，其条件是R_2和R_{2a}不都是

氢原子；

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$而R_3和R_{3a}一起形成O或S时，则R_4和R_{4a}一起形成O或S；

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$且R_3和R_{3a}一起形成O或S时，则Cy_1是噻吩-异噁唑、噻吩-吡唑、噻吩-噁二唑、噻吩-噻二唑、噻吩-三唑、噻吩-吡啶或苯基-三唑而Cy_2是氨基喹唑啉或吡咯并-吡啶；

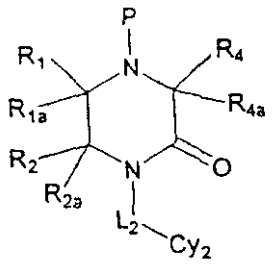
或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$，则R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_3和R_4 与R_3和R_4所连接的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或R_{3a}和R_{4a}不存在且R_3和R_4与R_3和R_4所连接的碳原子一起形成芳基或杂芳基；或一个或多个R_1和R_{1a}对与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_3和R_{3a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$时，则R_1、R_{1a}、R_2、R_{2a}、R_3、R_{3a}、R_4和R_{4a}独立地是$Y_1Y_2NC(O)-$而Y_1和Y_2独立地是氢原子、任选地被取代的烷氧基或任选地被取代的芳氧基，但Y_1和Y_2不同时是氢原子，

或当L_1是O、NR_5、$-S(O)_p-$、$-S(O)_pNR_5-$、$-C(X)Y-$或$-L_3-Q-L_4-Q'-L_5-$时，则Z是$-C(O)$。

另一方面，本发明涉及药物组合物，其中含有治疗有效量的式I或式II化合物以及药用载体。

另一方面，本发明涉及能通过抑制因子Xa调节的生理紊乱的治疗方法，其中包括给需要此治疗的患者使用治疗有效量的式I或式II化合物。

另一方面，本发明涉及式III的化合物

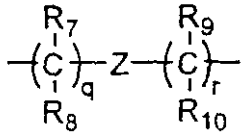


III

其中P是H或氮原子保护基；

R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)-$、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基，或R_1和R_{1a}、R_2和R_{2a}或R_4和R_{4a}一起形成O或S；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或者R_1和R_{1a}与它们连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与它们连接的碳原子一起形成3至7元环烷基或环烯基；

L_2不存在或是下式基团



Cy_2选自任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基和任选地被取代的稠合的杂芳基杂环烯基；

R_5是氢原子、任选地被取代的烷基、任选地被取代的芳烷基、任选地被取代的杂芳烷基、$R_6O(CH_2)_v-$、$R_6O_2C(CH_2)_x-$、$Y_1Y_2NC(O)(CH_2)_x-$或$Y_1Y_2N(CH_2)_v-$；

R_6是氢原子、任选地被取代的烷基、任选地被取代的芳烷基或任选地被取代的杂芳烷基；

Y_1和Y_2独立地是氢原子、任选地被取代的烷基、任选地被取代的烷氧基、任选地被取代的芳氧基、任选地被取代的芳基、任选地被取代的芳烷基或任选地被取代的杂芳烷基，或Y_1和Y_2与Y_1和Y_2所连接的氮原子一起形成单环杂环基；

R_7、R_8、R_9和R_{10}独立地选自氢原子、羟基、烷氧基、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的芳烷基和任选地被取代的杂芳烷基，其条件是R_7和R_8中只有一个或R_9和R_{10}中只有一个是羟基或烷氧基，且另一个条件是当R_7、R_8、R_9和R_{10}是羟基或烷氧基时，则此羟基或烷氧基对于Z中的N、O或S而言不是α-取代的；

Z不存在或选自任选地被取代的低级亚烯基、任选地被取代的低级亚炔基、O、$S(O)_p$、-C(O)-、NR_5、$-NR_5C(O)-$和$-C(O)NR_5-$；

x是1、2、 3或4；

v是2、3或4；而

q和r独立地是0、1、2或3，其条件是q和r 不都是0，

这是制备式I或式II化合物的有用的中间体。

发明详述

定义

如上所用，以及在本发明的整个说明书中，除非另行说明，下列术语应理解为具有以下含义：

“衍生物”指化学修饰的化合物，其中本领域普通化学工作者认为此修饰是常规的，如某种酸的酯或酰胺，保护基如保护醇或硫醇的苄基，以及保护氨基的叔丁氧羰基。

“患者”包括人和其它哺乳动物。

“烷基”指脂族烃基，其可以是直链或支链，所述链中具有约1至约

20碳原子。优选的烷基链中具有1至约12碳原子。支链指一个或多个低级烷基如甲基、乙基或丙基连接直链烷基链。“低级烷基”指链中有约1至约4碳原子，其可以是直链或支链。所述烷基可以取代有一个或多个“烷基的取代基”，它们可以相同或不同，并包括卤素、环烷基、环烯基、杂环基、杂环烯基、羟基、肟、烷硫基、烷基亚磺酰基、烷基磺酰基、芳硫基、芳基亚磺酰基、芳基磺酰基、杂芳基硫基、杂芳基亚磺酰基、杂芳基磺酰基、异脲、胍基、酰肼基、烷氧基、氨基、氨基甲酰基、酰基氨基、芳酰基氨基、羧基、烷氧羰基、芳烷氧羰基和杂芳烷氧羰基。代表性烷基包括甲基、三氟甲基、环丙基甲基、环戊基甲基、乙基、正丙基、异丙基、正丁基、叔丁基、正戊基、3-戊基、甲氧基乙基、羧甲基、甲氧基羰基乙基、苄氧基羰基甲基和吡啶基甲氧羰基甲基。

“链烯基”指直链或支链脂族烃基，其中含有碳碳双键并在链中具有约2至约15碳原子。优选的链烯基链中具有2至约6碳原子。支链酯一个或多个低级烷基如甲基、乙基或丙基连接直链链烯基链。“低级链烯基”指链中有约2至约4碳原子，其可以是直链或支链。此链烯基可以被一个或多个本文中所定义的烷基的取代基取代。代表性链烯基包括乙烯基、丙烯基、正丁烯基、异丁烯基、3-甲基丁-2-烯基、正戊烯基、庚烯基、辛烯基、癸烯基等。

“亚烷基”指具有1至约20碳原子的直链或支链二价烃链。优选的亚烷基为具有1至约6碳原子的低级亚烷基。亚烷基可以被一个或多个本文中所定义的烷基的取代基取代。代表性亚烷基包括亚甲基、亚乙基等

“亚烯基”指得自至少含一个碳碳双键的直链或支链烃的二价基团。优选的亚烯基为具有1至约6碳原子的低级亚烯基。亚烯基可以被一个或多个本文中所定义的烷基的取代基取代。代表性亚烯基 包括-CH=CH-、$-CH_2CH=CH-$、$-C(CH_3)=CH-$、$-CH_2CH=CHCH_2-$等。

“亚炔基”指得自至少含一个碳碳三键的直链或支链烃的二价基团。优选的亚炔基为具有1至约6碳原子的低级炔烯基。亚炔基可以被

一个或多个本文中所定义的烷基的取代基取代。代表性亚炔基包括-CH≡CH-、-CH≡CH-CH_2-、-CH≡CH-CH(CH_3)等。

“芳烷基氨基”指(芳基烷基)(Y_2)N-基团，其中所述芳基烷基部分和Y_2如本文所定义。

“杂芳烷基氨基”指(杂芳烷基)(Y_2)N-基团，其中所述杂芳烷基部分和Y_2 如本文中所定义。

“杂环基烷基”指杂环基-亚烷基-基团，其中所述杂环基部分和亚烷基部分如本文中所定义。

“杂环基烷基氨基”指(杂环基烷基)(Y_2)N-基团，其中所述杂环基烷基部分和Y_2 如本文中所定义。

“杂环烯基烷基”指杂环烯基-亚烷基-基团，其中所述杂环烯基部分和亚烷基部分如本文中所定义。

“杂环烯基烷基氨基”指(杂环烯基烷基)(Y_2)N-基团，其中所述杂环烯基烷基部分和Y_2 如本文中所定义。

“烷氧基烷基”指烷氧基-亚烷基-基团，其中所述烷氧基部分和亚烷基部分如本文中所定义。

“烷硫基烷基”指烷硫基-亚烷基-基团，其中所述烷硫基部分和亚烷基部分如本文中所定义。

“烷基亚磺酰基烷基”指烷基亚磺酰基-亚烷基-基团，其中所述烷基亚磺酰基部分和亚烷基部分如本文中所定义。

“烷基磺酰基烷基”指烷基亚磺酰基-亚烷基-基团，其中所述烷基亚磺酰基部分和亚烷基部分如本文中所定义。

“酰基烷基”指酰基-亚烷基-基团，其中所述酰基部分和亚烷基部分如本文中所定义。

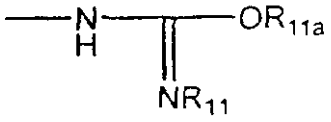
“酰基氨基烷基”指酰基-NH-亚烷基-基团，其中所述酰基部分和亚烷基部分如本文中所定义。

“氨基甲酰基烷基”指氨基甲酰基-亚烷基-基团，其中所述氨基甲酰基部分和亚烷基部分如本文中所定义。

“杂环基烷氧羰基”指杂环基烷基-O-C(O)-基团，其中所述杂环基

烷基部分如本文中所定义。

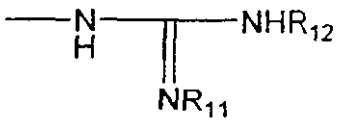
“异脲”指下式的基团



其中R_{11}如本文中所定义而R_{11a}是氢原子、任选地被取代的低级烷基、任选地被取代的芳基或任选地被取代的杂芳基。

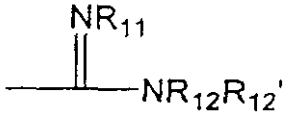
“酰肼基”指式Y_1Y_2N-NHC(O)-的基团，其中Y_1和Y_2 如本文中所定义。

“胍基”或“胍”指下式的基团



其中R_{11}和R_{12}如本文中所定义。

“脒基”或“脒”指下式的基团



其中R_{11}选自氢原子、R_6O_2C-、R_6O-、$R_6C(O)$-、氰基、任选地被取代的低级烷基、硝基或Y_1Y_2N-而R_{12}和$R_{12'}$独立地选自氢原子、任选地被取代的低级烷基、任选地被取代的芳烷基和任选地被取代的杂芳烷基。优选的脒基为其中R_{11}是氢原子、R_6O或任选地被取代的低级烷基且R_{12}定义如上的基团。首选的脒基为其中R_{11}和R_{12}是氢原子的基团。

“氨基甲酸酯”指式$Y_1Y_2C(O)NH$-的基团，其中Y_1如本文中所定义；Y_2选自任选地被取代的烷氧基或任选地被取代的芳氧基。“烷基氨基甲酸酯”指式$Y_1Y_2C(O)NH$-的基团，其中一和Y_2独立地是烷基。更优选的烷基氨基甲酸酯为甲基氨基甲酸酯、乙基氨基甲酸酯、叔丁基氨基甲酸酯、苄基氨基甲酸酯和苯基氨基甲酸酯。

“氨基烷基氨基”酯Y_1Y_2N-亚烷基-$(Y_2)N$-基团，其中Y_1、Y_2和亚烷基

如本文中所定义。

“芳氧羰基烷基”指芳基-O-C(O)-亚烷基基团，其中芳基部分和亚烷基部分如本文所定义。

“杂芳氧基羰基烷基”指杂芳基-O-C(O)-亚烷基，其中所述杂芳基部分和亚烷基部分如本文中所定义。

“杂环氧基羰基烷基”指杂环基-O-C(O)-亚烷基，其中所述杂环基部分和亚烷基如本文中所定义。

“杂环烯基氧基羰基烷基”指杂环烯基-O-C(O)-亚烷基，其中所述杂环烯基部分和亚烷基部分如本文中所定义。

“碱性氮原子”指具有未键合电子对的sp2或sp3 杂化的氮原子，其可以被质子化。碱性氮原子的实例，可能的话其可以任选地被取代，包括存在于杂芳基、杂环基、杂环烯基、稠合的芳基杂环基、稠合的芳基杂环烯基、稠合的杂芳基环烷基、稠合的杂芳基环烯基、稠合的杂芳基杂环基、稠合的杂环基杂环烯基、亚氨基、氨基、异脲、酰肼基、胍基和脒基中的那些。

“环烷基”指约3至约10碳原子的非芳族的单或多环烃环系。代表性单环环烷基环包括环戊基、环己基、环庚基等。代表性多环环烷基环包括十氢萘基、降菠烷基、金刚烷基等。此环烷基是任选地被一个或多个“环烷基的取代基”取代，取代基可以相同或不同，其中“环烷基的取代基”包括氧代(O=)、硫代(S=)、亚甲基(H_2C=)、肟(HO-N=)、烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、芳烷基、杂芳烷基、羟基、羟基烷基、烷氧基、芳基氧基、芳烷氧基、酰基、芳酰基、卤素、硝基、氰基、羧基、烷氧羰基、芳基氧基羰基、芳烷氧羰基、酰基氨基、芳酰基氨基、烷基磺酰基、芳基磺酰基、杂芳基磺酰基、烷基亚磺酰基、芳基亚磺酰基、杂芳基亚磺酰基、烷硫基、芳硫基、杂芳基硫基、芳烷硫基、杂芳烷硫基、脒基、氨基、氨基甲酰基或氨磺酰基。优选的环烷基取代基是氨基和脒基。

“环烯基”指含碳碳双键并具有约3至约10碳原子的非芳族的单环或多环烃环系。此环烯基是任选地被被一个或多个本文所述的环烷基

的取代基取代。代表性单环环烯基环包括环戊烯基、环己烯基或环庚烯基等。代表性多环环烯基环是降菠烯基。优选的环烯基的取代基是氨基和脒基。

“羧基”指烯HO(O)C-(羧酸基团)。

“杂环基”指约3至约10环原子的非芳族的饱和单环或多环环系，其中此环系含有一个或多个碳原子以外的元素。优选的杂环基含有约5至约7环原子，更优选5至6个环原子，其中一个或两个所述的环原子分别独立地选自氧原子、氮原子或硫原子。“氮杂”、“氧杂”或“硫杂”，用作杂环基的前缀时指此环系含有至少一个氮原子、氧原子和硫原子。例如，“氮杂环基”指环系中一个或多个原子是氮原子的杂环基。该杂环基任选地被一个或多个杂环基的取代基取代，取代基可以相同或不同，其中“杂环基的取代基”括氧代(O=)、硫代(S=)、亚甲基(H_2C=)、肟(HO-N=)、烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、芳烷基、杂芳烷基、羟基、羟基烷基、烷氧基、芳基氧基、芳烷氧基、酰基、芳酰基、卤素、硝基、氰基、羧基、烷氧羰基、芳基氧基羰基、芳烷氧羰基、酰基氨基、芳酰基氨基、烷基磺酰基、芳基磺酰基、杂芳基磺酰基、烷基亚磺酰基、芳基亚磺酰基、杂芳基亚磺酰基、烷硫基、芳硫基、杂芳基硫基、芳烷硫基、杂芳烷硫基、氨基、氨基甲酰基和氨磺酰基。优选的杂环基的取代基包括氨基、脒基、卤素、羟基、烷氧羰基烷基和羧基烷基. 代表性杂环基包括哌啶基、吡咯烷基、哌嗪基、吡唑烷基、咪唑啉基、六亚甲基亚胺、高哌嗪基、四氢呋喃基、吗啉基、硫代吗啉基、噻唑烷基、1,3-二氧杂环戊烷基、1,4-二氧杂环己烷基、1,4-二噻烷基、1,3,5-三硫杂苯基(triathianyl)、四氢噻吩基、四氢噻喃基、奎宁环基等。此杂环基的硫或氮原子部分还可以被任选地氧化为相应的S-氧化物、S,S-二氧化物或N-氧化物。

“杂环烯基”指其中含有至少一个碳碳或碳氮双键的本文中描述的杂环基。“氮杂”、“氧杂”或“硫杂”，当用作杂环烯基的前缀时指此环系分别含有至少一个氮原子，氧原子或硫原子。此杂环烯基任选地被

本文描述的一个或多个杂环基的取代基取代。代表性杂环烯基包括2H-吡咯基，2-吡咯啉基、3-吡咯啉基、2-咪唑啉基、2-吡唑啉基、2H-吡喃基、1,2-二氢吡啶基、1,4-二氢吡啶基、1,2,3,4-四氢吡啶基、四氢嘧吩基、四氢噻喃基等。优选的杂环烯基的取代基包括氨基、脒基、卤素、羟基、氧代、硫代、亚甲基、肟、烷氧羰基烷基和羧基烷基。此杂环基的硫原子或氮原子部分还可以任选地被氧化为相应N-氧化物、S-氧化物或S,S-二氧化物。

“芳基”指6至10元芳族单环或多环烃环系。芳基任选地被一个或多个“芳基的取代基”取代，取代基可以相同或不同，其中“芳基的取代基”包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、芳烷基、杂芳烷基、芳基重氮基、杂芳基重氮基、羟基、烷基氨基甲酸酯、酰肼基、烷氧基、芳基氧基、芳烷氧基、酰基、芳酰基、卤素、硝基、氰基、羧基、烷氧羰基、芳基氧基羰基、芳烷氧羰基、酰基氨基、芳酰基氨基、烷基磺酰基、芳基磺酰基、杂芳基磺酰基、烷基亚磺酰基、芳基亚磺酰基、杂芳基亚磺酰基、烷硫基、芳硫基、杂芳基硫基、芳烷硫基、杂芳烷硫基、芳基偶氮基、杂芳基偶氮基、氨基、脒基、烷基氨基、氨基甲酰基和氨磺酰基。优选的芳基是任选地被取代的苯基或任选地被取代的萘基。优选的芳基的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羧基、氨磺酰基、烷基氨基甲酸酯、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。

“杂芳基”指约5至约10-元芳族单环或多环环系，其中该环系的一个或多个原子是碳原子以外的元素。优选的杂芳基含有1至约4选自氧原子，氮原子和硫原子的杂原子。“氮杂”、“氧杂”或“硫杂”，当用作杂芳基的前缀时指此环系含有至少一个氮原子、氧原子或硫原子。杂芳基任选地被一个或多个本文中定义的芳基的取代基取代。代表性杂芳基包括吡咯基、吡嗪基、呋喃基、噻吩基、吡啶基、嘧啶基、哒嗪基、异噁唑基、异噻唑基、噁唑基、噻唑基、吡唑基、三唑基、噁二

唑基、噻二唑基、噻吩并吡啶基、噻吩并吡咯基、噻吩并[3,2-d]嘧啶基、吡咯并吡啶基、呋喃并吡啶基、呋哺基、喹喔啉基、喹唑啉基、喹噁基、咪唑并[1,2-a]吡啶基、酞噁基、咪唑并[2,1-b]噻唑基、苯并呋喃基、吲哚基、异吲哚基、吲噁基、吲唑基、氮杂吲哚基、苯并咪唑基、苯并噻吩基、苯并异噁唑基、苯并噻唑基、嘌呤基、苯并三唑基、1,8-萘啶基、蝶啶基、喹啉基、咪唑基、异喹啉基、噌啉基、三噁基、苯并三噁基等。优选的杂芳基的取代基包括氢原子、烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、羧基、酰肼基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。当此杂芳基含有氮原子时，该氮原子 可以被氧化为N-氧化物。

“稠合的芳基环烷基”指稠合的芳基和环烷基，其中该芳基和环烷基部分如本文中所定义。优选的稠合的芳基环烷基为其中芳基是苯基而环烷基由约5至约6碳原子组成的那些。代表性稠合的苯基环烷基包括1,2,3,4-四氢萘基，二氢茚基等。稠合的芳基环烷基任选地被一个或多个稠合芳基环烷基的取代基取代，取代基选自烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、芳烷基、杂芳烷基、芳基重氮基、杂芳基重氮基、羟基、羟基烷基、烷氧基、芳基氧基、芳烷氧基、酰基、芳酰基、卤素、硝基、氰基、羧基、烷氧羰基、芳基氧基羰基、芳烷氧羰基、酰基氨基、芳酰基氨基、烷基磺酰基、芳基磺酰基、杂芳基磺酰基、烷基亚磺酰基、芳基亚磺酰基、杂芳基亚磺酰基、烷硫基、芳硫基、杂芳基硫基、芳烷硫基、杂芳烷硫基、芳基偶氮基、杂芳基偶氮基、氨基、烷基氨基、氨基甲酰基和氨磺酰基。该环烷基部分进一步任选地被氧代(O=)、硫代(S=)、亚甲基(H_2C=)或肟(HO-N=)取代。优选的稠合苯基环烷基的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。

“稠合的芳基环烯基”指稠合的芳基和环烯基，其中芳基和环烯基

部分如本文中所定义。优选的稠合的芳基环烯基是其中芳基是苯基而环烯基由约5至约6碳原子组成的那些。稠合的芳基环烯基任选地被一个或多个如本文所定义的稠合芳基环烷基的取代基取代。代表性稠合苯基环烯基包括1,2-二氢萘基基、茚基等。环烷基部分进一步任选地被氧代(O=)、硫代(S=)、亚甲基(H_2C=)、肟(HO-N=)取代。优选的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。

“稠合的芳基杂环基”指稠合的芳基和杂环基，其中芳基和杂环基部分如本文中所定义。优选的稠合的芳基杂环基为其中芳基部分是苯基而杂环基部分由约5至约7个环原子，更优选由5至6个环原子组成的那些，其中一个或两个环原子 独立地选自氧原子、氮原子和硫原子。“氮杂”、“氧杂”或”硫杂”，当用作此稠合的芳基杂环基的杂环基部分的前缀时，指此杂环基含有至少一个氮原子、氧原子或硫原子。代表性优选的稠合的苯基杂环基环系包括吲哚啉基、1,2,3,4-四氢异喹啉基、1,2,3,4-四氢喹啉基、2,3-二氢苯并呋喃、1H-2,3-二氢异吲哚基、2,3二氢苯并[f]异吲哚基、1,2,3,4-四氢苯并[g]异喹啉基等。稠合的苯基杂环基任选地被一个或多个本文中所定义的稠合苯基环烷基的取代基。杂环基部分进一步任选地被氧代(O=)、硫代(S=)、亚甲基(H_2C=)或肟(HO-N=)取代。优选的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。杂环基的氮原子或硫原子还可以任选地被氧化为相应N-氧化物、S-氧化物或S,S-二氧化物。

“稠合的芳基杂环烯基”指稠合的芳基和杂环烯基，其中芳基和杂环烯基部分如本文中所定义。“氮杂”、“氧杂”或”硫杂”，当用作稠合的芳基杂环烯基的杂环烯基的前缀时指此杂环烯基部分含有至少一个氮原子、氧原子或硫原子。优选的稠合的芳基杂环基是其中芳基是苯

基而杂环基由约5至6个环原子组成，其中一个或两个环原子 独立地选自氧原子、氮原子和硫原子的那些。代表性优选的稠合的芳基杂环烯基环系包括3H-吲哚啉基、3H-喹唑啉-4-酮、1,1-二氧代-苯并[d]异噻唑基、1H-2-氧代喹啉基、2H-1-氧代异喹啉基等。稠合的芳基杂环烯基任选地被一个或多个本文中所定义的稠合芳基环烷基的取代基取代。杂环基部分进一步任选地被氧代(O=)、硫代(S=)、亚甲基(H_2C=)或肟(HO-N=)取代。优选的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。杂环烯基的氮原子或硫原子任选地被氧化为相应N-氧化物、S-氧化物或S,S-二氧化物。

“稠合的杂芳基环烷基”指稠合的杂芳基和环烷基，其中杂芳基和环烷基部分如本文中所定义。“氮杂”、“氧杂”或”硫杂”，当用作稠合的杂芳基环烷基的杂芳基部分的前缀时，指此杂芳基部分含有至少一个氮原子、氧原子或硫原子。优选的稠合的杂芳基环烷基为其中杂芳基部分由约5至约6个环原子组成，其中一个或两个环原子 独立地选自氧原子、氮原子和硫原子而环烷基由约5至约6个环原子组成的那些。代表性优选的稠合的杂芳基环烷基包括5,6,7,8-四氢异喹啉基、5,6,7,8-四氢喹喔啉基、5,6,7,8-四氢喹唑啉基、4,5,6,7-四氢-1H-苯并咪唑基、4,5,6,7-四氢苯并噁唑基、1H-4-氧杂-1,5-二氮杂萘-2-酮基、1,3-二氢咪唑-[4,5]-吡啶-2-酮基、5,6,7,8-四氢苯并噻唑基、5,6-二氢-4H-苯并噻唑-7-酮等。稠合的杂芳基环烷基任选地被一个或多个本文中所定义的稠合苯基环烷基的取代基取代。环烷基部分进一步任选地被氧代(O=)、硫代(S=)、亚甲基(H_2C=)或肟(HO-N=)取代。优选的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。稠合的杂芳基环烷基的杂芳基部分的氮原子任选地被氧化为N-氧化物。

“稠合的杂芳基环烯基”指与环烯基环稠合的5-或6-元杂芳基。“氮杂”、“氧杂”或”硫杂”，当用作稠合的杂芳基环烯基的杂芳基部分的前缀时，指此环烯基含有至少一个氮原子、氧原子或硫原子。优选的稠合的杂芳基环烯基为其中杂芳基由约5至约6个环原子组成，其中一个或两个环原子独立地选自氧原子、氮原子和硫原子而环烯基由约5至约6个环原子组成的那些。代表性优选的稠合的杂芳基环烯基包括5,6-二氢异喹啉基、5,6-二氢喹喔啉基、5,6-二氢喹唑啉基，4,5-二氢-1H-苯并咪唑基、4,5-二氢苯并噁唑基等。稠合的杂芳基环烯基任选地被一个或多个本文中所定义的稠合的苯基环烷基的取代基取代。环烯基部分进一步任选地被氧代(O=)、硫代(S=)、亚甲基(H_2C=)或肟(HO-N=)取代。优选的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。稠合的杂芳基环烷基的杂芳基部分的氮原子任选地被氧化为N-氧化物。

“稠合的杂芳基杂环基”指与杂环基稠合的杂芳基，其中杂芳基和杂环基部分如本文中所定义。“氮杂”、“氧杂”或”硫杂”，当用作稠合的杂芳基杂环基的杂芳基或杂环基部分的前缀时，指此杂芳基或杂环基部分含有至少一个氮原子、氧原子或硫原子。优选的稠合的杂芳基杂环基是其中杂芳基的一个或两个环原子独立地选自氧原子、氮原子和硫原子而杂环基部分由约5至约6个环原子组成，其中一个或两个环原子独立地选自氧原子、氮原子和硫原子的环系。代表性稠合的杂芳基杂环基包括4,7-二氢-5H-噻唑并[5,4-c]吡啶-6-酮、5,6,7,8-四氢-噻唑并[4,5-c]氮杂环庚三烯-4-酮、2,3-二氢-1H- 吡咯并[3,4-b]喹啉-2-基、1,2,3,4-四氢苯并[b][1,7]萘啶-2-基、1,2,3,4-四氢苯并[b][1,6]萘啶-2-基、1,2,3,4-四氢-9H-吡啶并[3,4-b]吲哚-2-基、4-四氢-9H-吡啶并[4,3-b]吲哚-2-基、2,3-二氢-1H-吡咯并[3,4-b]吲哚-2-基、1H-2,3,4,5-四氢氮杂环庚三烯并[3,4-b]吲哚-2-基、1H-2,3,4,5-四氢氮杂环庚三烯并[4,3-b]吲哚-3-基、1H-

2,3,4,5-四氢氮杂环庚三烯并[4,5-b]吲哚-2-基、5,6,7,8-四氢[1,7]萘啶基、1,2,3,4-四氢[2,7]萘啶基、2,3-二氢[1,4]二噁英[2,3-b]吡啶基、2,3-二氢[1,4]二噁英[2,3-b]吡啶基、3,4-二氢-2H-1-氧杂-4,6-二氮杂萘基、4,5,6,7-四氢-3H-咪唑并[4,5-c]吡啶基、6,7-二氢-5,8-二氮杂萘基等。稠合的杂芳基杂环基任选地被一个或多个本文中所定义的稠合的芳基环烷基取代基取代。杂环基部分进一步任选地被氧代(O=)、硫代(S=)、亚甲基(H_2C=)或肟(HO-N=)取代。优选的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。杂芳基部分的氮原子任选地被氧化为N-氧化物。杂环基部分的氮原子或硫原子任选地被氧化为相应N-氧化物、S-氧化物或S,S-二氧化物。

“稠合的杂芳基杂环烯基”指稠合的杂芳基和杂环烯基，其中杂芳基和杂环烯基部分如本文中所定义。“氮杂”、“氧杂”或”硫杂”，当用作稠合的杂芳基杂环烯基的杂芳基或杂环烯基部分前缀时，指此杂芳基或杂环烯基部分含有至少一个氮原子、氧原子或硫原子。优选的稠合的杂芳基环烯基是其中杂芳基部分由约5至约6个环原子组成，其中一个或两个环原子独立地选自氧原子、氮原子和硫原子而杂环烯基部分由约5至约6个环原子组成，其中一个或两个环原子 独立地选自氧原子、氮原子和硫原子的环系。代表性稠合的杂芳基杂环烯基包括7,8-二氢[1,7]萘啶基、1,2-二氢[2,7]萘啶基、6,7-二氢-3H-咪唑并[4,5-c]吡啶基等。稠合的杂芳基杂环烯基任选地被一个或多个本文中所定义的稠合的芳基环烷基的取代基取代。杂环烯基部分进一步任选地被氧代(O=)、 硫代(S=)、亚甲基(H_2C=)或肟(HO-N=)取代。优选的取代基包括烷基、芳基、杂芳基、杂环基、杂环烯基、环烷基、环烯基、酰肼基、羟基、酰基、芳酰基、卤素、硝基、氰基、烷氧羰基、酰基氨基、烷硫基、烷基氨基、氨基、氨基甲酰基、硫代氨基甲酰基和脒基。杂芳基部分的氮原子任选地被氧化为N-氧化物。杂环烯基的

氮原子或硫原子任选地被氧化为相应N-氧化物、S-氧化物或S,S-二氧化物。

”芳烷基“指芳基-烷基-基团，其中所述芳基部分和烷基部分如本文中所定义。优选的芳烷基含有低级烷基部分。代表性芳烷基包括苄基、2-苯乙基和萘甲基。

“杂芳烷基”指杂芳基-烷基-基团，其中所述杂芳基部分和烷基部分如本文中所定义。优选的杂芳烷基含有低级烷基部分。代表性杂芳烷基可以含有噻吩基甲基、吡啶基甲基、咪唑基甲基和吡嗪基甲基。

“芳链烯基”指芳基-链烯基-基团，其中所述芳基部分和链烯基部分如本文中所定义。优选的芳链烯基含有低级链烯基部分。代表性芳链烯基2-苯乙烯基。

“杂芳链烯基”指杂芳基-链烯基-基团，其中所述杂芳基部分和链烯基部分如本文中所定义。优选的杂芳链烯基含有低级链烯基部分。代表性杂芳链烯基可以包括噻吩基乙烯基、吡啶基乙烯基、咪唑基乙烯基和吡嗪基乙烯基。

“羟基烷基”指HO-亚烷基-基团，其中所述亚烷基部分如本文中所定义。优选的羟基烷基包括低级亚烷基。代表性羟基烷基包括羟基甲基和2-羟基乙基。

“酰基”指H-CO-或烷基-CO-基团，其中所述烷基部分如本文中所定义。优选的酰基含有一低级烷基。代表性酰基包括甲酰基、丙酰基、丙酰基、2-甲基丙酰基、丁酰基和棕榈酰基。

“芳酰基”指芳基-CO-基团，其中所述芳基部分如本文中所定义。代表性芳酰基包括苯甲酰基和1-和2-萘甲酰基。

“芳基重氮基”指芳基-N=N-基团，其中所述芳基部分如本文中所定义。代表性芳基重氮基包括苯基重氮基和萘基重氮基。

“杂芳酰基”指杂芳基-CO-基团，其中所述杂芳基部分如本文中所定义。代表性杂芳基包括噻吩甲酰基和吡啶甲酰基。

“杂芳基重氮基”指杂芳基-N=N-基团，其中所述杂芳基如本文中所定义。代表性杂芳基重氮基包括吡啶基重氮基和噻吩基重氮基。

“烷氧基”指烷基-O-基团，其中所述烷基部分如本文中所定义。代表性烷氧基包括甲氧基，乙氧基，正丙氧基，异丙氧基，正丁氧基和庚氧基。

“芳氧基”指芳基-O-基团，其中所述芳基部分如本文中所定义。代表性芳氧基包括苯氧基和萘氧基。

“芳烷氧基”指芳烷基-O-基团，其中芳烷基部分如本文中所定义。代表性芳烷氧基包括苄氧基和1或2-萘甲氧基。

“烷硫基”指烷基-S-基团，其中烷基部分如本文所定义。代表性烷硫基包括甲硫基、乙硫基、异丙硫基和庚硫基。

“芳硫基”指芳基-S-基团，其中芳基部分如本文所定义。代表性芳硫基包括苯硫基和萘硫基。

“芳烷硫基”指芳烷基-S-基团，其中芳烷基部分如本文所定义。代表性芳烷硫基是苄硫基。

“氨基”指式Y_1Y_2N-的基团，其中Y_1和Y_2如本文所定义。优选的氨基包括氨基(H_2N-)、甲基氨基、二甲基氨基、二乙基氨基、苄基氨基、苯乙基氨基、5-氨基吲哚基、2-氨基-2-噻唑啉基、N-(2-氨基乙基)吗啉、2-(氨基甲基)吡啶或4-(氨基甲基)吡啶。

“氨基烷基”指Y_1Y_2N-亚烷基-基团，其中Y_1、Y_2和亚烷基部分在本文中定义。

“烷氧羰基”和“烷基氧基羰基”指烷基-O-CO-基团，其中所述烷基部分如本文中所定义。代表性烷氧羰基包括甲氧基羰基、乙氧基羰基，或叔丁基氧基羰基。

“杂环基烷氧羰基”指杂环基-烷氧羰基，其中杂环基部分和烷氧羰基部分如本文中所定义。代表性的杂环基烷氧羰基的实例是吡咯烷基乙氧基羰基。

“杂环烯基烷氧羰基”指杂环烯基-烷氧羰基，其中杂环烯基部分和烷氧羰基部分如本文中所定义。杂环烯基烷氧羰基的代表性实例是吡咯啉基乙氧基羰基。

“杂芳烷氧羰基”指杂芳基-烷氧羰基，其中杂芳基部分和烷氧羰基

部分如本文中所定义。杂芳烷氧羰基的代表性实例是吡啶基乙氧基羰基。

“芳基烷氧羰基”指芳基-烷氧羰基，其中芳基部分和烷氧羰基部分如本文中所定义。芳烷氧羰基代表性实例是苯基乙氧基羰基。

“环烷基烷氧羰基”指环烷基-烷氧羰基，其中环烷基部分和烷氧羰基部分如本文中所定义。环烷基烷氧羰基的代表性实例是环己基乙氧基羰基。

“环烯基烷氧羰基”指环烯基-烷氧羰基，其中环烯基部分和烷氧羰基部分如本文中所定义。环烯基烷氧羰基的代表性实例是环己烯基乙氧基羰基。

“烷氧羰基烷基”指烷基-O-CO-亚烷基-基团，其中烷基部分和亚烷基部分在本文中定义。

“芳氧基羰基”指芳基-O-CO-基团，其中芳基部分如本文中所定义。代表性芳氧基羰基包括苯氧基羰基和萘氧基羰基。

“芳烷氧羰基”指芳烷基-O-CO-基团，其中芳烷基部分如本文中所定义。代表性芳烷氧羰基是苄氧基羰基。

“氨基甲酰基”指Y_1Y_2NCO-基团，其中Y_1和Y_2在本文中定义。代表性氨基甲酰基为氨基甲酰基(H_2NCO-)和二甲基氨基氨基甲酰基(Me_2NCO-)。

“杂环基烷基氨基甲酰基”指杂环基-亚烷基-氨基甲酰基，其中所述杂环基、亚烷基和氨基甲酰基部分如本文中所定义。杂环基亚烷基氨基甲酰基的代表性实例是吡咯烷基乙基氨基甲酰基。

“杂环烯基烷基氨基甲酰基”指杂环烯基-亚烷基-氨基甲酰基，其中所述杂环烯基、亚烷基和氨基甲酰基部分如本文中所定义。杂环烯基亚烷基氨基甲酰基的代表性实例是吡咯啉基乙基氨基甲酰基。

“杂芳烷基氨基甲酰基”指杂芳基-亚烷基-氨基甲酰基，其中所述杂芳基、亚烷基和氨基甲酰基部分如本文中所定义。杂芳亚烷基氨基甲酰基的代表性实例是吡啶基乙基氨基甲酰基。

“芳基烷基氨基甲酰基”指芳基-亚烷基-氨基甲酰基，其中所述芳

基、亚烷基和氨基甲酰基部分如本文中所定义。芳基亚烷基氨基甲酰基的代表性实例是苯基乙基氨基甲酰基。

“环烷基烷基氨基甲酰基”指环烷基-亚烷基-氨基甲酰基，其中所述环烷基、亚烷基和氨基甲酰基部分如本文中所定义。环烷基烷基氨基甲酰基的代表性实例是环己基乙基氨基甲酰基。

“环烯基氨基甲酰基”指环烯基-亚烷基-氨基甲酰基，其中所述环烯基、亚烷基和氨基甲酰基部分如本文中所定义。环烷基链烯基氨基甲酰基的代表性实例是环己烯基乙基氨基甲酰基。

“氨磺酰基”指式$Y_1Y_2NSO_2$-基团，其中Y_1和Y_2在本文中定义。代表性氨磺酰基为氨基磺酰基(H_2NSO_2-)和二甲基氨基磺酰基(Me_2NSO_2-)。

“酰基氨基”指酰基-NH-基团，其中所述酰基部分如本文中所定义。

“芳酰基氨基”指芳酰基-NH-基团，其中所述芳酰基部分如本文中所定义。

“烷基磺酰基”指烷基-SO_2-基团，其中所述烷基部分如本文中所定义。优选的烷基磺酰基是其中烷基是低级烷基的那些。

“烷基亚磺酰基”指烷基-SO-基团，其中所述烷基部分如本文中所定义。优选的烷基亚磺酰基是其中烷基部分是低级烷基的那些。

“芳基磺酰基”指芳基-SO_2-基团，其中所述芳基部分如本文中所定义。

“芳基亚磺酰基”指芳基-SO-基团，其中所述芳基部分如本文中所定义。

“卤素”或“卤原子”指氟、氯、溴或碘。优选的是氟、氯或溴，而更优选的是氟或氯。

“氮原子保护基”指容易除去的基团，其是本领域已知的，用于保护氨基防止在合成方法中的不需要的反应，并可以选择性地除去。N-保护基的使用是本领域熟知的，用于防止合成方法中不需要的反应，而很多这样的保护基是已知的，例如，参见，T. H. Greene和P. G. M. Wuts, Protective Groups in Organic Synthesis, 第2版, John Wiley

& Sons, New York(1991)，引入本文作为参考。优选的N-保护基是酰基，包括甲酰基、丙酰基、氯丙酰基、三氯丙酰基、邻硝基苯基丙酰基、邻硝基苯氧基丙酰基、三氟丙酰基、乙酰基丙酰基、氯丁酰基、异丁酰基、邻硝基肉桂酰基、吡啶甲酰基、酰基异硫氰酸酯、氨基己酰基、苯甲酰基等，以及酰基氧基包括甲氧基羰基、9-芴基甲氧基羰基、2,2,2-三氯乙氧基羰基、2-三甲基硅烷基乙氧基羰基、乙烯氧基羰基、烯丙基氧基羰基、叔丁基氧基羰基(BOC)、1,1-二甲基丙炔氧基羰基、苄氧基羰基(CBZ)、对硝基苯基亚磺酰基、对硝基苄氧基羰基、2,4-二氯苄氧基羰基、烯丙基氧基羰基(Alloc)等。

“本发明的化合物”，及等同的表述，用来包括上述通式I或通式II的化合物，该术语包括前药、药用盐和溶剂化物，例如水合物，只要允许。应理解式I或式II具体化合物的活性会随该具体化合物及所使用的检测方法变化。在本文中，本发明的化合物包括在本文描述的体外酶检测中对因子Xa在3.9□M时体外活性大于10%的式I或式II的所有化合物。类似地，对于中间体，不论它们本身是否要求了保护，用来包括其盐和溶剂化物，如果允许的话。 为了清楚起见，有时在本文中给出了特定的实例，但这些实例只是举例说明，而不是用来排除其它实例。

“前药”指式I或式II化合物的形式，其本身可以具有或不具有生理活性，但是其可能转变为具有生理活性的物质(例如，通过代谢、溶解或其它生理方式)，并适于给患者使用，没有不适当的毒性、刺激性、过敏反应等，并就其预计的用途是有效的，前药包括缩酮、酯和两性离子形式。前药在体内转变为上述结构式的母体化合物，例如，通过在血液中水解。以下文献中提供了完整的讨论：T. Higuchi和V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series, 及Edward B. Roche编辑, Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987，将它们引入本文作为参考。

“溶剂化物”指本发明的化合物与一种或多种溶剂分子的物理缔合

形式。此物理缔合包括改变离子和共价键包括氢键的强度。在某些实例中溶剂化物能够被分离，例如当一种或多种溶剂分子掺入结晶固体的晶格中。“溶剂化物”包括溶液相和不溶的溶剂化物。代表性溶剂化物包括乙醇合物、甲醇合物等。“水合物”是其中溶剂分子(一个或多个)是水的溶剂化物。

在特定的实施方案中，术语“约”或“大约”指在给出数值或范围的20%，优选10%并更优选5%左右。

当本发明的化合物被碱性部分取代时，可以形成酸加成盐。可以用来制备酸加成盐的酸优选包括当与此游离碱混合时产生药用盐的那些，所谓药用盐是在盐的药用剂量中其阴离子对患者无毒的盐，故游离碱固有的有益作用不会被阴离子带来的副作用损害。虽然优选所述碱性化合物的药用盐，但是所有酸加成盐可用作游离碱形式的来源，即使特定的盐只是需要作为中间体产物，例如，当此盐只是为了纯化和鉴定目的而形成，或者当其用作通过离子交换方法制备药用盐的中间体时。本发明范围内的药用盐得自下列酸：无机酸如盐酸、硫酸、磷酸和氨基磺酸；以及有机酸如乙酸、枸橼酸、乳酸、酒石酸、丙二酸、甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、环己基氨基磺酸、奎尼酸等。相应的酸加成盐分别包括如下：氢卤酸盐如盐酸盐和氢溴酸盐、硫酸盐、磷酸盐、硝酸盐、氨基磺酸盐、乙酸盐、枸橼酸盐、乳酸盐、酒石酸盐、丙二酸盐、草酸盐、水杨酸盐、丙酸盐、琥珀酸盐、富马酸盐、马来酸盐、亚甲基-双-β-羟基萘甲酸盐、龙胆酸盐，甲磺酸盐，羟乙基磺酸盐和二-对甲苯甲酰基酒石酸盐甲磺酸盐、乙磺酸盐、苯磺酸盐、对甲苯磺酸，环己基氨基磺酸盐和奎尼酸盐。

本发明的酸加成盐通过此游离碱与适当的酸通过应用或采用已知的方法来制备。例如，本发明化合物的酸加成盐按照如下方法制备：或者通过将此游离碱溶解于含有适当酸的水溶液或水-醇溶液或其它适宜的溶剂中，并通过蒸发此溶液分离此盐，或者通过该游离碱与酸在有机溶剂中反应，此情况下直接分离盐或通过浓缩此溶液获得该盐。

通过应用或采用已知的方法，本发明的化合物可以从酸加成盐中

再生。例如，通过用碱金属盐如碳酸氢钠水溶液或氨水溶液处理，本发明的母体化合物可以从其酸加成盐中再生。

当本发明的化合物被酸性部分取代时，可以形成碱加成盐。可以用于制备碱加成盐的碱优选包括当与该游离酸混合时产生药用盐的那些，所谓药用盐就是在这些盐的药物剂量中其中阳离子对动物组织无毒的盐，故该游离酸中固有的有益作用不会被这些阳离子产生的副作用损害。本发明范围内的药用盐，包括例如碱金属和碱土金属盐，得自如下碱：氢化钠、氢氧化钠、氢氧化钾、氢氧化钙、氢氧化铝、氢氧化锂、氢氧化镁、氢氧化锌、氨、三甲基胺、三乙基胺、亚乙基二胺、正甲基葡糖胺、赖氨酸、精氨酸、鸟氨酸、胆碱、N,N'-二苄基亚乙基二胺、氯普鲁卡因、二乙醇胺、正苄基苯乙基胺、二乙基胺、哌嗪，三(羟基甲基)氨基甲烷、四甲基氢氧化铵等。

本发明的金属盐可以通过所选金属的氢化物、氢氧化物、碳酸盐或类似的活性化合物在含水或有机溶剂中接触化合物的游离酸形式来制备。所用含水溶剂可以是水，或者其可以是水与有机溶剂的混合物，有机溶剂优选醇如甲醇或乙醇、酮如丙酮、脂族醚如四氢呋喃或者酯如乙酸乙酯。该反应一般在室温下进行，但是如果需要可以加热。

本发明化合物的胺盐可以通过胺在含水或有机溶剂中与此化合物的游离酸形式接触来制备。适宜的含水溶剂包括水及水与下列溶剂的混合物：醇如甲醇或乙醇、醚如四氢呋喃、腈如乙腈或酮如丙酮。氨基酸盐可以类似地制备。

本发明的化合物可以通过应用或采用已知方法从这些碱加成盐中再生。例如，通过用酸如氢氯酸处理可以从其碱加成盐中再生本发明的母体化合物。

除其本身用作活性化合物外，发明化合物的盐也用于化合物的纯化，例如通过利用盐与母体化合物、副产物和/或起始物之间的溶解度差别，通过本领域技术人员熟知的技术进行。

应意识到本发明的化合物可以含有不对称中心。这些不对称中心可以独立地是R或S构型。对本领域技术人员来说，本发明的某些化合

物显然还可以存在几何异构体。应理解本发明包括上述式I或式II化合物的单个立体异构体及其混合物，包括外消旋混合物。可以从其混合物中分离这些异构体，通过应用或采用已知方法，例如色谱技术和重结晶技术，或它们分别由其中间体的适当异构体制备。

本发明的混合物还可以表现出几何异构现象。几何异构体包括具有链烯基或亚链烯基部分的本发明化合物的顺式和反式形式。本发明包括单个的几何异构体及立体异构体及其混合物。

为此，应理解互变异构体包括在上述基团的叙述中，例如，硫代/巯基或氧代/羟基。

优选的实施方案

本发明另一个优选的方面是式I的化合物，其中q是0而Z不存在。

本发明另一个优选的方面是式I的化合物，其中q是0，r是1而Z不存在。

本发明另一个优选的方面是式I的化合物，其中Cy_2是任选地被取代的杂芳基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的稠合的杂芳基杂环基、任选地被取代的稠合的杂芳基杂环烯基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基环烷基、稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基或任选地被取代的芳基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是任选地被取代的氮杂杂芳基、任选地被取代的氮杂环基、任选地被取代的氮杂环烯基、任选地被取代的稠合的芳基氮杂杂环基、任选地被取代的稠合的芳基氮杂环烯基、任选地被取代的稠合的杂芳基氮杂杂环基、任选地被取代的稠合的杂芳基氮杂环烯基、任选地被取代的稠合的氮杂杂芳基环烷基、任选地被取代的稠合的氮杂杂芳基环烯基、任选地被取代的氮杂环基或任选地被取代的杂环烯基。

本发明另一个优选的方面是式I的化合物，其中Cy_2任选地被一个

或多个选自如下的基团取代：氨基、氨基甲酰基、酰基氨基、杂芳基、杂环烯基、杂环基、烷基、烷氧羰基、脒基、羟基、烷氧基、芳基、异脲、胍基、酰肼基、酰基、氰基、羧基、氨磺酰基或卤素。

本发明另一个优选的方面是式I的化合物，其中Cy_2任选地被一个或多个选自如下的基团取代：芳烷基氨基、杂芳烷基氨基、杂环基烷基氨基、杂环烯基烷基氨基、烷基氨基甲酸酯、氨基烷基氨基、芳氧基羰基烷基、杂芳氧基羰基烷基、杂环氧基羰基烷基、杂环烯基氧基羰基烷基和烷氧羰基烷基。

本发明另一个优选的方面是式I的化合物，当Cy_2是环烷基、环烯基、杂环基、杂环烯基、稠合的芳基环烷基、稠合的芳基环烯基、稠合的芳基杂环基、稠合的芳基杂环烯基、稠合的杂芳基环烷基、稠合的杂芳基环烯基、稠合的杂芳基杂环基或稠合的杂芳基杂环烯基时，其中Cy_2任选地含有至少一个选自肟和氧代基团的取代基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_2、R_{2a}、R_4或R_{4a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_4与R_{4a}一起形成O或S。

本发明另一个优选的方面是式I的化合物，其中R_4与R_{4a}一起形成O。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_2和R_{2a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_4和R_{4a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_4和R_{4a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_4是任选地被取代的低级烷基。

本发明另一个优选的方面是式I的化合物，其中R_4是烷氧基烷基、烷硫基烷基、烷基亚磺酰基烷基、烷基磺酰基烷基、烷氧羰基烷基、羟基烷基、酰基烷基、酰基氨基烷基或氨基甲酰基烷基。

本发明另一个优选的方面是式I的化合物，其中R_2是任选地被取代的低级烷基。

本发明另一个优选的方面是式I的化合物，其中R_2和R_{2a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_2 烷氧基烷基、烷氧羰基烷基、羧基烷基、羟基烷基或杂环基烷氧羰基，而R_{2a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_1和R_{1a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_1是低级烷基、羧基、烷氧羰基或氨基甲酰基，而R_{1a}是氢原子。

本发明另一个优选的方面是式I的化合物，其中R_1是烷氧基烷基、羧基烷基、烷氧羰基烷基或氨基甲酰基烷基。

本发明另一个优选的方面是式I的化合物，其中R_1和R_{1a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基。

本发明另一个优选的方面是式I的化合物，其中R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基。

本发明另一个优选的方面是式I的化合物，其中R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基。

本发明另一个优选的方面是式I的化合物，其中R_{1a}和R_{2a}不存在，而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基。

本发明另一个优选的方面是式I的化合物，其中R_1和R_2与连接R_1和R_2的碳原子一起形成环己基。

本发明另一个优选的方面是式I的化合物，其中R_1和R_2与连接R_1和R_2的碳原子一起形成环己烯基。

本发明另一个优选的方面是式I的化合物，其中L_1不存在，或是任选地被取代的亚烷基、任选地被取代的亚烯基、$-C(O)NR_5-$、$-S(O)_p-$、$-C(O)-$、$-C(O)Y-C(X)Y-$、$-C(O)O-$、$C(O)NR_5-S(O)_p-$、$-C(O)-C(O)NR_5S(O)_p-$、$-S(O)_pNR_5-$、$-C(O)-$亚烷基$-O-$、$-C(O)-$亚烯基$-O-$、

-S(O)$_p$-亚烯基-、-S(O)$_p$-亚烷基-、-C(O)-亚烷基-C(O)-、-C(O)-亚烷基-S(O)$_p$-、-S(O)$_p$-亚烷基-C(O)-、-C(O)-亚烷基、-C(O)-亚烯基-、-亚烷基-C(O)NR$_5$-或-C(O)CH(OH)-亚烷基-。

本发明另一个优选的方面是式I的化合物，其中L_1是亚甲基、-C(O)-亚烷基-O-、-C(O)-亚烯基-、-S(O)$_p$-亚烯基-、-C(O)C(O)NR$_5$-或-S(O)$_p$-。

本发明另一个优选的方面是式I的化合物，其中Cy_1是任选地被取代的芳基、杂芳基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的环烷基、任选地被取代的环链烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基。

本发明另一个优选的方面是式I的化合物，其中Cy_1是任选地被取代的芳基、杂芳基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的环烷基或任选地被取代的环链烯基。

本发明另一个优选的方面是式I的化合物，其中Cy_1任选地被一个或多个选自如下的基团取代：氨基、卤素、羟基、芳基、杂芳基、脒基、烷基、酰基氨基、氨基甲酰基、氰基、烷氧基、硝基、氨基甲酸酯、氨磺酰基。

本发明另一个优选的方面是式I的化合物，其中Cy_1任选地被选自-NH$_2$、氯、氨基甲酸酯或氨基磺酰基的一个或多个基团取代。

本发明另一个优选的方面是式I的化合物，其中当Cy_1是环烷基、环烯基、杂环基、杂环烯基、稠合的芳基环烷基、稠合的芳基环烯基、稠合的芳基杂环基、稠合的芳基杂环烯基、稠合的杂芳基环烷基稠合的杂芳基环烯基、稠合的杂芳基杂环基或稠合的杂芳基杂环烯基时，Cy_1任选地含有至少选自肟和氧代基团的取代基。

本发明另一个优选的方面是式I的化合物，其中R_1是烷基、氢原子

或烷氧羰基。

本发明另一个优选的方面是式I的化合物，其中R_1是烷氧羰基烷基。

本发明另一个优选的方面是式I的化合物，其中R_1是烷基，R_4是烷基，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基-或-S(0)2-亚烷基而-Cy_1任选地被取代的杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基-或-S(0)$_2$-亚烷基-，而Cy_1是任选地被取代的芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-，-S(0)$_2$-亚烯基-或-S(0)$_2$-亚烷基-，而Cy_1是任选地被取代的杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基-或-S(0)$_2$-亚烷基-，而Cy_1是任选地被取代的氮杂杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基-或-S(0)$_2$-亚烷基-，而Cy_1是任选地被取代的硫杂杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基-或-S(0)$_2$-亚烷基-，而Cy_1是任选地被取代的苯并噻吩基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基-或-S(0)$_2$-亚烷基，而Cy_1是任选地被取代的吲哚基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基或-S(0)$_2$-亚烷基，而Cy_1是任选地被取代的苯并咪唑基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基或-S(0)$_2$-亚烷基，而Cy_1是

任选地被取代的噻吩基。

本发明另一个优选的方面是式I的化合物，其中R_1是烷基，R_4是烷基，L_1是-S(O)$_2$-、-S(O)$_2$-亚烯基或-S(O)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的杂芳基而Cy_2是任选地被取代的杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(O)$_2$-、-S(O)$_2$-亚烯基或-S(O)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的杂芳基，而Cy_2是任选地被取代的芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂芳基、任选地被取代的杂环基或任选地被取代的杂环烯基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(O)$_2$-、-S(O)$_2$-亚烯基或-S(O)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的杂芳基，而Cy_2是任选地被取代的杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(O)$_2$-、-S(O)$_2$-亚烯基或-S(O)$_2$-亚烷基，L_2是亚烷基，Cy_1是杂芳基，而Cy_2是任选地被取代的氮杂吲哚基、任选地被取代的喹唑啉基或任选地被取代的哌啶基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(O)$_2$-、-S(O)$_2$-亚烯基或-S(O)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的氮杂杂芳基，而Cy_2是任选地被取代的氮杂杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(O)$_2$-、-S(O)$_2$-亚烯基或-S(O)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的硫杂杂芳基，而Cy_2是任选地被取代的氮杂吲哚基、任选地被取代的喹唑啉基或任选地被取代的哌啶基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(O)$_2$-、-S(O)$_2$-亚烯基或-S(O)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的苯并噻吩基，而Cy_2是任选地被取代的氮杂吲哚基、任选地被取代的喹唑啉基或任选地被取代的哌啶基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和

R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基或-S(0)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的吲哚基，而Cy_2是任选地被取代的氮杂吲哚基、任选地被取代的喹唑啉基或任选地被取代的哌啶基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基或-S(0)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的苯并咪唑基，而Cy_2是任选地被取代的氮杂吲哚基、任选地被取代的喹唑啉基或任选地被取代的哌啶基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_{1a}、R_{1a}、R_4和R_{4a}是氢原子，L_1是-S(0)$_2$-、-S(0)$_2$-亚烯基或-S(0)$_2$-亚烷基，L_2是亚烷基，Cy_1是任选地被取代的噻吩基，而Cy_2是任选地被取代的氮杂吲哚基或任选地被取代的喹唑啉基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是被氨基取代基取代的喹唑啉基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是-NH_2或-N(烷基)$_2$取代的喹唑啉基。

本发明另一个优选的方面是式I的化合物，其中R_2是氢原子、羧基烷基、烷氧基烷基、羟基烷基、烷氧羰基烷基、酰基氨基或氨基甲酰基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是N-取代的哌啶基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是N-取代的哌啶基且此哌啶基部分在此哌啶环的4位与母体部分连接。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环原子氮原子被芳基或杂芳基取代。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环原子氮原子被氮杂杂芳基取代。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环原子氮原子被2-吡啶基、4-吡啶基或4-嘧啶基取代。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环原子氮原子上取代有任选地被取代的嘧啶基。

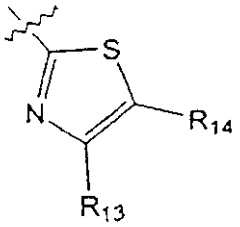
本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环原子氮原子上取代有嘧啶基，其中所述嘧啶基在所述嘧啶基的4位与哌啶基部分连接。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环原子氮原子上取代有嘧啶基，其中所述嘧啶基被芳基的取代基取代，更优选所述嘧啶基在其2位被选自如下的基团取代：卤素、烷氧基、烷硫基和Y_1Y_2N-，其中Y_1和Y_2独立地是氢原子、烷基或芳烷基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是任选地被取代的噻唑基。

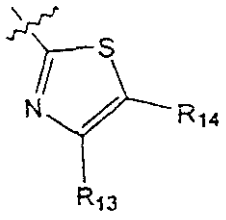
本发明另一个优选的方面是式I的化合物，其中Cy_2是噻唑基，其被至少一个选自如下的取代基取代：低级烷基、芳基、杂芳基、氨基、酰基氨基烷基、烷氧羰基烷基、氨基甲酰基烷基和烷氧基烷基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是下式的基团



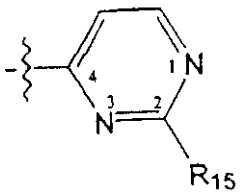
其中R_{13}和R_{14}独立地是氢原子、低级烷基、芳基、杂芳基、氨基、酰基氨基烷基、烷氧羰基烷基、氨基甲酰基烷基或烷氧基烷基；或R_{13}和R_{14}与连接R_{13}和R_{14}的碳原子一起形成环烷基、环烯基、杂环基、杂环烯基、芳基或杂芳基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是下式的基团



其中R_{13}和R_{14}与连接R_{13}和R_{14}的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基，其任选地被氧代部分取代。

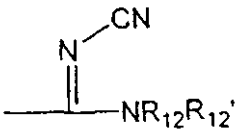
本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环氮原子上取代有下式的嘧啶基



其中R_{15}选自卤素、烷氧基、烷硫基和Y_1Y_2N-，其中Y_1和Y_2独立地是氢原子、烷基和芳烷基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中环原子氮原子上取代有选自如下的基团：烷氧羰基、氨基甲酰基、酰基、烷基和脒基。

本发明另一个优选的方面是式I的化合物，其中Cy_2是哌啶基部分，其中氮环原子上取代有



其中R_{12}和$R_{12'}$独立地选自氢原子或任选地被取代的低级烷基。

其它优选的化合物具有式I，其中m是1；而n是1。

其它优选的化合物具有式I，其中A是N。

其它优选的化合物具有式I，其中R_3和R_{3a}一起是O；而R_1、R_2、R_{2a}、R_4和R_{4a}是氢原子。

其它优选的化合物具有式I，其中R_3和R_{3a}一起是O；R_1、R_{1a}、R_2、R_{2a}和R_4是氢原子；而R_{4a}是任选地被取代的烷基。

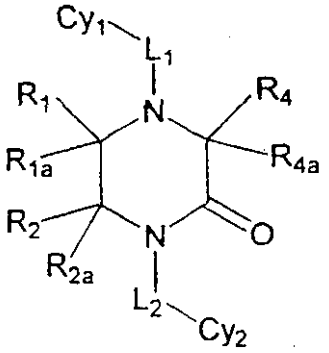
其它优选的化合物具有式I，其中R_3和R_{3a}一起是O；R_1、R_{1a}，R_2和R_4是氢原子；而R_{2a}和R_{4a}是任选地被取代的烷基。

其它优选的化合物具有式I，其中R_3和R_{3a}一起是O；R_1、R_2、R_{2a}和R_4是氢原子；而R_{1a}和R_{4a}是任选地被取代的烷基。

其它优选的化合物具有式I，其中R_3和R_{3a}一起是O；R_1、R_2、R_{2a}、R_4和R_{4a}是氢原子；而R_{1a}是羧基、烷氧羰基、Y_1Y_2NCO或任选地被取代的烷基。

其它优选的化合物具有式I，其中R_3和R_{3a}一起是O；而R_1、R_{1a}、R_2、R_4和R_{4a}是氢原子；而R_{2a}是羧基、烷氧羰基、Y_1Y_2NCO或任选地被取代的烷基。

本发明的其它优选的方面涉及式II的化合物



II

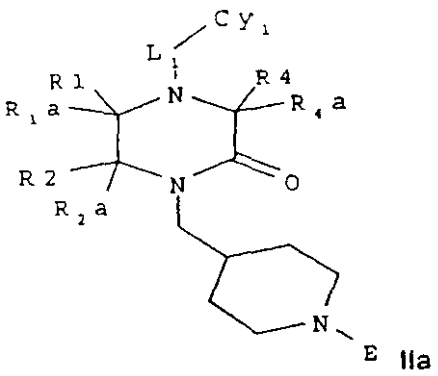
或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中R_1、R_{1a}、R_2、R_{2a}、R_4、R_{4a}、Cy_1、Cy_2、L_1和L_2如式I所定义。

优选的化合物具有式I或式II，其中Cy_2含有至少一个氮原子且当Cy_2是任选地被取代的芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的稠合的苯基环烷基或任选地被取代的稠合的苯基环烯基时，则所述氮原子是碱性氮原子。

本发明另一个优选的方面是式I或式II化合物，其中Z不存在或选自O、$S(O)_p$和NR_5。

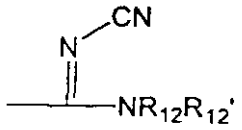
本发明另一个优选的方面是式I或式II化合物，其中Z是$-NR_5C(O)-$或$-C(O)NR_5-$。

本发明另一个优选的方面是式IIa的化合物

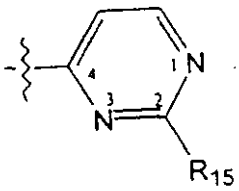


IIa

其中R_1，R_{1a}，R_2，R_{2a}，R_3，R_{3a}，R_4，R_{4a}，Cy_1和L_1如式I所定义，E是烷氧羰基，氨基甲酰基，酰基，烷基，吡啶基，脒基；



其中R_{12}和$R_{12'}$独立地选自氢原子或任选地被取代的低级烷基；或者



其中R_{15}选自卤素、烷氧基、烷硫基和Y_1Y_2N-，其中Y_1和Y_2独立地是氢原子、烷基和芳烷基。

本发明另一个优选的方面是式I或式II化合物，其中L_1是-$S(O)_p$-、-C(X)Y-或-L_3-Q-L_4-Q'-L_5-。

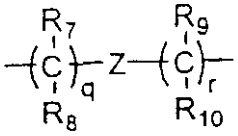
本发明另一个优选的方面是式I或式II的化合物，其中Cy_1是任选地被取代的芳基或任选地被取代的杂芳基。

本发明另一个优选的方面是式I的化合物，其中R_1、R_2、R_3和R_4独立地是烷基、烷氧基烷基、氨基烷基、氨基烷基烷氧基、杂环基、杂环烯基、杂芳基、芳基、环烷基或环烯基，或R_4和R_{4a}一起形成O。

更优选的化合物是具有式I或式II结构的化合物，其中L_2是1至3个碳原子的亚烷基。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_2是-CH_2-。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_2是下式的基团



其中Z是NR_5；q是2；r是0；R_5是氢原子或任选地被取代的烷基；而R_7和R_8是氢原子。

其它更优选的化合物是具有式I或式II结构的化合物，其中R_5是氢原子。

其它更优选的化合物是具有式I或式II结构的化合物，其中Cy_2是任选地被取代的芳基或任选地被取代的杂芳基。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_1是-$S(O)_2$-。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_1是-C(X)Y-；X是O；而Y是NH。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_1是-L_3-Q-L_4-Q'-L_5-；Q是-$S(O)_2$-或-C(O)-；而L_4是任选地被取代的亚烯基。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_1是-L_3-Q-L_4-Q'-L_5-；而L_4是任选地被取代的亚烷基。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_1是-L_3-Q-L_4-Q'-L_5-；Q是-C(O)-；Q'是O；而L_4是任选地被取代的亚烷基。

其它更优选的化合物是具有式I或式II结构的化合物，其中L_1是亚甲基、-L_3-Q-L_4-Q'-L_5-；L_3是任选地被取代的亚烷基；而L_4是任选地被取代的亚烯基。

其它更优选的化合物是具有式I或式II结构的化合物，其中Cy_1是任选地被取代的苯基、任选地被取代的噻吩基、任选地被取代的苯并

噻吩基、任选地被取代的异喹啉基、任选地被取代的吲哚基、任选地被取代的噻吩并吡啶基、任选地被取代的呋喃基、任选地被取代的吡啶基或任选地被取代的苯并咪唑基。

其它更优选的化合物是具有式I或式II结构的化合物，其中Cy_2任选地被取代的苯基、任选地被取代的吡啶基、任选地被取代的咪唑基、任选地被取代的喹啉基、任选地被取代的异喹啉基、任选地被取代的喹唑啉基、任选地被取代的噌啉基、任选地被取代的氮杂吲哚基或任选地被取代的噻吩并吡啶基。

其它更优选的化合物是结构式I的化合物，其中A是N;

G_1是L_1-Cy_1而G_2是L_2-Cy_2; L_1和L_2独立地是不存在、亚甲基、亚乙基、磺酰基、亚烷基磺酰基或亚烷基;

Cy_1是硫杂杂芳基、硫杂杂环基、硫杂杂环烯基、稠合的硫杂杂芳基环烷基、稠合的硫杂杂芳基环烯基、稠合的杂芳基硫杂环烷基或稠合的杂芳基硫杂环烯基、噻吩-异噁唑基、噻吩并-吡啶基、苯并噻吩基、吲哚基、吗啉基、氨基吡啶苄基、嘧啶-苄基、氨基喹唑啉、嘧啶-哌啶基、噻吩-吡唑、噻吩-噁二唑、噻吩-噻二唑、噻吩-三唑、噻吩-吡啶、任选地被取代的芳基的苯基-三唑、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基;

Cy_2是氨基-喹唑啉、二苯亚甲基-氨基、吡咯并-吡啶、联吡啶基、吡啶-苄基、噻吩基、噻吩-苄基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被

取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基、任选地被取代的稠合的杂芳基杂环烯基、氮杂杂芳基、氮杂环基、氮杂环烯基、稠合的氮杂杂芳基环烷基、稠合的氮杂杂芳基环烯基、稠合的杂芳基氮杂环烷基或稠合的杂芳基氮杂环烯基；

R_3和R_{3a}一起形成O或S；

R_2和R_{2a} 独立地选自氢原子、烷基、氨基烷基、烷基氨基烷基、烷氧基、烷氧基烷基、烷氧基氨基烷基、环烷基烷基氨基、苄氧基烷基、异丙基、氨基甲基、甲氧基乙基氨基甲基、哌嗪基、吡咯烷基、乙氧基甲基、苄氧基甲基、甲氧基甲基、异丁基、异丙基氨基或异丙基氨基甲基，其条件是R_2和R_{2a}不都是氢原子，或羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如式I所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

R_1和R_{1a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如式I所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；

或R_1和R_{1a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；

R_4和R_{4a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如式I所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基，或R_4和R_{4a}一起形成O或S；而m和n各是1。

其它更优选的化合物是具有结构式I的化合物，其中A是N；

G_1是L_1-Cy_1而G_2是L_2-Cy_2；

L_1是磺酰基或亚烷基磺酰基；

L_2是不存在、亚甲基、亚乙基或亚烷基；

Cy_1是硫杂杂芳基、硫杂杂环基、硫杂杂环烯基、稠合的硫杂杂芳基环烷基、稠合的硫杂杂芳基环烯基、稠合的杂芳基硫杂环烷基或稠合的杂芳基硫杂环烯基、噻吩-异噁唑基、噻吩并-吡啶基、苯并噻吩基、吲哚基、吗啉基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基；

Cy_2是氨基-喹唑啉、二苯亚甲基-氨基、吡咯并-吡啶、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基、任选地被取代的稠合的杂芳基杂环烯基、氮杂杂芳基、氮杂环基、氮杂环烯基、稠合的氮杂杂芳基环烷基、稠合的氮杂杂芳基环烯基、稠合的杂芳基氮杂环烷基或稠合的杂芳基氮杂环烯基；

R_3和R_{3a}一起形成O或S ；

R_2和R_{2a} 独立地选自氢原子、烷基、氨基烷基、烷基氨基烷基、烷氧基、烷氧基烷基、烷氧基氨基烷基、环烷基烷基氨基、苄氧基烷基、异丙基、氨基甲基、甲氧基乙基氨基甲基、哌嗪基、吡咯烷基、乙氧基甲基、苄氧基甲基、甲氧基甲基、异丁基、异丙基氨基或异丙基氨基甲基，其条件是R_2和R_{2a}不都是氢原子；

R_1、R_{1a}、R_4和R_{4a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；

或R_1和R_{1a}与它们连接的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；而m和n各是1。

其它更优选的化合物是具有结构式I的化合物，其中A是N；

G_1是L_1-Cy_1而G_2是L_2-Cy_2；

L_1和L_2独立地是不存在、亚甲基、亚乙基或亚烷基；

Cy_1是噻吩-异噁唑基、氨基吡啶-苄基、苯并噻吩基、嘧啶-苄基、氨基喹唑啉、嘧啶-哌啶基、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基；

Cy_2是联吡啶基、氨基-喹唑啉、吡啶-苄基、噻吩基、噻吩-苄基、吡咯并-吡啶、任选地被取代的芳基、任选地被取代的杂芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的杂环基、任选地被取代的杂环烯基、任选地被取代的稠合的芳基环烷基、任选地被取代的稠合的芳基环烯基、任选地被取代的稠合的芳基杂环基、任选地被取代的稠合的芳基杂环烯基、任选地被取代的稠合的杂芳基环烷基、任选地被取代的稠合的杂芳基环烯基、任选地被取代的稠合的杂芳基杂环基或任选地被取代的稠合的杂芳基杂环烯基；

R_3和R_{3a}一起形成O或S；且

R_4和R_{4a}一起形成O或S；

R_1、R_{1a}、R_2、R_{2a}独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如权利要求1所定义、任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或一对或多对R_1和R_{1a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；而m和n各是1。

其它更优选的化合物是具有结构式I的化合物，其中A是N；

G_1是 L_1-Cy_1而G_2是L_2-Cy_2；

L_1和L_2独立地是不存在、亚甲基、亚乙基或亚烷基；

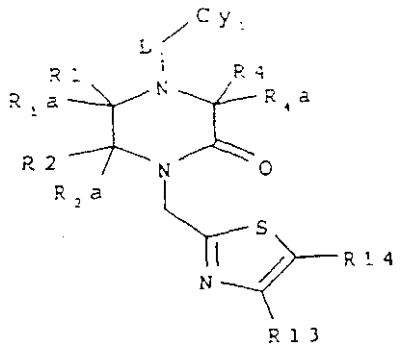
Cy_1是噻吩-异噁唑、噻吩-吡唑、噻吩-噁二唑、噻吩-噻二唑、噻吩三唑、噻吩-吡啶或苯基-三唑；

Cy_2是氨基-喹唑啉或吡咯并-吡啶；

R_3和R_{3a}一起形成O或S；

R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a} 独立地选自氢原子、羧基、烷氧羰基、$Y_1Y_2NC(O)$-，其中Y_1和Y_2如权利要求1所定义；任选地被取代的烷基、任选地被取代的芳基、任选地被取代的芳烷基、任选地被取代的杂芳基和任选地被取代的杂芳烷基；或R_1和R_2与连接R_1和R_2的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基；或R_{1a}和R_{2a}不存在而R_1和R_2与连接R_1和R_2的碳原子一起形成芳基或杂芳基；或一对或多对R_1和R_{1a}与它们所连接的碳原子一起形成3至7元环烷基或环烯基；或R_2和R_{2a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；或R_4和R_{4a}与连接它们的碳原子一起形成3至7元环烷基或环烯基；而m和n各是1。

本发明另一个优选的方面是式IIb的化合物



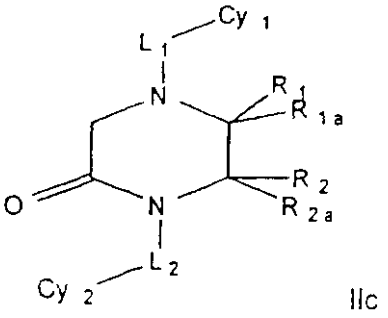
IIb

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中L_1、Cy_1、R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a}如式I化合物中所述，

R_{13}和R_{14}独立地是氢原子、低级烷基、芳基、杂芳基、氨基、酰基氨基烷基、烷氧羰基烷基、氨基甲酰基烷基或烷氧基烷基；或R_{13}和R_{14}与连接R_{13}和R_{14}的碳原子一起形成环烷基、环烯基、杂环基、杂环烯基、芳基或杂芳基。

本发明另一个优选的方面是式IIb的化合物，其中R_{13}和R_{14} 与连接R_{13}和R_{14}的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基，其任选地被氧代部分取代。

其它优选的化合物是同时抑制因子Xa和因子IIa(凝血酶)活性的化合物，其具有式IIc的结构



IIc

或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物，其中：

Cy_1是硫杂杂芳基、苯并噻吩基或氮杂杂芳基，其未被取代或被卤素取代，L_1是$-S(O)_2-$、$-S(O)_2-$亚烷基-、$-S(O)_2-$亚烯基-或$-S(O)_2-$亚炔基-；R_1、R_{1a}、R_2、R_{2a}独立地是氢原子、烷基、烷氧基烷基、氨基烷

基、氨基烷基烷氧基、羧基、烷氧羰基或氨基甲酰基；L_2是亚甲基；而

Cy_2是氮杂杂芳基、氮杂环基、氮杂环烯基、稠合的氮杂杂芳基环烷基、稠合的氮杂杂芳基环烯基、稠合的杂芳基氮杂环烷基或稠合的杂芳基氮杂环烯基。

同时抑制因子Xa和因子IIa(凝血酶)活性的化合物是具有式IIc的化合物，其中：

Cy_1是硫杂杂芳基或氮杂杂芳基，

L_1是$-S(O)_2-$、$-S(O)_2-$亚烷基-、$-S(O)_2-$亚烯基-或$-S(O)_2-$亚炔基-；

R_1、R_{1a}、R_2、R_{2a}独立地是氢原子、烷氧基烷基、羟基烷基、氨基烷基、烷基氨基烷基、羧基、烷氧羰基或氨基甲酰基；

L_2是亚甲基；而

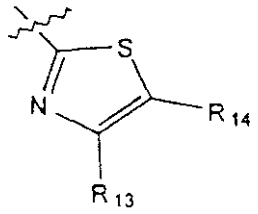
Cy_2是氮杂杂芳基、氮杂环基、氮杂环烯基、稠合的氮杂杂芳基环烷基、稠合的氮杂杂芳基环烯基、稠合的杂芳基氮杂环烷基或稠合的杂芳基氮杂环烯基。

其它优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中Cy_2是任选地被取代的氮杂吲哚基、任选地被取代的喹唑啉基或任选地被取代的哌啶基。

其它优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中R_1、R_{1a}、R_2和R_{2a}独立地是芳基、杂芳基、环烷基、环烯基、杂环基或杂环烯基。

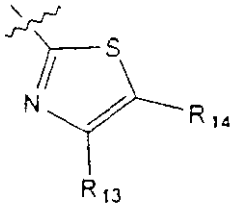
其它优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中Cy_2是任选地被取代的噻唑基。

其它优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中Cy_2是下式基团



其中R_{13}和R_{14}独立地是氢原子、低级烷基、芳基、杂芳基、氨基、酰基氨基烷基、烷氧羰基烷基、氨基甲酰基烷基或烷氧基烷基；或R_{13}和R_{14}与连接R_{13}和R_{14}的碳原子一起形成环烷基、环烯基、杂环基、杂环烯基、芳基或杂芳基。

其它优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中Cy_2是下式基团



其中R_{13}和R_{14} 与连接R_{13}和R_{14}的碳原子一起形成环烷基、环烯基、杂环基或杂环烯基，其任选地被氧代或肟取代基取代。

其它优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物，为结构式IIc的化合物，其中Cy_2是任选地被取代的氮杂吲哚基。

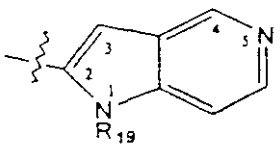
更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物，为具有式IIc结构的化合物，其中Cy_2是任选地被取代的5-氮杂吲哚基。

更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物，为具有式IIc结构的化合物，其中，

当Cy_2是任选地被取代的氮杂吲哚基时，母体分子连接于此氮杂吲哚基的2位。

更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中

Cy_2是



其中R_{19}是氢原子或任选地被取代的烷基。

更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中

CY_2任选地被取代的氮杂吲哚基；

L_1是$-S(O)_2-$、$-S(O)_2-$亚烯基；

Cy_1是任选地被取代的噻吩基或任选地被取代的苯并噻吩基，

R_1和R_2是氢原子；

R_{1a}和R_{2a}独立地是氢原子、烷基、羧基、烷氧羰基或氨基甲酰基。

更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中

R_1、R_{1a}和R_2是氢原子；且

R_{2a}是烷基、羧基、烷氧羰基或氨基甲酰基。

更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中

Cy_2是任选地被取代的氮杂吲哚基；

L_1是$-S(O)_2-$或$-S(O)_2-$亚烯基；

Cy_1是任选地被取代的噻吩基或任选地被取代的苯并噻吩基、任选地被取代的苯并咪唑基或任选地被取代的吲哚基，

R_1、R_{1a}和R_2是氢原子；且

R_{2a}是烷基、羧基、烷氧羰基或氨基甲酰基。

更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中

R_1、R_2和R_{2a}是氢原子；而R_{1a}是烷基、羧基、烷氧羰基或氨基甲酰基。

更优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物为具有式IIc结构的化合物，其中

Cy_2是任选地被取代的氮杂吲哚基；

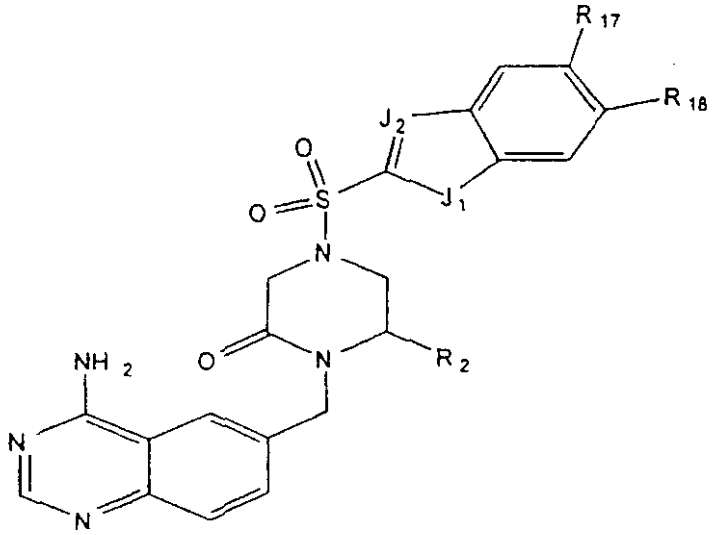
L_1是$-S(O)_2-$或$-S(O)_2-$亚烯基；

Cy_1是任选地被取代的噻吩基或任选地被取代的苯并噻吩基，

R_{1a}是烷基、羧基、烷氧羰基或氨基甲酰基；且

R_1、R_2和R_{2a}是氢原子。

其它优选的既抑制因子Xa又抑制抑制IIa(凝血酶)活性的化合物是具有IId结构的化合物



IId

其中R_{17}和R_{18}独立地是氢原子或卤素；

J_1是S或NH；J2是CH或N；且

R_2是氢原子、烷基、羧基、烷氧羰基或氨基甲酰基。

本发明另一个优选的方面是式IId的化合物，其中R_2是杂环基烷氧羰基、杂环烯基烷氧羰基、杂芳烷氧羰基、芳基烷氧羰基、环烷基烷氧羰基或环烯基烷氧羰基。

本发明另一个优选的方面是式IId的化合物，其中R_2是杂环基烷基氨基甲酰基、杂环烯基烷基氨基甲酰基、杂芳烷基氨基甲酰基、芳基烷基氨基甲酰基、环烷基氨基甲酰基或环烯基氨基甲酰基。

本发明另一个优选的方面是式IId的化合物，其中R_2是杂环基、杂环烯基、杂芳基、芳基、环烷基或环烯基。

本发明另一个优选的方面是式IId的化合物，其中R_2是杂环基烷氧羰基烷基、杂环烯基烷氧羰基烷基、杂芳烷氧羰基烷基、芳基烷氧羰基烷基、环烷基烷氧羰基烷基或环烯基烷氧羰基烷基。

本发明另一个优选的方面是式IId的化合物、其中R_2是杂环基烷基氨基甲酰基烷基、杂环烯基烷基氨基甲酰基烷基、杂芳烷基氨基甲酰

基烷基、芳基烷基氨基甲酰基烷基、环烷基氨基甲酰基烷基或环烯基氨基甲酰基烷基。

本发明另一个优选的方面是式IId的化合物 其中R_2是烷氧基烷基、羟基烷基或氨基烷基。

本发明另一个优选的方面是式IId的化合物，其中R_2是烷基(H)N-烷基-。

本发明范围内的化合物包括但不限于：

所选择的优选的化合物，其中Z是$-NR_5C(O)-$或$-C(O)NR_5-$，或其药用盐、其药学可接受的前药、其N-氧化物、其水合物或其溶剂化物。

本发明优选的中间体具有式III，其中Cy_2含有至少一个氮原子且当Cy_2是任选地被取代的芳基、任选地被取代的环烷基、任选地被取代的环烯基、任选地被取代的稠合的苯基环烷基或任选地被取代的稠合的苯基环烯基时，则所述氮原子是碱性氮原子。

本发明的其它优选的中间体具有式III，其中Z不存在。

本发明的其它优选的中间体具有式III，其中R_1、R_{1a}、R_2、R_{2a}、R_4和R_{4a}是氢原子。

本发明的其它优选的中间体具有式II，其中L_1和L_2独立地是亚甲基、亚乙基、亚丙基或亚丁基；R_1、R_{1a}、R_2、R_{2a}独立地是氢原子、烷基、烷氧基烷基、氨基烷基、氨基烷基烷氧基、羧基、烷氧羰基或氨基甲酰基；Cy_1是杂芳基、硫杂杂芳基、联杂芳基、噻吩基、异噁唑基、异噁唑基-噻吩基或氮杂杂芳基，它们未被取代或被卤素取代；Cy_2是氮杂杂芳基、喹唑啉、氨基-喹唑啉或4-氨基喹唑啉。

本发明更优选的中间体选自：

(2S,6RS)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯，

(3S,5RS)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮，

(3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮，

(3S,5S)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮，

(3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮，

(2S,6R)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯,

(3S,5S)-1-(4-氯-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮,

(3S,5R)-1-(4-氯-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基哌嗪-2-酮,

4-(2-氧代哌嗪-1-基甲基)苯甲脒,

1-(2-氨基喹啉-6-基甲基)哌嗪-2-酮,

1-(1-氨基异喹啉-6-基甲基)哌嗪-2-酮,

2-(2-氧代哌嗪-1-基甲基)吡咯并[3,2-c]吡啶-1-甲酸叔丁酯,

2-(5-(±)-甲氧基羰基-2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯,

2-(2-(±)-甲氧基羰基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯,

1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮,

1-(4-氨基-噻吩并[2,3-d]嘧啶-6-基甲基)-哌嗪-2-酮,

4-[3-(2-氧代-哌嗪-1-基)-丙基]-哌啶-1-甲酸叔丁酯,

1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮,

1-(4-氨基喹唑啉-7-基甲基)-3-丁基-哌嗪-2-酮,

1-(4-氨基喹唑啉-7-基甲基)-3-乙基-哌嗪-2-酮,

1-(4-氨基喹唑啉-7-基甲基)-3-丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-乙氧基甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-苄基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-(1-甲氧基乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3,3-二甲基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-异丙基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-异丁基-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-(2-甲氧基乙基)-哌嗪-2-酮,

1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-6-甲基-哌嗪-2-酮,

(3S,5RS)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮,

1-(4-氯喹啉-7-基甲基)-哌嗪-2-酮,

1-(4-氯噌啉-7-基甲基)-哌嗪-2-酮,

1-(4-氯喹啉-7-基甲基)-3-(S)-甲基哌嗪-2-酮,

1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮,

1-[2-{(甲基)-(吡啶-4-基)-氨基}-乙基]-哌嗪-2-酮三氟乙酸盐,

1-[2-(3-甲基吡啶-4-基-氨基)-乙基]-哌嗪-2-酮,

1-[2-(哒嗪-4-基氨基)-乙基]-哌嗪-2-酮,

4-[3-(4-叔丁氧基羰基氨基-吡啶-3-基)-丙烯基]-3-氧代-哌嗪-1-甲酸叔丁酯,

4-[3-(4-叔丁氧基羰基氨基-吡啶-3-基)-烯丙基]-3-氧代-哌嗪-1-甲酸叔丁酯,

4-[3-(4-叔丁氧基羰基氨基-吡啶-3-基)-丙基]-3-氧代-哌嗪-1-甲酸叔丁酯,

4-(苄氧基羰基)-1-(2-吡咯并[3,2-c]吡啶-1-基乙基)-哌嗪-2-酮,

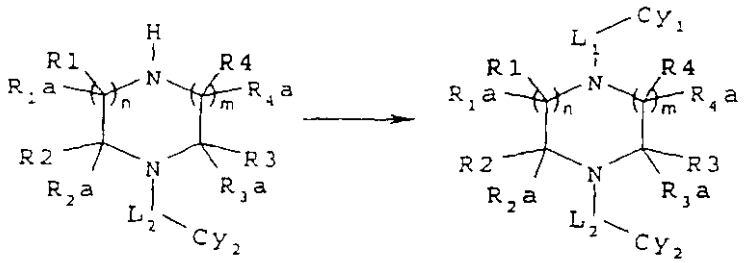
(±)-1-(3-氨基-4-氯基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酯, 和

(±)-1-(3-氨基-4-氯基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸。

本发明化合物的制备

在下面的反应路线1中, 示出了本发明化合物的一般制备过程, 其中, A为N, R_1、R_{1a}、R_2、R_{2a}、R_3、R_{3a}、R_4、R_{4a}、L_1、L_2、Cy_1、Cy_2、m和n如式I定义。

反应路线1

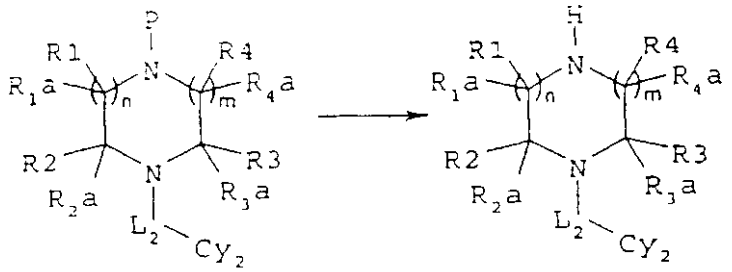


III I'

如反应路线1所示，在适宜的溶剂中，式III的化合物与磺酰基氯化物，烷基卤化物，酸或其活化化合物，如酸酐或酰氯化物，异氰酸酯，氯代甲酸酯或活化氨磺酰基酯进行偶联反应，产生式I化合物，其中，L_1-Cy_1部分分别为磺酰胺、烷基胺、酰胺、脲、氨基甲酸酯或氨磺酰基脲。磺酰胺的形成是在惰性溶剂如二氯甲烷、THF或乙腈中，在约0℃至约100℃下，在活化剂如二甲基氨基吡啶(DMAP)存在或不存在下用碱如三烷基胺完成的。烷基胺的形成可在适宜的溶剂如DMF或乙腈中，在约0℃至约100℃下，采用适宜的碱，如碳酸钾或三烷基胺完成。酰胺，脲，氨基甲酸酯和氨磺酰基脲的形成可采用酸和偶联试剂如EDC或TBTU完成，或者采用活泼酸衍生物的各种变体，并采用一种适宜的碱添加剂如三乙胺、N-甲基吗啉或二异丙基乙基胺。

在下面的反应路线2中，示出了式III化合物的一般制备过程，其中，R_1、R_{1a}、R_2、R_{2a}、R_3、R_{3a}、R_4、R_{4a}、L_2、Cy_2、m和n如式I定义。

反应路线2



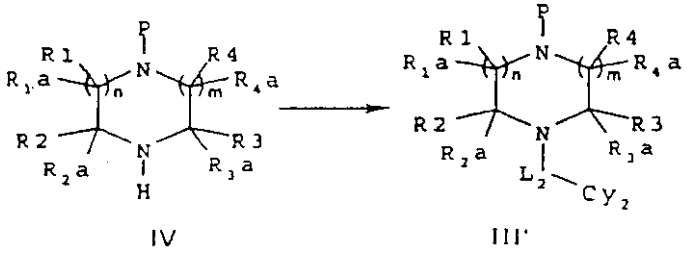
III' III

如反应路线2所示，式III的化合物是由式III'化合物除去氮原子保护基P而制得。在优选的方面，P为烷基、芳烷基或芳基氨基甲酸酯部分，其可采用强酸、强碱或催化氢化在适宜的溶剂如甲醇或乙醇中

除去。

在下面的反应路线3中，示出了式III'化合物的一般制备过程，其中，R_1、R_{1a}、R_2、R_{2a}、R_3、R_{3a}、R_4、R_{4a}、L_1、L_2、Cy_1、Cy_2、m和n和P如前定义。

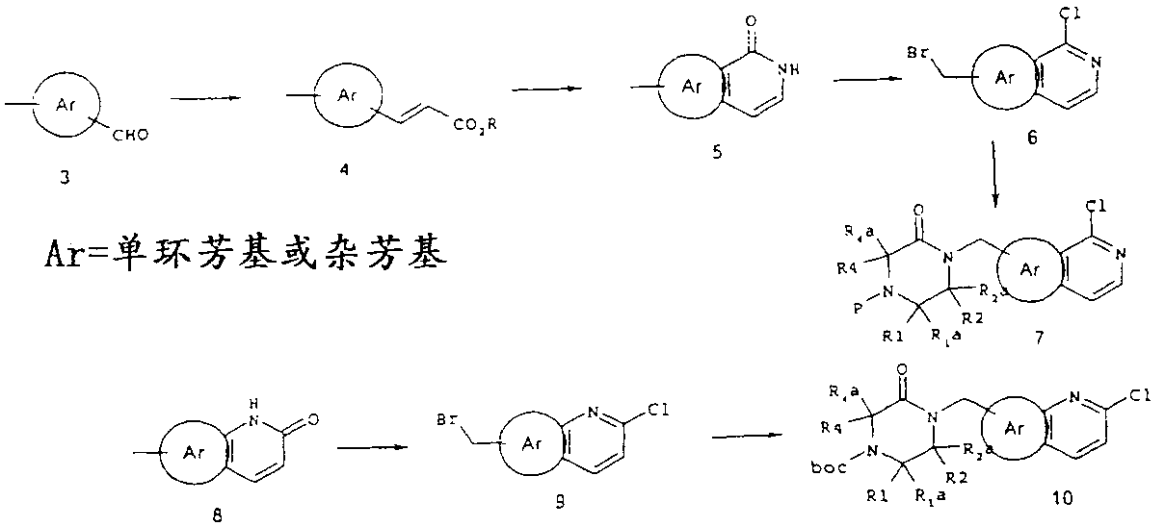
反应路线3



如反应路线3所示，式III'化合物是通过使式IV的化合物与适宜的Cy_2-L_2-LG化合物进行偶联反应获得的，其中LG为离去基团，如氯、溴、碘，或任选地被取代的低级烷基磺酰基氧基或芳基磺酰基氧基，该反应在惰性有机溶剂如THF、乙醚或DMF中，在强碱如氢化钠、六甲基二甲硅烷基叠氮化锂或二异丙基氨化锂存在下进行。在优选的方面，P为烷基、芳烷基或芳基氨基甲酸酯基团。

式7和10的中间体化合物在反应路线4中列出。

反应路线4



Ar=单环芳基或杂芳基

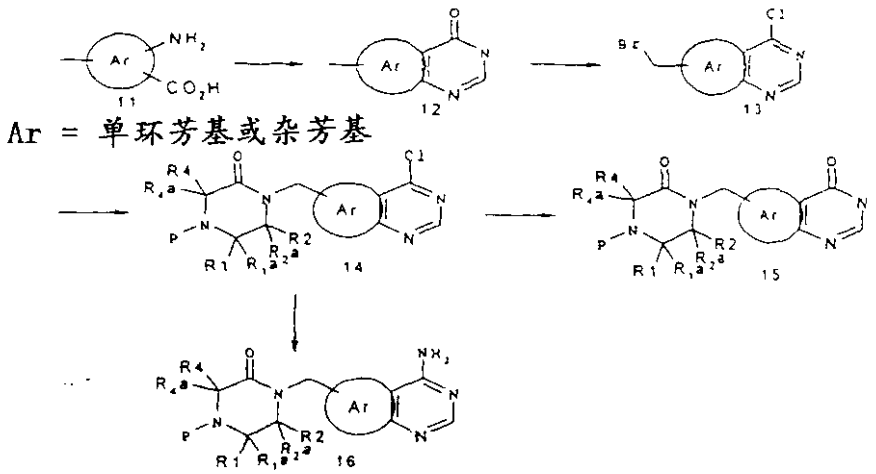
如反应路线4所示，式3的化合物与适宜的丙二酸在极性溶剂如吡啶或乙醇中，和一种碱如哌啶或吡啶在回流下反应，得到式4的化合

物，其中R为H。或者，式3的化合物可与适宜的Wittig或Horner-Emmons试剂在惰性溶剂如THF中反应，得到式4的化合物，其中R为低级烷基。当R为低级烷基时，采用适宜的强酸或碱性碱，酯水解成相应羧酸(R为H)。相应的酸转变为酸氯化物，采用标准试剂如亚硫酰基氯化物，或转变为混合酸酐，转变过程在极性溶剂如丙酮或THF中进行，形成活化酰基化合物。然后，将活化酰基化合物用NaN_3水溶液在约-10℃至约25℃下处理，得到相应酰基叠氮化物。然后，将此酰基叠氮化物化合物在惰性溶剂如苯或甲苯中，在约60℃至约110℃下缓慢加热，然后进行真空浓缩，并在高沸点的惰性溶剂如1,2-二氯苯或苯基醚中，在约180℃至约240℃下，采用催化剂如碘或三丁基胺进行加热，获得式5的化合物。或者，酰基叠氮化物化合物可直接加至高沸点惰性溶剂如苯基醚中，在约180℃至约240℃下加热，采用催化剂如碘或三丁基胺，获得式5的化合物。

按照Syn.，739 (1975)(该文献引入本文作为参考)所述制备的式8化合物或如上的式5化合物可采用标准试剂如$POCl_3$或$POCl_3/PCl_5$氯化并采用标准条件进行卤化，如N-卤代琥珀酰亚胺和苯氧基过氧化物，在惰性溶剂如四氯化碳中进行，分别得到相应的氯-卤代甲基化合物6和9。式6或9的化合物被偶联成式IV的化合物，其中，R_3和R_{3a}合在一起形成氧代基团，在碱性条件下采用氢化钠或KOtBu或某些基团的去质子碱，得到式7或10的化合物。

氨基喹唑啉、喹唑啉酮或氨基-噻吩并嘧啶中间体的制备示于反应路线5。

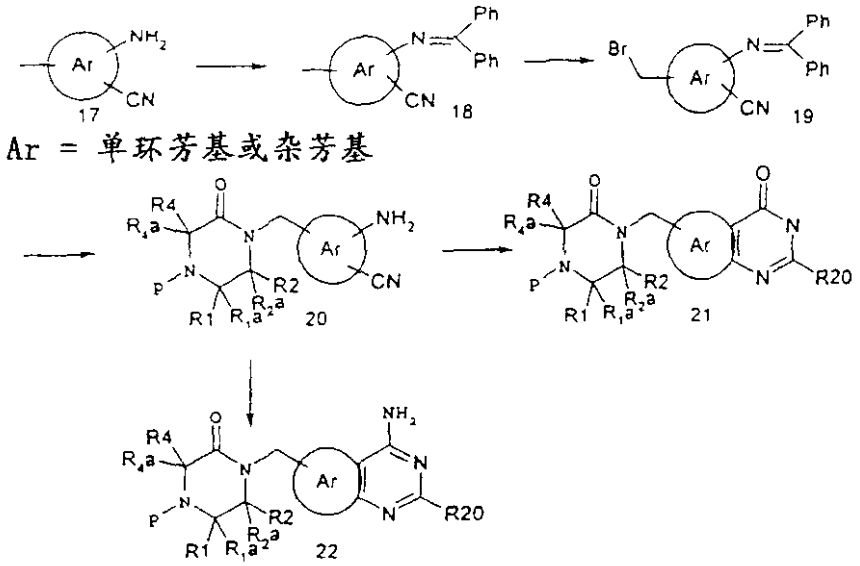
反应路线5



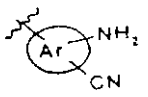
如反应路线5所示，式11的氨基杂芳基羧酸或氨基芳基羧酸，其中氨基和羧酸相互为邻位，在加热下用甲脒处理，形成相应的喹唑啉酮或噻吩并嘧啶酮12。然后，将喹唑啉酮或噻吩并嘧啶酮12转变成氯代喹唑啉或氯代噻吩并嘧啶，采用氯代试剂如$P(O)Cl_3$和加热。氯代喹唑啉或氯代噻吩并嘧啶在芳基碳上被溴化，采用自由基溴代条件。或者，包含羟基-亚甲基的氯代喹唑啉或氯代噻吩并嘧啶转变为相应的溴化物，采用CBr_4/PPh_3；或PBr_3。然后，在惰性溶剂如THF，DMF，乙醚或DME中，溴化物13再与式III化合物的环氮阴离子反应，采用氢化钠，$LiN(SiMe_3)_3$，$NaN(SiMe_3)_3$，LDA，锂醇盐，钠醇盐或适宜的碱。从而形成的式14的化合物，其包含氯代-喹唑啉或氯代-噻吩并嘧啶基团。氯基团采用NH_3在乙醇中在催化剂量的酸如HOAc存在下转变为氨基，得到式16的化合物。或者，在惰性溶剂中，采用伯或仲胺将氯基团转变为取代的氨基基团。或者，在水中采用乙酸，并进行加热，将氯基团转变为羟基基团或采用氢氧化物源，得到式15的化合物。或者，采用醇溶剂并在碱存在下进行加热将氯转变为烷氧基。

另一种合成喹唑啉和噻吩并喹唑啉的合成方法列于反应路线6。

反应路线6



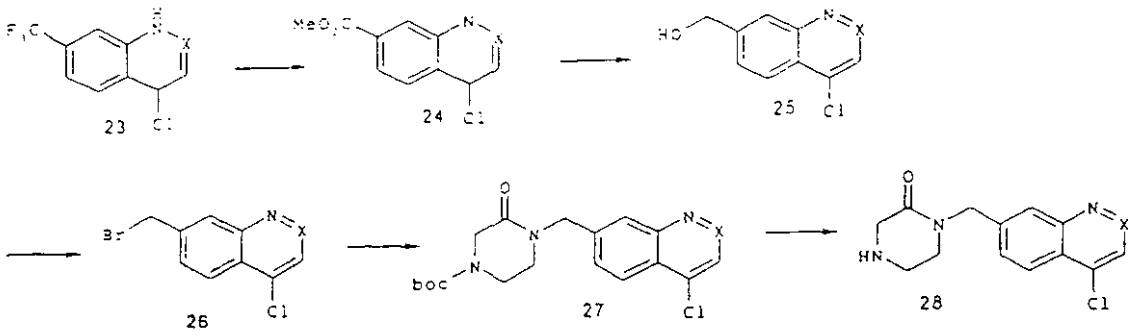
如反应路线6所示，氨基-芳基腈或氨基杂芳基腈17用醛或酮在形成亚胺的条件下进行处理。相应的芳基或杂芳基亚胺采用使用NBS的自由基溴化方法进行溴化。然后，将溴化物用式IV的化合物在碱性条件下偶联，碱性条件如氢化钠、$LiN(SiMe_3)_3$、$NaN(SiMe_3)_3$、LDA、锂醇盐、钠醇盐或适宜的碱，在惰性溶剂，如THF、DMF、乙醚或DME中进行。得到式20的化合物，其中



为亚氨基-芳基腈或亚氨基杂芳基腈。采用酸如盐酸使亚胺脱保护，相应的苯胺。苯胺-芳基-腈或苯胺杂芳基腈20，转变为氨基-喹唑啉或噻吩并嘧啶，式22(其中R_{20}=H)，采用三嗪或甲脒。喹唑啉酮或噻吩并嘧啶酮，式21，其中R_{20}=H，由式20的化合物采用甲酰胺形成。或者，式20的化合物可在酸性条件下反应，如HCl(气体)，在溶剂如乙醇中，在腈存在下，得到式22的化合物，其中R_{20}为烷基、芳基或氨基，这取决于与腈相连的基团。

噌啉(X =N)和喹啉(X =CH)中间体的制备过程如反应路线7所示。

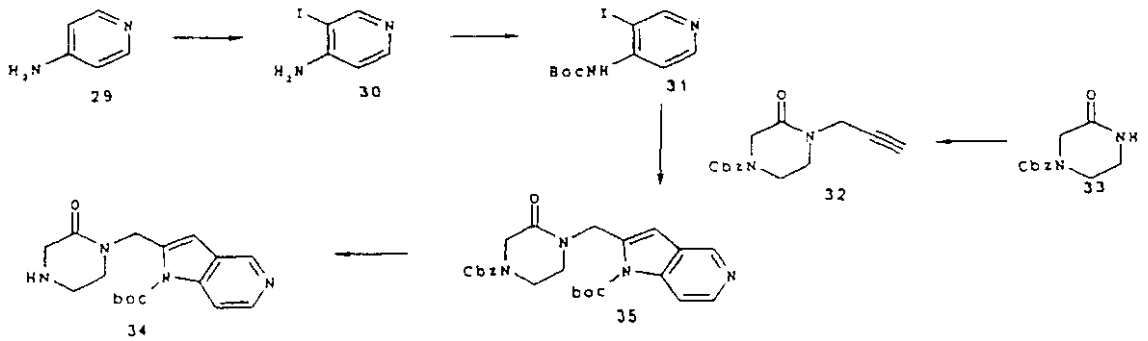
反应路线7



如反应路线7所示，卤代氮杂芳烃23，如4-氯-7三氟甲基喹啉或噌啉，在密封的反应容器中用硫酸(70-95％)在180-220℃下处理约16-48小时。将溶液冷却，倒入水中，用碱中和至pH约3-4。将产物溶解于含水碱中，并通过酸化而沉淀，得到7-羧基-4-氯喹啉或噌啉。通过标准方法将这种物质转变为烷基酯，如甲基(24)或乙基酯。将7-烷氧羰基-4-氯喹啉或噌啉溶解于无水的质子惰性溶剂(THF或乙醚)中。将溶液冷却(-60至-95℃)和用还原剂如氢化铝锂处理。将溶液升温(至约-40至-50℃)约15至30分钟，并用溶剂如乙酸乙酯中止反应。进行标准处理，得到产物7-羟基甲基-4-氯喹啉，或噌啉(25)。物质25用45-50％HBr处理并加热至约100-140℃加热约45-90分钟。冷却后，进行标准处理，获得7-溴甲基-4-氯喹啉(或噌啉)26。如前所述进行烷基化，得到4-氯喹啉(或噌啉)27，再在常规酸化条件下进行脱质子处理，得到4-氯喹啉(或噌啉)28。

吡咯并吡啶衍生物的制备如反应路线8所示。

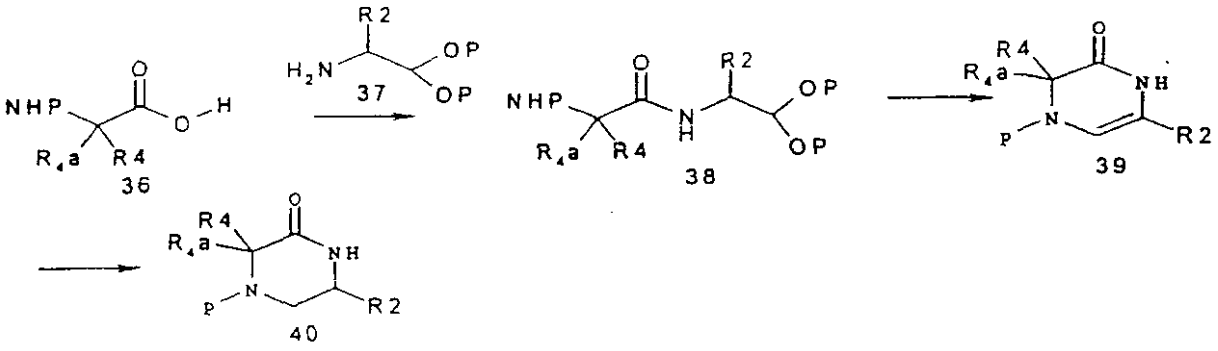
反应路线8



如反应路线8所示，吡咯并吡啶衍生物的制备过程是：在碱如氢化钠存在下用炔丙基溴对适宜保护的氧代哌嗪33进行烷基化处理。形成的炔烃32与卤代吡啶31一起加热(100-120℃)，31任选地用羟基、烷氧羰基氨基或巯基取代，过程中还包括催化剂如$Pd(PPh_3)_2Cl_2$、碘化铜和三乙胺，过程在适宜的溶剂中进行，如乙腈，在密封的容器中，或在DMF中2-20小时。当吡啶用烷氧羰基氨基部分取代时，还用DBU在约60℃下在DMF中进行处理，得到吡咯并吡啶35。随后，采用转化氢化条件如Pd黑在甲酸中进行氨基甲酸酯脱保护，得到所需的氧代哌嗪吡咯并吡啶34。在使34进一步与L_1-Cy_1基团反应后，为产生用L_1-Cy_1代替的氧代哌嗪吡咯并吡啶，需要附加脱保护如采用例如TFA，HCl除去Boc。卤代吡啶31由4-氨基吡啶29进行碘化得到碘代-氨基吡啶30，再进行Boc保护制得。

式40化合物的制备如反应路线9所示。

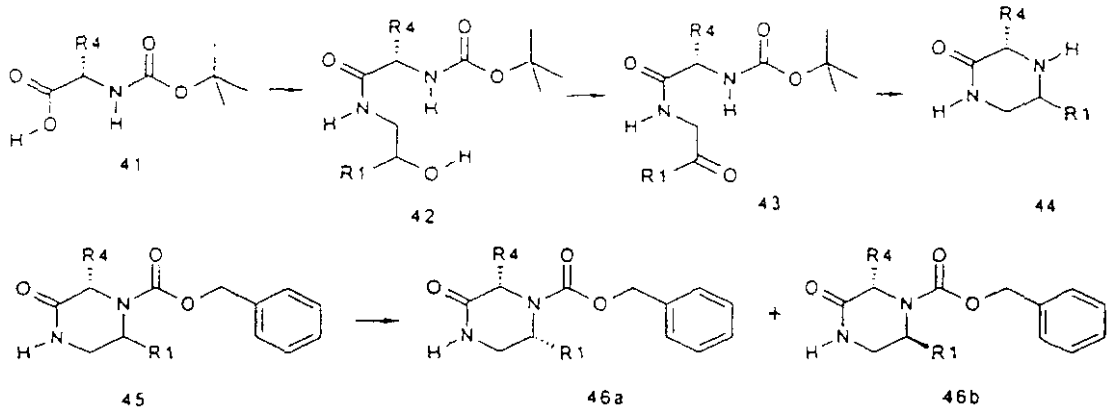
反应路线9



如反应路线9所示，式40的化合物由适宜的保护的单或二取代的氨基-酸36制备。这其中加入氨基-乙醛，如乙缩醛衍生物37所示保护，在标准肽偶联过程中，采用活化试剂如EDC、TBTU或BOP。将形成的二肽基部分38置于除去乙缩醛的条件下，如酸性条件(TsOH)。所得环状物质39采用氢化条件还原，得到式40的化合物。该还原反应也可采用具有氢化物源作用的试剂进行如LAH或氢化钠。

式46a和46b化合物的制备如反应路线10所示。

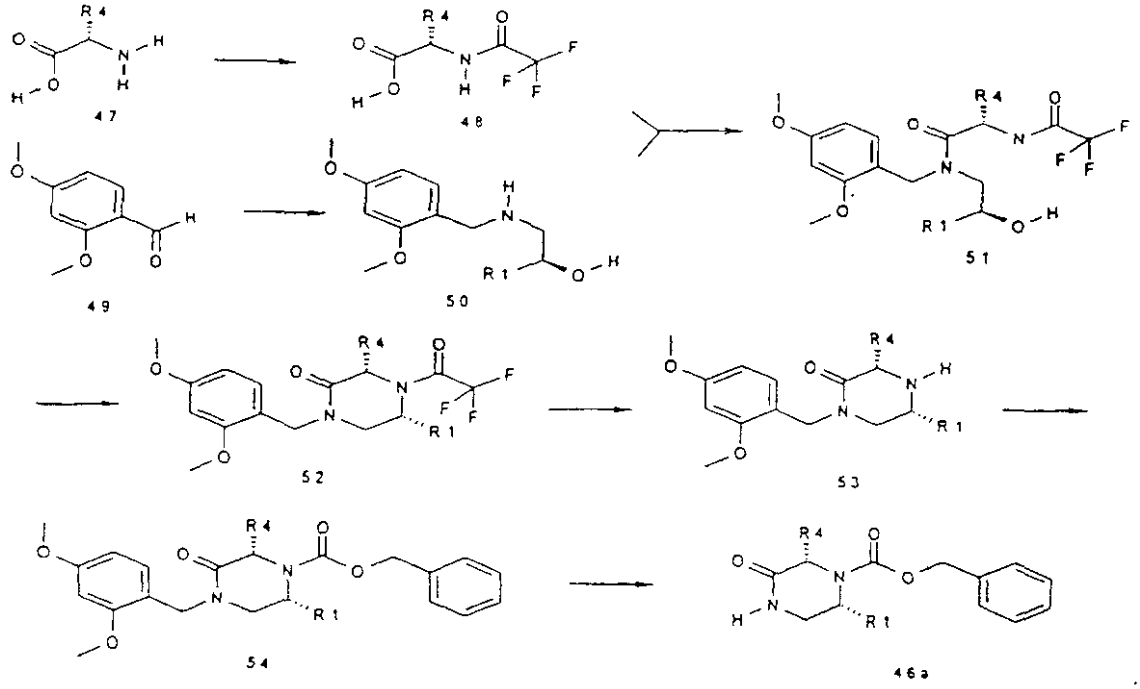
反应路线10



如反应路线10所示，保护的氨基酸41偶联至β-氨基醇上，采用标准肽偶联方法(氯代甲酸异丙基和三乙胺)。然后，使醇42氧化成酮43，例如采用Swern氧化条件。采用三氟乙酸除去保护基，所得环状化合物在氢化条件下还原，得到2-哌啶酮44。使哌嗪-2-酮酮基哌嗪与N-(苄氧基羰基氧基)-琥珀酰亚胺反应，得到非对映体45的混合物，通过色谱法可将其分离，或在某些情形下通过重结晶进行分离，得到化合物46a和46b。

式46a的化合物的手性合成如反应路线11所示。

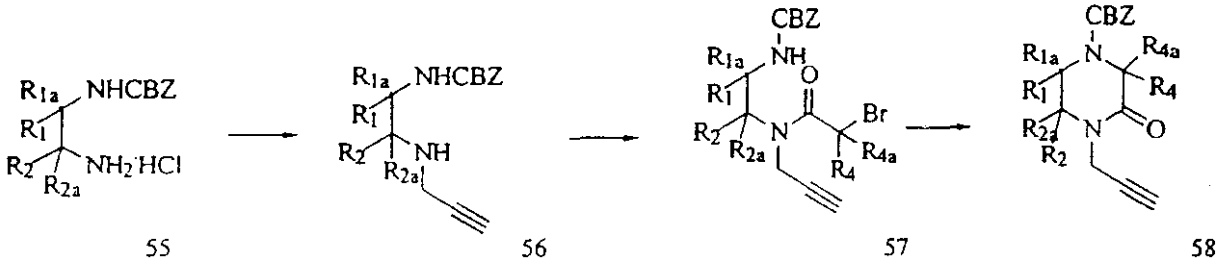
反应路线11



如反应路线11所示，采用三氟乙酸酐和一种碱使氨基酸47以其三氟乙酸酯衍生物被保护，得到化合物48。经还原胺化条件，采用苯甲醛衍生物如2,4-二甲氧基苯甲醛49和相应的伯胺获得氨基-醇50。然后，采用标准的肽偶联方法(氯代甲酸异丙酯和三乙胺)将形成的氨基-醇50偶联至氨基-酸48，得到化合物51。然后，采用Mitsinobu条件完成化合物51的环封闭，得到2-哌嗪酮52。在碱性条件下除去化合物52的三氟乙酸酯基团，得到胺53，其再与N-(苄氧基羰基氧基)琥珀酰亚胺反应，得到氨基甲酸酯54。采用过硫酸钾和磷酸钠的水溶液和加热，使化合物54脱保护，产生化合物46a。反应路线2c所示的哌啶-2-酮的所有可能的旋光对映体可由相应的氨基-醇50和氨基酸47制备。

反应路线12示出了式58化合物的制备，其中，R_1、R_2、R_{2a}、R_4和R_{4a}为氢，R_{1a}为甲酯基、甲氧基甲基或保护的羟基甲基。

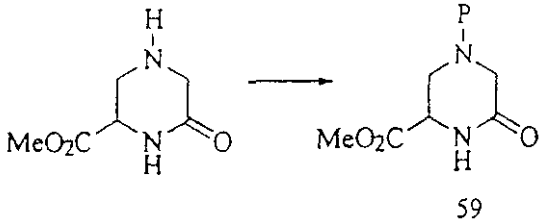
反应路线12



如反应路线12所示，式55的化合物用炔丙基溴在胺碱如三乙胺存在下炔基化，得到式56的化合物。采用标准试剂如DCC用溴代乙酸进行偶联，得到式57的化合物，采用非亲核强碱如氢化钠，在溶剂如THF中进行环化，得到所需的式58化合物。

式59的化合物的制备过程如反应路线13所示。

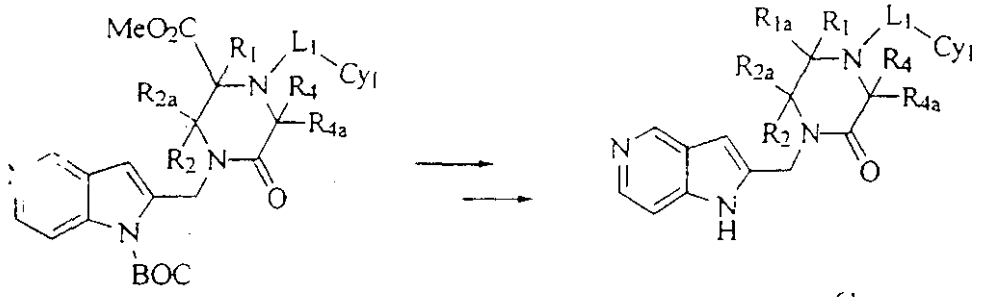
反应路线13



如反应路线13所示，6-氧代哌嗪-2-甲酸甲酯(Aebischer, B., Helv. Chim. Acta 1989, 72, 1043-1051)例如采用氯代甲酸苄酯或氯代甲酸烯丙酯，采用标准条件进行保护，得到化合物59。采用炔丙基溴，采用强碱如氢化钠，在极性溶剂如HF或DMF中，将化合物59进行炔基化，得到式58的化合物(反应路线12)。

反应路线14列出了式61化合物的制备过程，其中，R_1、R_2、R_4、R_{4a}、L_1和Cy_1如上式I定义，R_{1a}和R_{2a}独立地是羧基、乙酰氨基或羟基甲基。

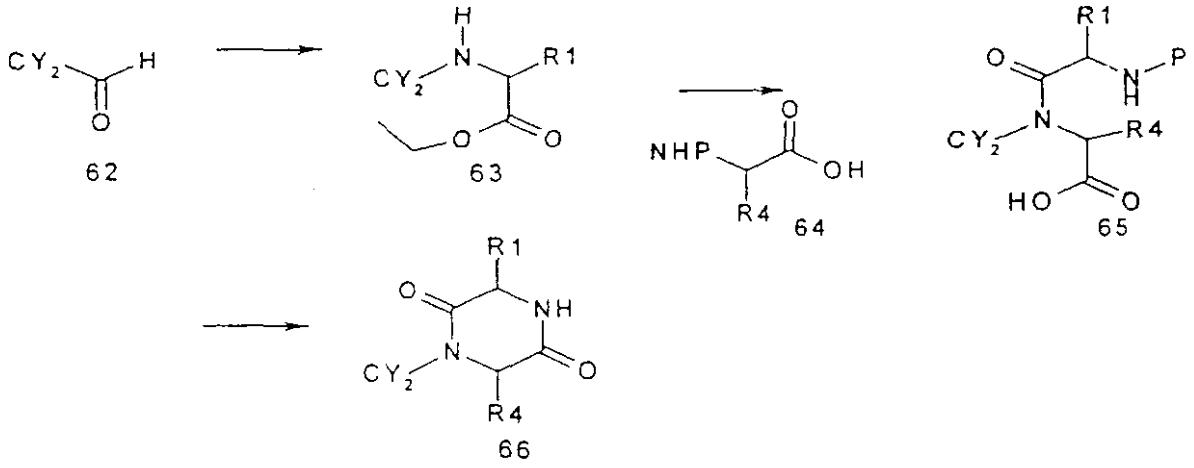
反应路线14



如反应路线14所示，式61的化合物是通过用碱如氢氧化钠或氢氧化锂使相应的酯进行水解得到酸61而制得。采用标准偶联剂如TBTU或EDC使酸与伯或仲胺或氨进行偶联，得到酰胺61。或者，采用还原剂如硼氢化钠还原酯，得到羟甲基树脂61。

式66的二酮基哌嗪化合物的制备如反应路线15所示。

反应路线15

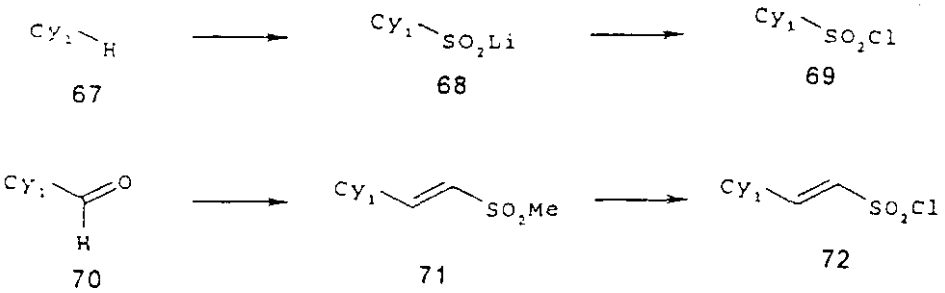


如反应路线15所示，包含Cy_2基团的醛62在还原胺化条件下与氨基酸酯进行缩合。形成的仲胺63再与N-保护的氨基酸64偶联。形成的二

肽65被脱保护，其通常导致环化成N-Cy_2二酮基哌嗪66。或者，对于不环化的二肽65来说，形成二酮基哌嗪66可采用肽偶联剂如EDC、TBTU或BOP来实现。

磺酰基氯化物中间体69和72的制备过程如反应路线16所示。

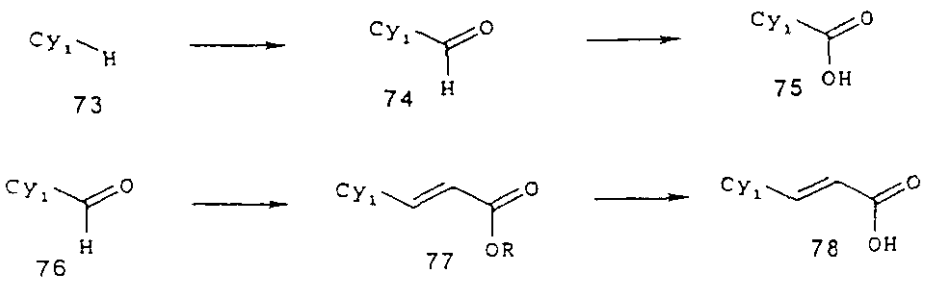
反应路线16



如反应路线16所示，Cy_1取代的磺酰基氯化物69和72是这样制备的：在-78℃下，用一种强碱如正丁基锂处理适宜的芳基或杂芳基化合物67，再加入SO_2气体，再用氯化试剂如NCS或SO_2Cl_2处理形成的芳基或杂芳基磺酸锂68，得到化合物69，或者，例如采用甲磺酸乙酯使适宜的芳基或杂芳基醛70进行同系化反应，得到化合物71，和采用氯代膦酸乙酯得到化合物72。

式Cy_1-CO_2H的中间体化合物75和78的制备过程如反应路线17所示。

反应路线17

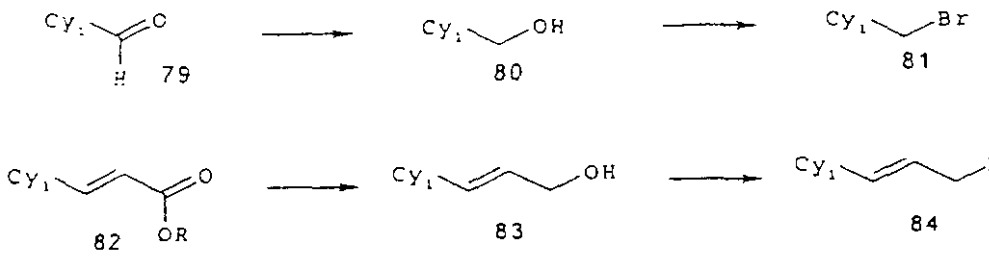


如反应路线17所示，所需产物Cy_1酸75和78可这样获得：在适宜的溶剂如二氯甲烷或水/乙醇中，采用例如MnO_2，PDC或$AgNO_3$，将相应的醇或醛74氧化。Cy_1取代的芳基和杂芳基基团73可通过脱质子化方法官能

化，采用适宜的非亲核碱，如正丁基锂，在适宜的溶剂如乙醚或THF中进行，并用适宜的羰基亲电试剂如DMF、CO_2或氯代甲酸烷基酯中止(quenching)。或者，酸也可通过使相应的酯77进行水解而产生，例如采用氢氧化钠或氢氧化锂。例如，在丙烯酸酯中，如前定义的Cy_1-(亚烯基)-基团可通过使Cy_1醛76进行同系化反应而产生，采用常用的Wittig型或Horner-Emmons型试剂，在适宜的溶剂如二氯甲烷或THF中。

Cy_1烷基(81)和链烯基(84)卤化物的制备过程如反应路线18所示。

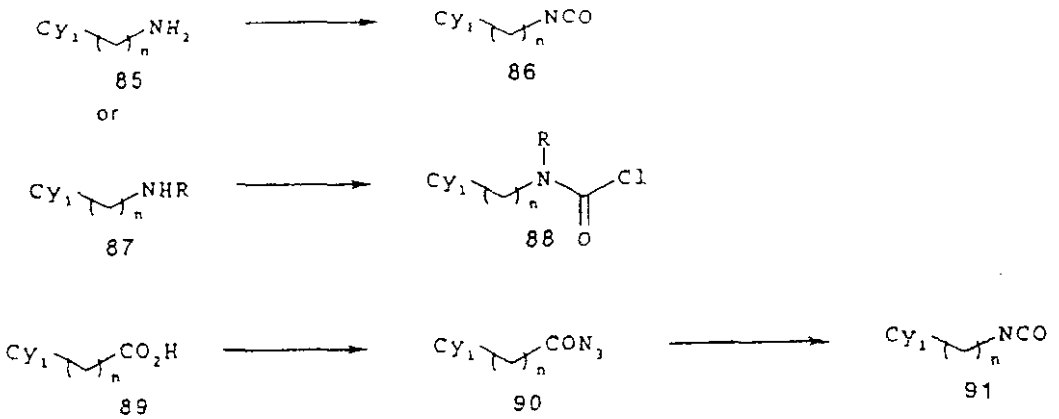
反应路线18



如反应路线18所示，Cy_1烷基和链烯基卤化物81和84可这样制备：采用NBS、CBr_4或PBr_3，在标准溶剂条件下，卤化相应的醇80和83。醇可通过在适宜的溶剂中，采用$NaBH_4$或DIBAL还原相应的醛79或酯82而产生。

Cy_1异氰酸酯中间体86、88和91的制备过程如反应路线19所示。

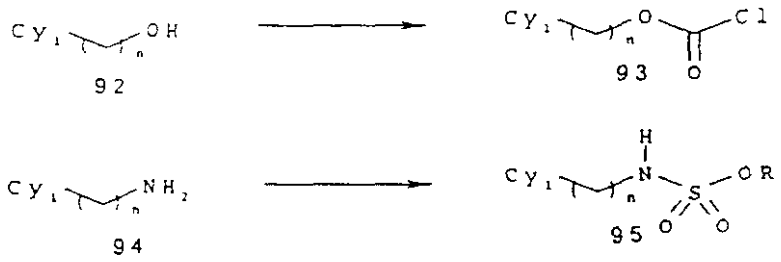
反应路线19



如反应路线19所示，Cy_1异氰酸酯86和88通过氯羰基化方法获得，采用光气或三光气，在适宜的溶剂如二氯甲烷中，用适宜的碱添加剂如三乙胺或吡啶对相应的伯胺或仲胺85和87进行作用。或者，异氰酸酯91也可通过在相应Cy_1羰基叠氮化物90的适宜的溶剂如甲苯、对二噁烷或DMF中，通过Curtius重排获得。反过来，羰基叠氮化物90又得自相应羧酸89，采用DPPA试剂，或者通过混合酸酐，经氯代甲酸烷基酯试剂进行，在适宜的溶剂如DMF或丙酮中，并采用适宜的碱添加剂如三乙胺。

Cy_1氯代甲酸酯中间体93和氨磺酰基酯95的制备过程如反应路线20所示。

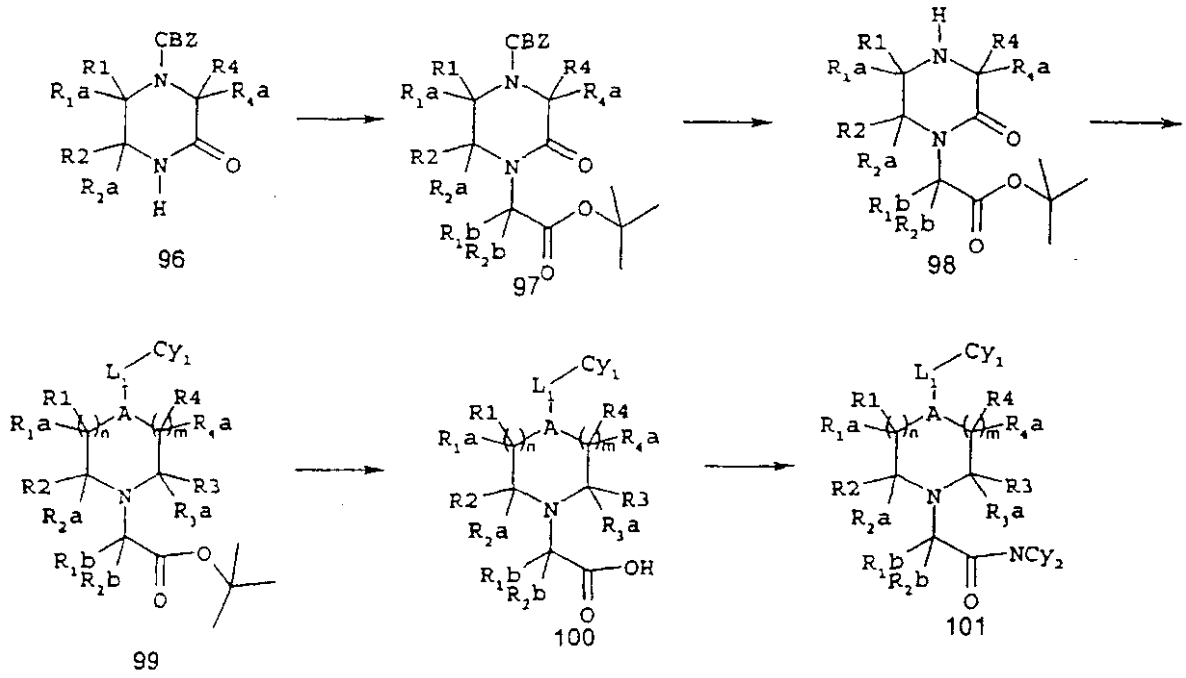
反应路线20



如反应路线20所示，Cy_1氯代甲酸酯93由相应的醇92进行氯羰基化反应获得，采用试剂如光气、三光气或1,1'-羰基二咪唑，在适宜的溶剂如二氯甲烷中。活化氨磺酰基酯95由相应的胺94制备，采用儿茶酚硫酸酯，在适宜的溶剂中。

本发明的化合物101的制备过程如反应路线21所示。

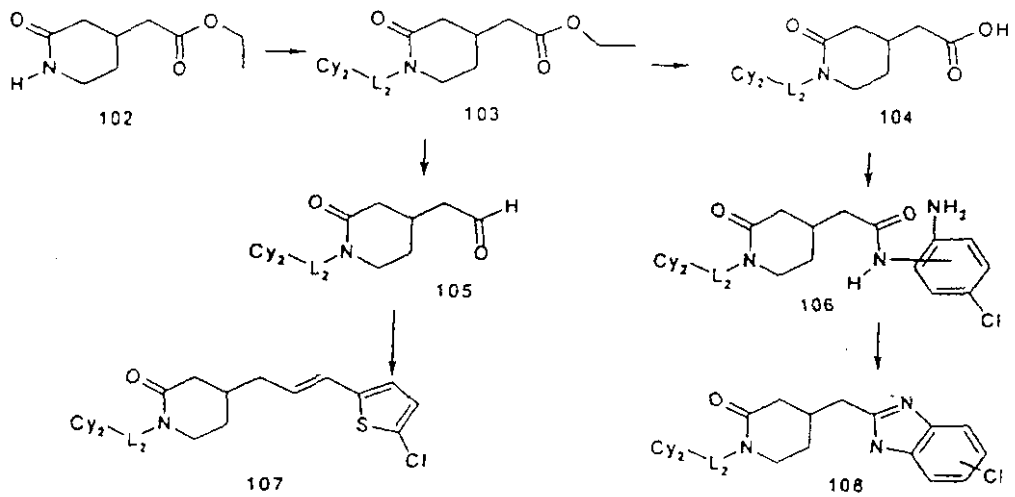
反应路线21



如反应路线21所示，哌嗪-2-酮96的烷基化反应可采用强碱如氢化钠和卤代乙酸叔丁基酯得到乙酸酯97来实现。Pd-催化的氢化反应使得从乙酸酯97上除去CBZ基团，得到胺98，胺又如反应路线1所示转变为L_1-Cy_1衍生物99。叔丁基酯99进行水解而形成相应的酸100是采用例如TFA/二氯甲烷完成的。所得酸100与选择性地保护的胺$HNCy_2$进行偶联，在通常酰胺键形成条件下进行，得到乙酰胺101。

Cy_1为苯并咪唑-2-基的本发明化合物107和108的制备过程如反应路线22所示。

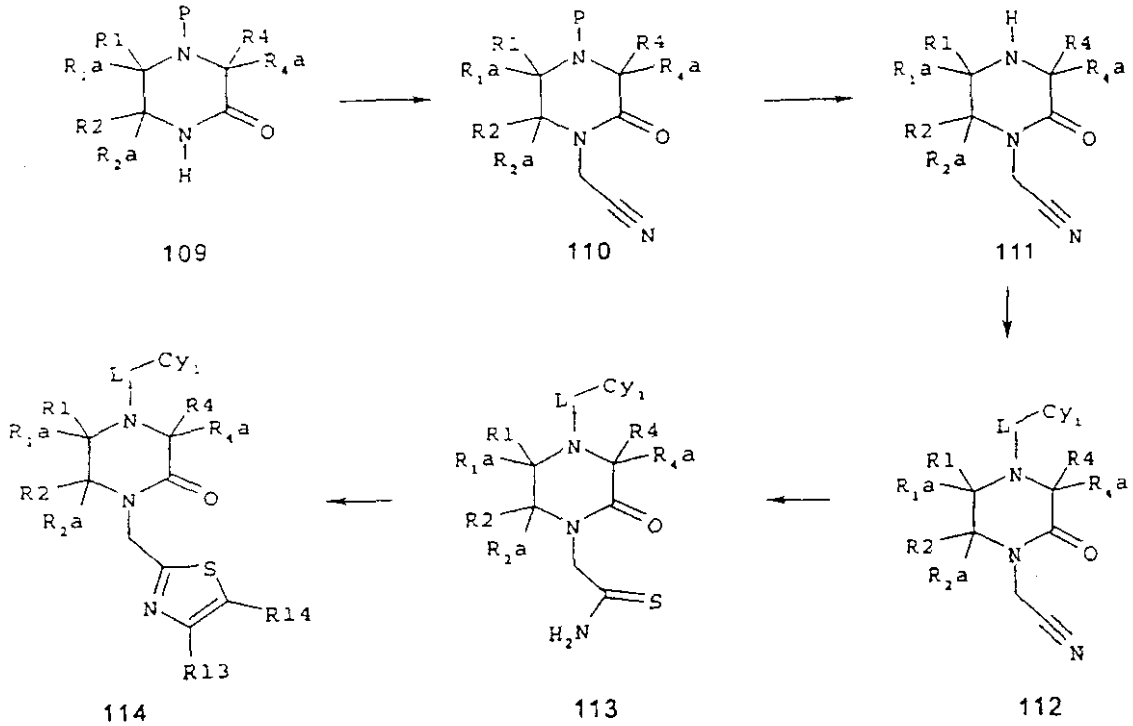
反应路线22



哌啶-2-酮102通过与反应路线3类似的过程进行烷基化，得到N-Cy_2-L_2酯衍生物103，其水解得到酸104或还原得到醛105。酸104与胺偶联得到酰胺106，其再与乙酸酐环化，得到化合物108。醛105进行Wittig-偶联产生化合物107。

反应路线23列出了式114化合物的制备过程，其中，R_1、R_{1a}、R_2、R_{2a}、R_4、R_{4a}、L_1、Cy_1、P如式I定义，R_{13}和R_{14}如本文定义。

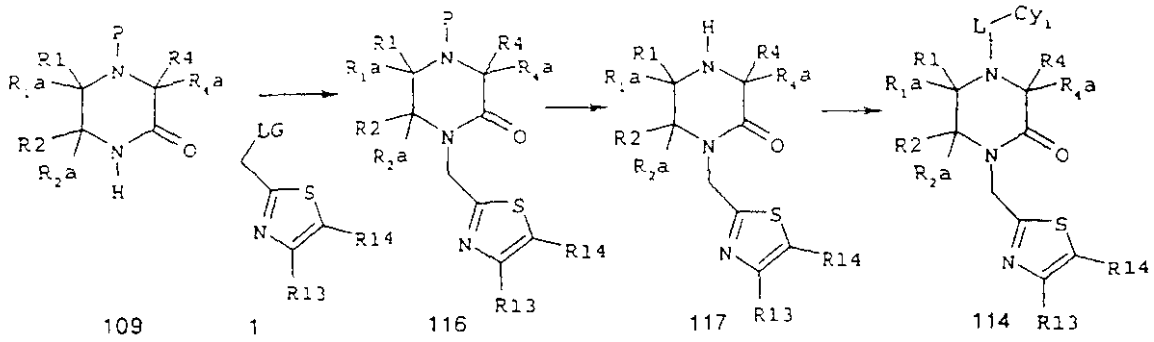
反应路线23



如反应路线23所示，式109的化合物用适宜的LG-CH2-CN基团进行烷基化而得到式110的化合物，其中，LG为离去基团，如氯、溴、碘或任选地被取代的低级烷基磺酰基氧基或芳基磺酰基氧基，烷基化过程在惰性有机溶剂如THF、乙醚或DMF中，在强碱如氢化钠、六甲基二甲硅烷基叠氮化锂或二异丙基氨化锂存在下进行。在优选的方面，P为叔芳烷基或芳烷基氨基甲酸酯。通过强酸如TFA、路易斯酸或试剂如三甲基甲硅烷基碘除去基团P，得到式111的化合物。式111的化合物与适宜的$LG-L_1-Cy_1$进行如反应路线1所述的偶联，得到式112的化合物，其中L_1-Cy_1部分为磺酰胺、烷基胺、酰胺、脲、氨基甲酸酯或氨磺酰基脲。在二异丙基乙基胺、三乙胺或其它适宜的碱存在下，在高温下，优选在>80℃下，式112的化合物与溶解于乙醇、甲醇或其它适宜溶剂中的硫化氢反应，得到式113的化合物。式114的化合物可通过在适宜的高沸点溶剂存在下，加热式$R_{13}-C(O)-CH(LG)-R_{14}$的酮基与式113的化合物制得。LG为如前定义的离去基团。如果R_{13}或R_{14}包含保护基，则该基团可在此时除去。

式114化合物(反应路线23)的另一种制备方法如反应路线24所示。

反应路线24

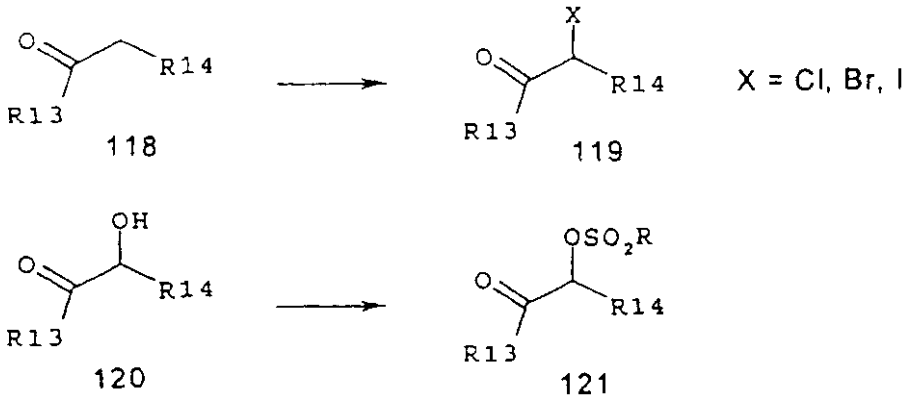


式116的化合物可由式109的化合物制备，采用如反应路线3所述用于烷基化Cy_2-Lg_2-LG的条件，其由式115的化合物表示。采用强酸、强碱或还原条件除去基团P可得到式117的化合物。式114的化合物由化

合物117采用反应路线1所述的条件制备。

反应路线25列出了显示式119和121化合物的基团R_{13}-C(O)-CH(LG)-R_{14}的酮基的制备过程。

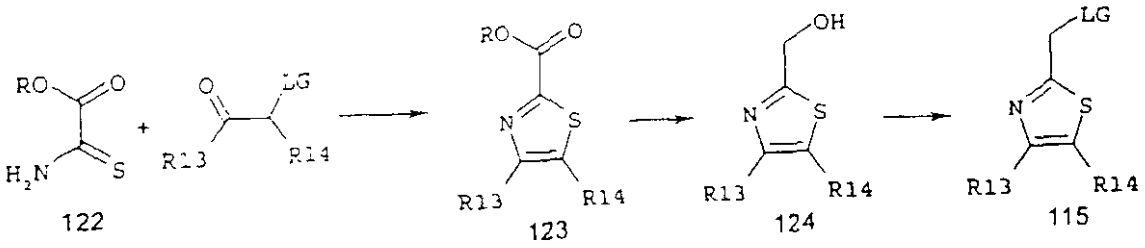
反应路线25



式118的化合物用适宜的试剂如亚硫酰氯化物、溴化物、溴化物/HOAc、NBS或碘化物进行卤化产生相应的式119的卤化物。式120的化合物可与磺酰氯和适宜的碱如吡啶或三乙胺反应，得到式121的化合物。

式115的噻唑的制备过程如反应路线26所述。

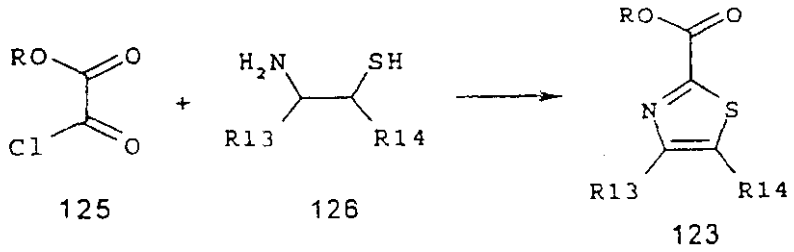
反应路线26



式122的硫代酰胺与式R_{13}-C (O)-CH(LG)-R_{14}的酮在升高的温度下进行缩合反应，得到式123的噻唑。用LAH、DIBAL或类似的试剂进行还原，得到式124的醇。采用PBr_3可制得式115的化合物，得到溴化物(或采用磺酰氯和碱得到磺酸酯)。

反应路线27显示了另一种制备式123的噻唑中间体的方法。

反应路线27

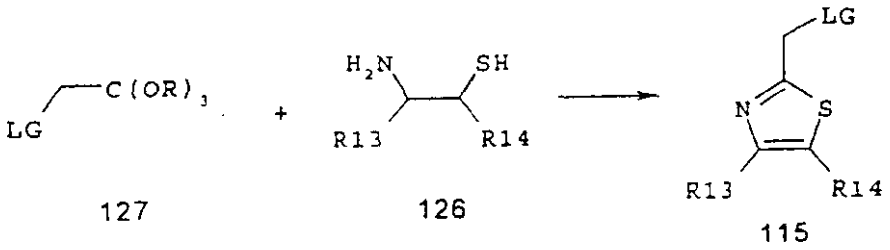


125 126 123

式125的化合物与式126的氨基-硫醇与一种碱如吡啶进行缩合，得到式123的噻唑。该方法特别适用于R_{13}与R_{14}组合形成芳环系统的时候。

反应路线28显示了另一种制备噻唑中间体的方法。

反应路线28

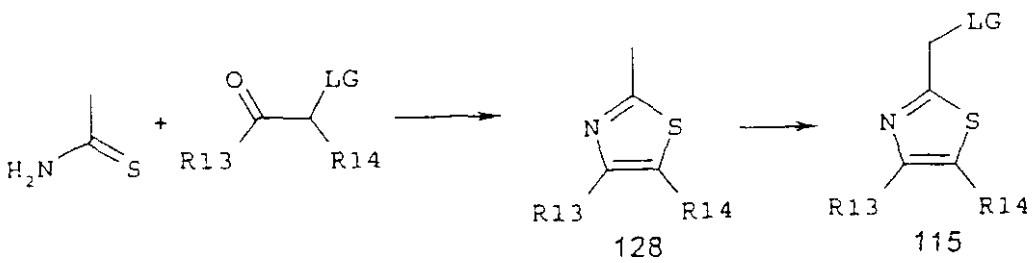


127 126 115

式127的化合物，如2-氯-1,1,1-三乙氧基乙烷可与式126的化合物在升高的温度下进行缩合，得到式115的化合物。该方法特别适用于R_{13}与R_{14}组合形成芳环系统的时候。

反应路线29显示了另一种制备式115的噻唑中间体的方法。

反应路线29

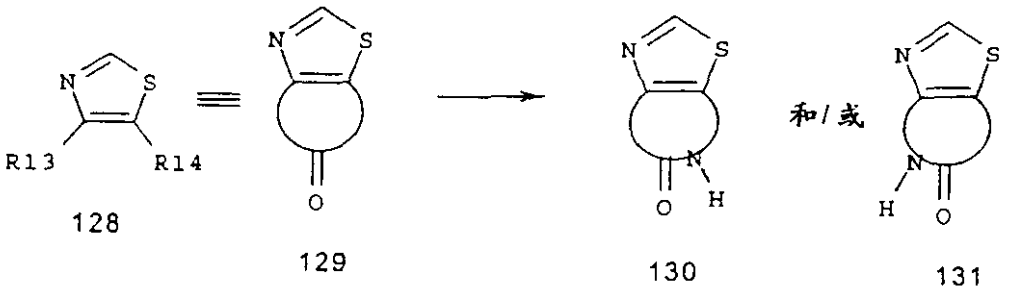


128 115

硫代乙酰胺与式R_{13}-C (O)-CH(LG)-R_{14}的酮的升高的温度下进行缩合，得到式128的噻唑。采用NBS和一种引发剂，在升高的温度下，在一种溶剂如四氯化碳中进行提供离去基团如Br的官能化反应，得到式115的化合物。该方法特别适用于R_{13}与R_{14}组合形成芳环系统的时候。

反应路线30示出了式128的化合物进行扩环反应以得到式130和131内酰胺产物的方法。

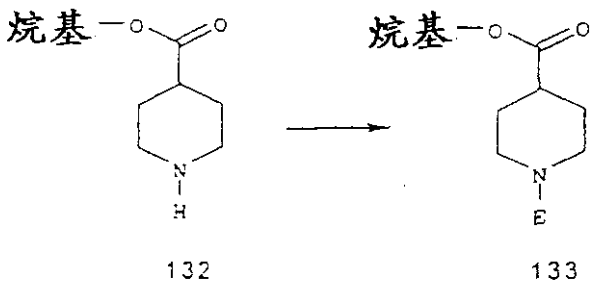
反应路线30



当R_{13}与R_{14}合并形成包含酮的如式21所示的碳环时，则可采用Schmidt反应实现扩环以形成内酰胺产物130和131。在0℃至室温下，将酮129与叠氮化钠的混合物在硫酸与氯仿中搅拌。当酮129首先用羟基胺盐酸盐处理得到中间体肟时，也可采用Beckman扩环反应。当采用噻唑-环己酮物质时，当Semmler-Wolf芳构化机理占优势时，也可观察到苯胺副产物。

式133中间体的制备如反应路线31所示。

反应路线31



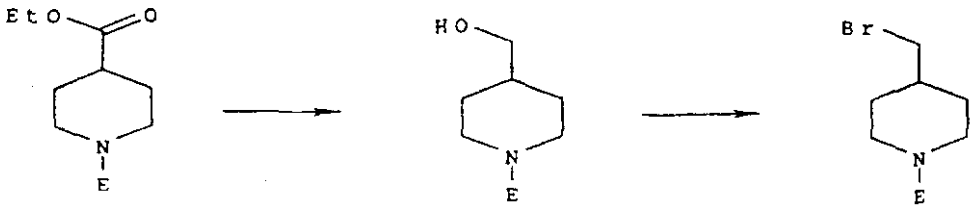
E =芳基，杂芳基，烷氧羰基氨基甲酰基，酰基，烷基氨基甲酰基，

烷基

当式133的E为芳基或杂芳基时，可采用Buchwald和Hartwig 发展的Pd催化的芳族碳-氮成键反应制备式133的化合物。该反应已有综述：Acc. Chem. Res. 1998 31, 805-818，并且可概括为包括以下反应：在惰性溶剂中，在Pd(0)催化剂存在下，在升高的温度下，芳族溴化物、氯化物或三氟磺酸盐与一种碱如叔丁醇钠，与伯或仲胺进行反应。当式133的E为烷氧羰基、酰基、烷基氨基甲酰基或烷基时，可采用相应的卤化物以在碱存在下偶联至式132化合物上。当式133的E为氨基甲酰基时，可采用异氰酸酯以从化合物132生产化合物133。

反应路线132示出了可用作中间体的式13化合物的制备过程。

反应路线32

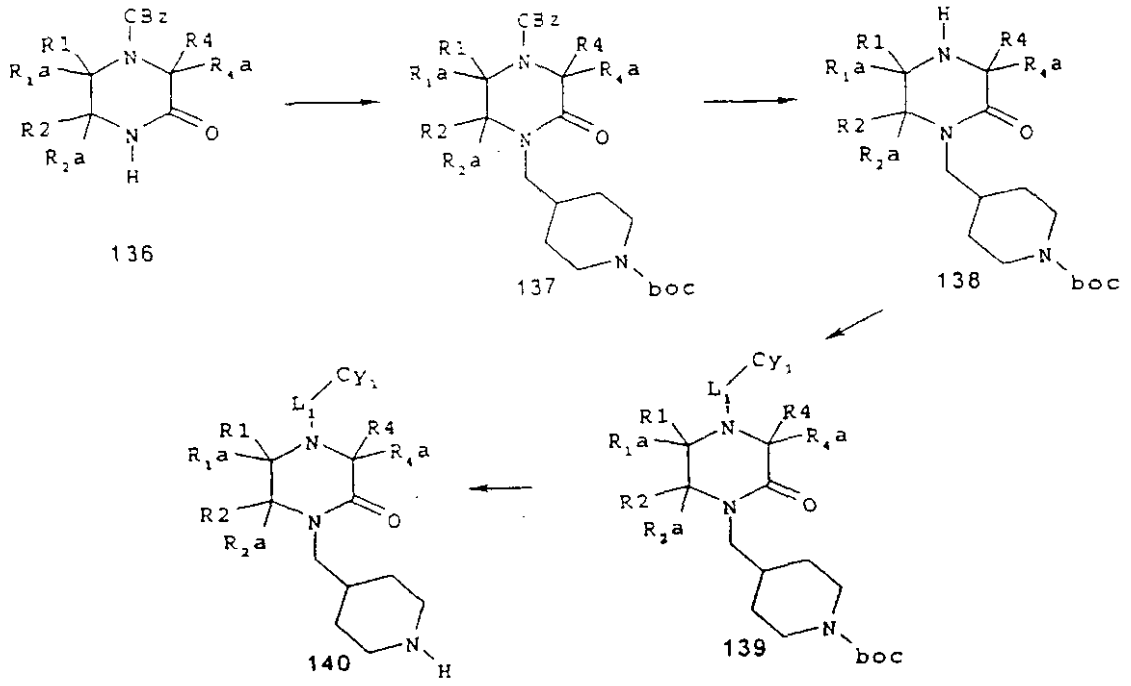


在非质子溶剂中，用还原剂如LAH、DIBAL或其它类似的试剂还原式133的化合物，可得到式134的醇。

采用CBr_4/PPh_3或其它类似的试剂将醇134转化成优良的离去基团如溴化物，可得到式135的化合物。

反应路线33列出了式140化合物的制备过程，其中，R_1、R_{1a}、R_2、R_{2a}、R_4、R_{4a}、L_1、Cy_1如前定义。

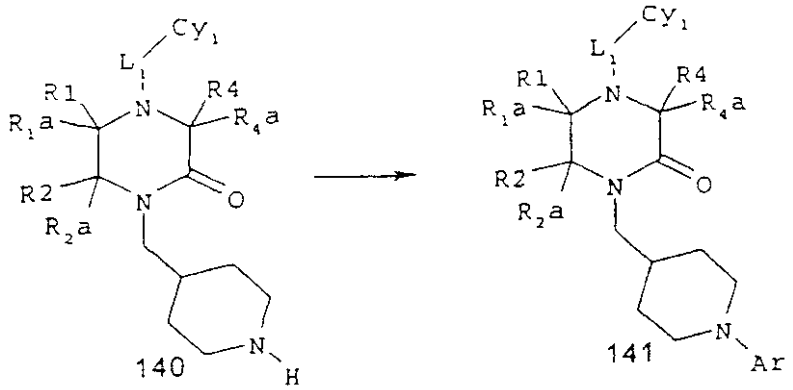
反应路线33



当E为叔丁氧羰基时，在惰性有机溶剂如DMF中，在强碱如氢化钠、六甲基二甲硅烷基叠氮化锂或二异丙基氨化锂存在下，式136化合物与式135化合物的烷基化反应，可得到式137的化合物。在适宜的溶剂如乙醇中通过催化氢化除去CBz(苄氧基羰基)基团，得到式138的化合物。式138的化合物与LG-L_1-Cy_1间的偶联反应可如前所述进行，以得到式139的化合物，其中，L_1-Cy_1部分为磺酰胺、烷基胺、酰胺、脲、氨基甲酸酯或氨磺酰基脲。采用强酸如TFA除去Boc(叔丁氧羰基)，得到式140的化合物。

反应路线34示出了式141化合物的制备方法，其中，Ar为芳环。

反应路线34

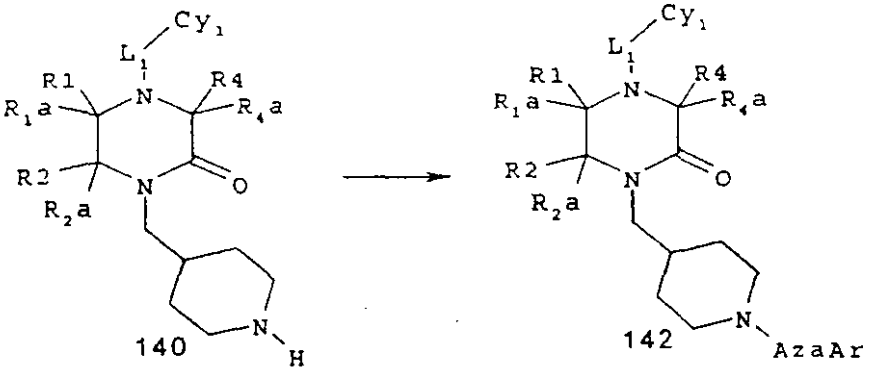


采用Buchwald和Hartwig 发展的Pd催化的芳族碳-氮成键反应，可

将式140的化合物转化成式141的化合物。该反应已有综述：Acc. Chem. Res. 1998 31, 805-818, 并且可概括为包括以下反应：在惰性溶剂中，在Pd(0)催化剂存在下，在升高的温度下，芳族溴化物、氯化物或三氟磺酸盐与一种碱如叔丁醇钠，与伯或仲胺进行反应。

反应路线35示出了式142化合物的制备方法，其中，AzaAr为氮杂芳环。

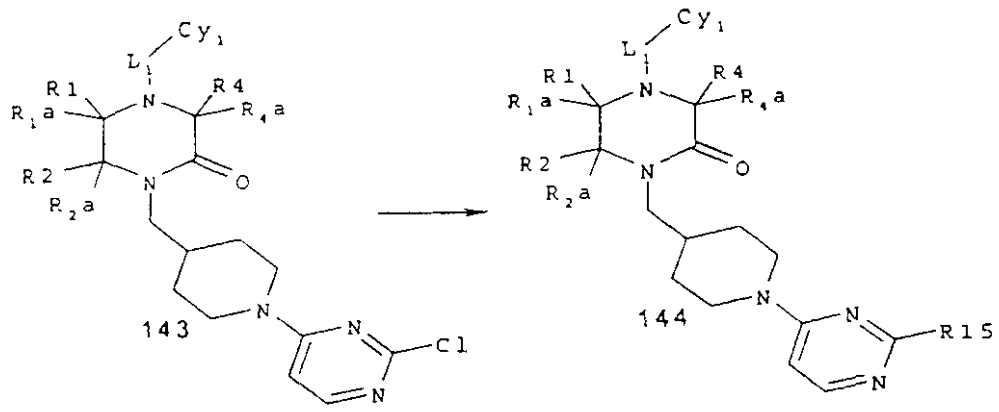
反应路线35



在升高的温度下，在惰性高沸点溶剂如正丁醇、二甲苯或NMP中，将卤代的化合物与式140的化合物加热，可由卤代的氮杂芳族化合物制备式142的化合物。最适用于该反应的氮杂芳族化合物的类型在向置换活化的环位置上采用有卤素离去基团。该体系可包括但不限于：2-氯吡啶、2-氯喹啉、2-氯嘧啶、4-氯-嘧啶和2，4-二氯-嘧啶。

反应路线36示出了式144化合物的制备过程，其中，R_{15}为烷基胺、烷基乙醚或烷硫基。

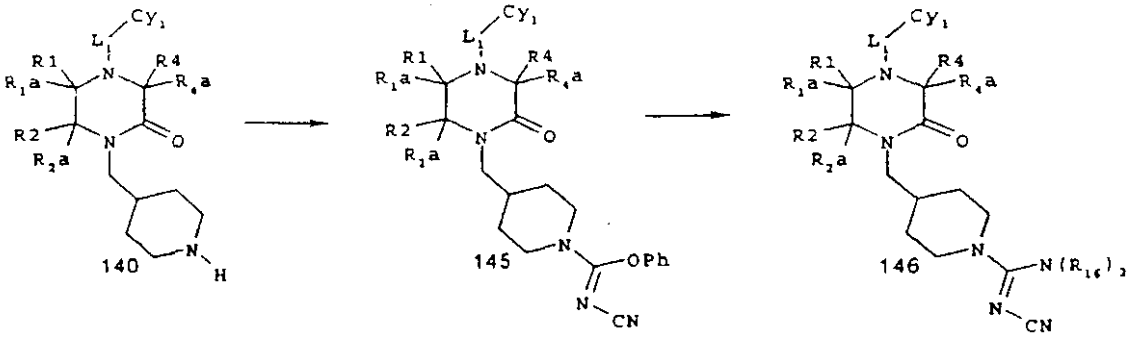
反应路线36



在惰性溶剂中使式143的化合物与胺、醇或硫醇一起加热，可得到相应的式144的化合物。

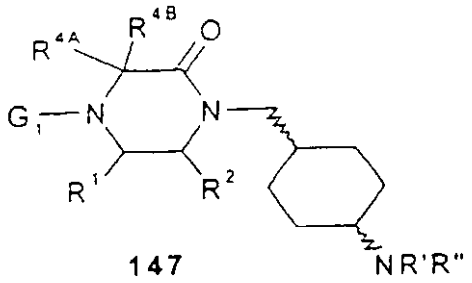
反应路线37示出了式145化合物的制备过程和转化成式146化合物的过程，其中，R_{16}独立地为H或烷基。

反应路线37



在室温或加热下，使式140的化合物与试剂如氰基亚氨基碳酸二苯酯偶联，制得式145的化合物。在惰性溶剂中加热化合物145与胺$NH(R_{16})_2$(其中，每一个R_{16}独立地为H或烷基)，得到式146的化合物。

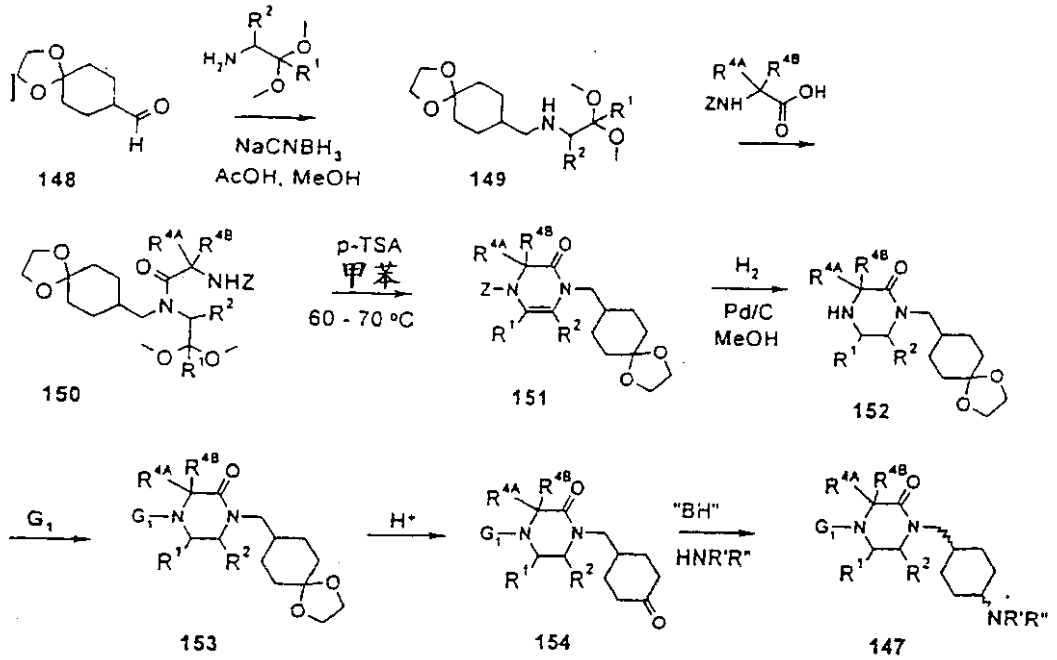
反应路线38示出了制备式147的1-(烷基，芳基)氨基-4-甲基环己基-酮基哌嗪的制备过程。



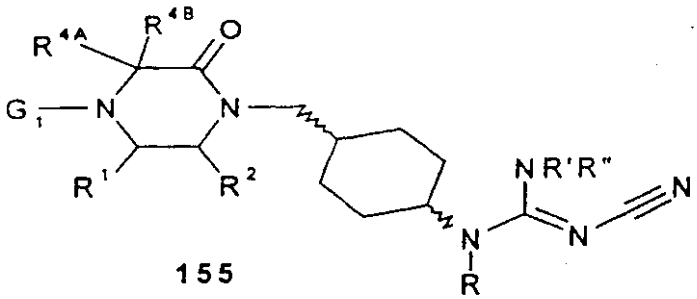
147

如反应路线38所示，式147化合物的优选制备方法包括：构造包含4-甲基环己-1-酮作为N-1取代基的环缩酮的酮基哌嗪152。中间体152的构造可通过中间体148(按照下述文献的方法制备：Pearson等；J. Org. Chem. 62, 1997, 5284)与氨基乙醛的取代乙缩醛进行还原胺化，得到中间体149。然后，中间体149再用适宜的N-保护的取代的α-氨基酸进行酰化，得到中间体150。再用对甲苯磺酸处理中间体150得到不饱和的酮基哌嗪151。将中间体151进行脱保护氢化，得到中间体152。使部分G_1连接得到中间体153。在酸性条件下使4-取代的环己酮的乙缩醛进行水解，得到中间体154。用适宜的胺进行还原胺化，得到式147的化合物。环己酮用选定的胺进行还原胺化可采用本领域技术人员公知的标准方法，采用硼氢化物如硼氢化钠或三叔丁基硼氢化锂，在适宜的溶剂如甲醇或乙酸中，在0-100℃下进行。通过硅胶色谱或PR-HPLC可分离出还原胺化的异构体顺/反产物。

反应路线38



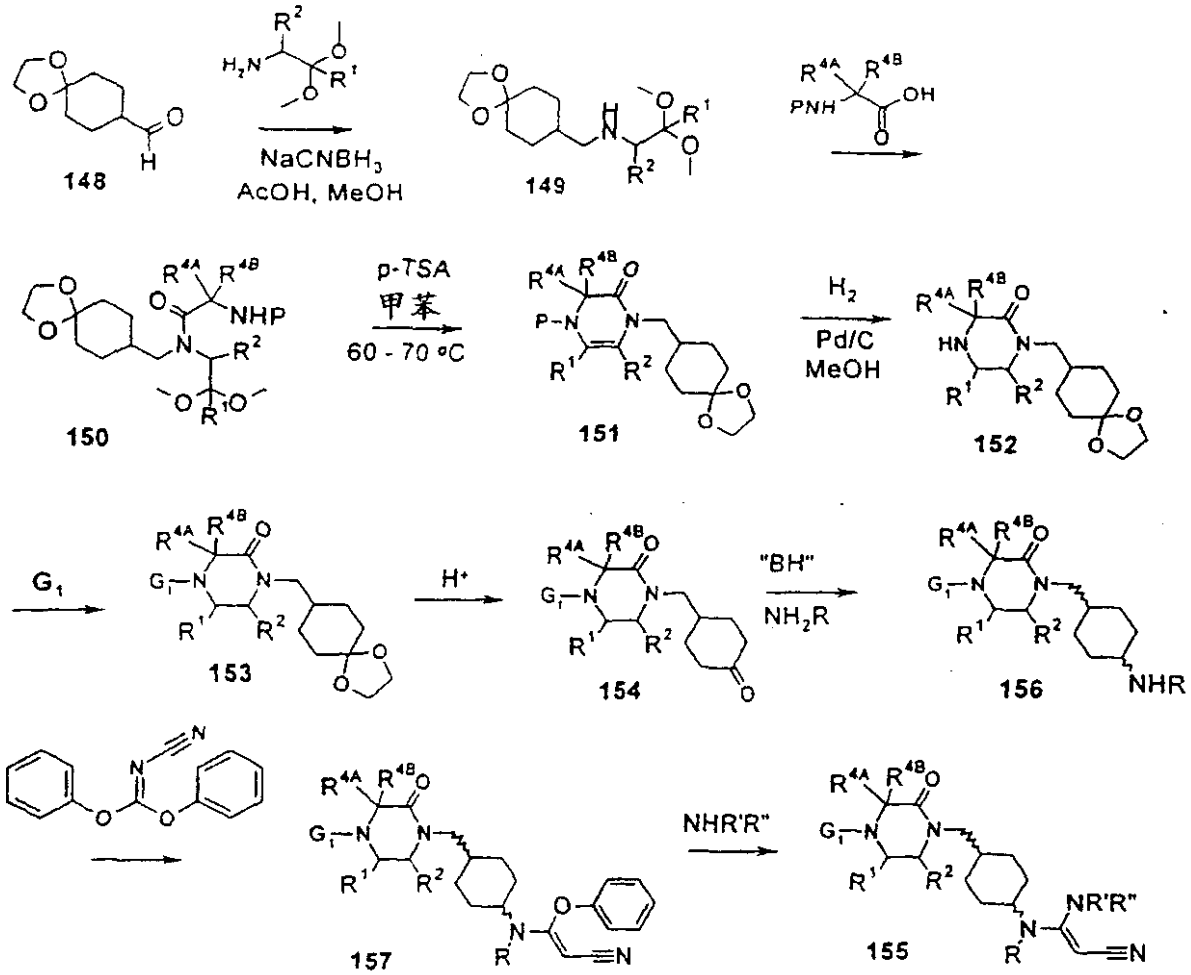
反应路线39示出了制备式155的1-(N,N'-芳基/烷基-氰基胍)-4-甲基环己基-酮基哌嗪的一般方法。



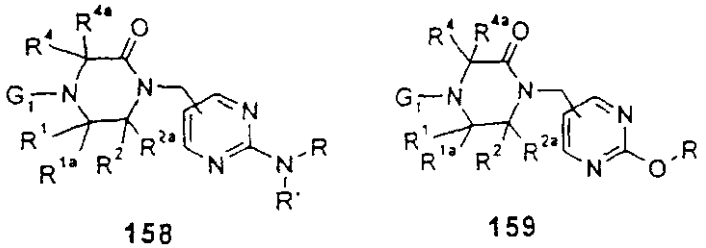
155

如反应路线39所述，式155化合物的优选制备方法包括：构造包含4-甲基环己-1-酮作为N-1取代基的环缩酮的酮基哌嗪152。中间体152的构造可通过中间体148(按照下述文献的方法制备：Pearson等；J. Org. Chem. 62, 1997, 5284)与氨基乙醛的取代乙缩醛进行还原胺化，得到中间体149。然后，中间体149再用适宜N-保护的取代的α-氨基酸进行酰化，得到中间体150。再用对甲苯磺酸处理中间体150得到不饱和的酮基哌嗪151。将中间体151进行脱保护氢化，得到中间体152。使部分G_1连接得到中间体153。在酸性条件下使4-取代的环己酮的乙缩醛进行水解，得到中间体154。用适宜的伯胺进行还原胺化，得到中间体156。环己酮用选定的胺进行还原胺化可采用本领域技术人员公知的标准方法，采用硼氢化物如硼氢化钠或三叔丁基硼氢化锂，在适宜的溶剂如甲醇或乙酸中，在0-100℃下进行。通过硅胶色谱或PR-HPLC可分离出还原胺化的异构体顺/反产物。中间体156与氰基亚氨基碳酸二苯酯反应得到中间体157。中间体157再与适宜的伯和仲胺反应，得到式155的化合物。

反应路线39



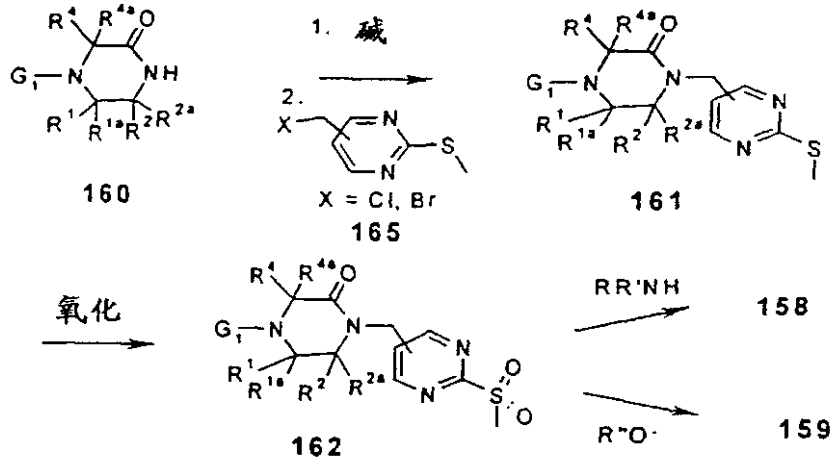
以下反应路线40示出了制备式158 & 159的2-取代-4 & 5-甲基嘧啶基-酮基哌嗪的一般方法。



如反应路线40所示，式158和159的化合物的优选制备方法包括：将含有所述N-4取代基(指定为G-1)的酮基哌嗪中间体160用4或5-卤代甲基2-硫基甲基嘧啶进行烷基化，得到中间体161。将中间体161的硫甲基氧化，得到中间体162，再用适宜的胺或烷氧化物进行置换分别得

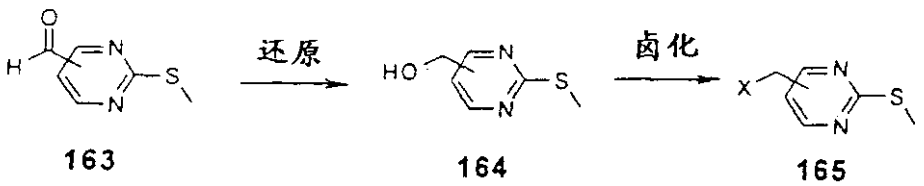
到式158或159的化合物。中间体160的酰胺的烷基化可采用本领域技术人员公知的标准方法，例如用氢化钠的DMF溶液或叔丁醇化的的叔丁醇溶液于-78至100℃下进行脱质子处理，随后加入卤化物中间体165，在0-100℃下搅拌0.5-24小时。中间体161的硫化物氧化成中间体162的砜可以标准方式实现，如采用甲醇与水或m-CPBA在二氯甲烷中的混合物。中间体162的砜与适宜的胺的置换可这样完成：在20-100℃下，简单地将纯组分或在不活泼溶剂如二氯甲烷或DMF中搅拌0.5-24小时。类似，醇化物在惰性溶剂中的反应将导致所需的置换产物。

反应路线40



4 & 5-卤代甲基-2-甲基硫基嘧啶中间体165可如在反应路线41中所述制备，分别采用相应的4 & 5-甲醛中间体163。2-甲基硫基嘧啶-4-甲醛可采用下述文献所述方法制备：Bredereck等，Chem. Ber. 1964，3407。2-甲基硫基嘧啶-5-甲醛可采用下述文献所述方法制备：Gupton等，J. Het. Chem. 28，1991，1281。

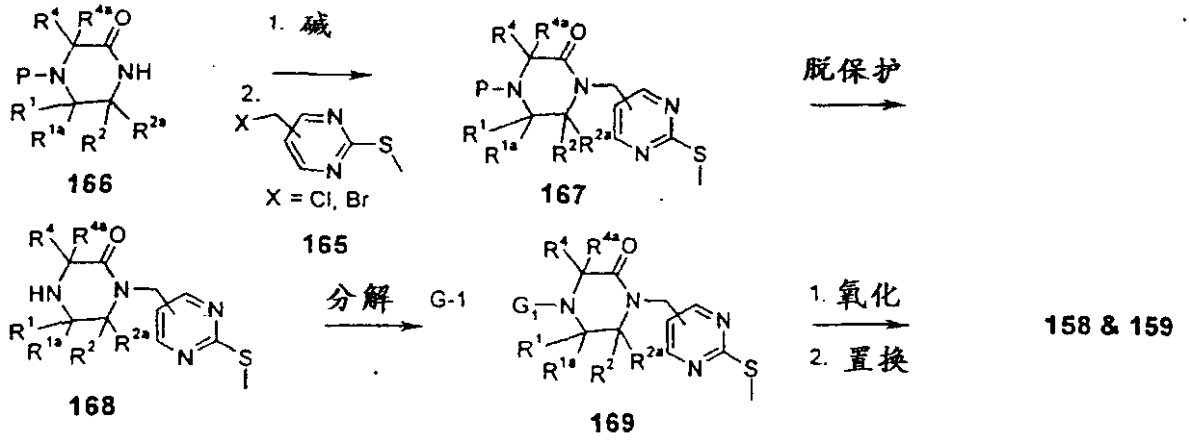
反应路线41



或者，如反应路线42所示，式158和159的化合物可这样制备：用4-或5-卤代甲基-2-甲基硫基嘧啶(中间体165)对适当保护的[在N-

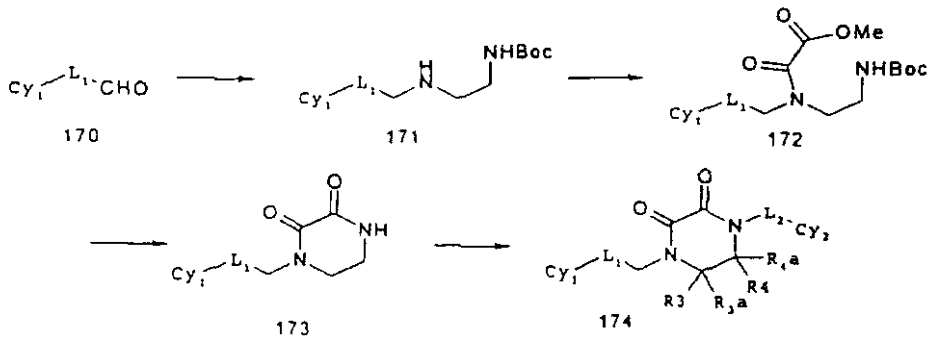
4(指定P)]酮基哌嗪中间体166进行烷基化处理，得到中间体167。然后，可除去中间体167的保护基，得到中间体168和将加上所需的G-1取代基，得到中间体169。适宜的保护基包括Boc、Cbz、Alloc和Fmoc，它们可以常规方式使用。

反应路线42



通常，按照J. Org. Chem. 1998, 63, 4131和Chem. Pharm. Bull. 1981, 29, 684所述，制备以下式I的二酮基哌嗪，其中，A为N，R_1和R_{1a}一起及R_2和R_{2a}一起为氧。所采用的合成路线如反应路线43所示。

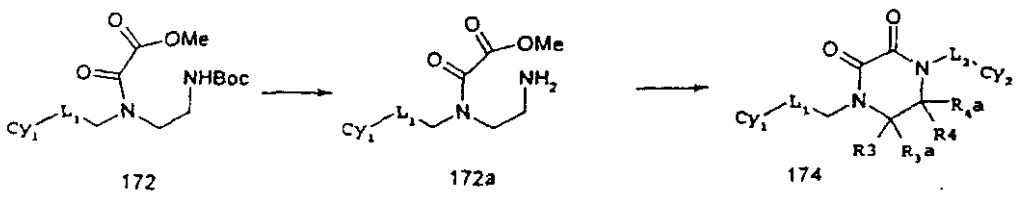
反应路线43



如上述反应路线43所示，采用诸如硼氢化钠的还原剂，用乙二胺适宜保护的形式可胺化由本文定义的Cy_1-L_1基团表示的芳基、杂芳基或二芳基醛或链烯基醛衍生物。仲胺171用适宜的草酰氯，特别是氯代乙醛酸甲酯在碱存在下进行处理，形成草醛酸(oxalamic)酯中间体

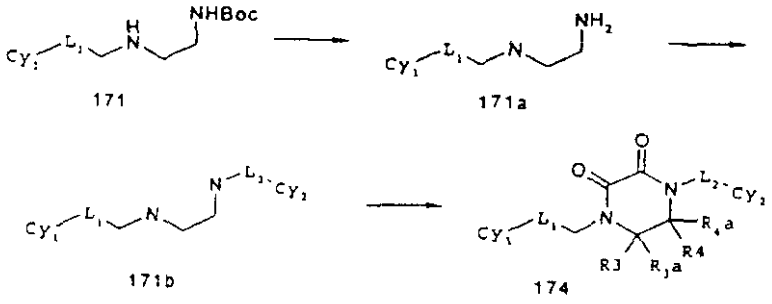
172。在酸性条件下(盐酸或TFA)除去保护基，再在碱性条件(TEA)下进行环化，形成2,3-二酮基哌嗪203。适宜的Cy_2-L_2基团可增补至式173化合物中，即用适宜的芳基氯代甲基或溴代甲基环体系进行烷基化，如式179的化合物，采用氢化钠、$LiN(SiMe_3)_3$、、$NaN(SiMe_3)_3$、LDA或适宜的碱，在惰性溶剂如THF或DMF中进行，得到式174的化合物，其中Cy_2为氯代喹唑啉、氯代喹啉、氨基喹唑啉或其它本文定义的基团。

反应路线43A



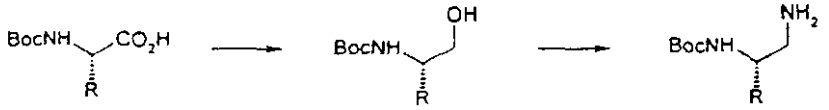
如反应路线43A所示，在酸性条件下上述草醛酸酯中间体172的脱保护也可用于分离中间体172a(反应路线43A)，随后直接置于采用芳基醛的还原胺化条件下以分别引入Cy_2-L_2基团，采用还原剂如硼氢化钠或氰基硼氢化钠。在这些条件下发生闭环，就地得到2,3-二酮基哌嗪174。

反应路线43B



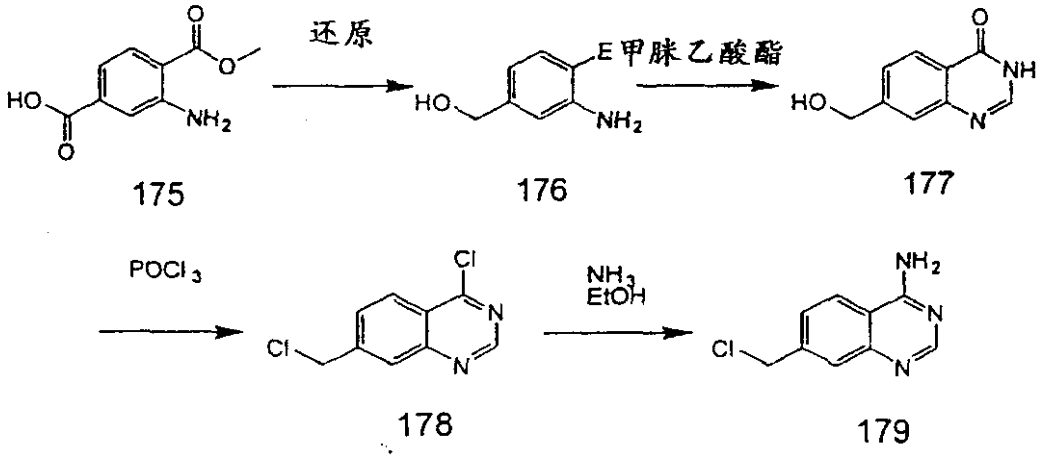
或者，可采用如上反应路线43B所示的路线，在酸性条件(盐酸或TFA)下使仲胺171脱保护成为二胺171a，再用芳基醛进行还原胺化，引入Cy_2-L_2基团，采用还原剂如硼氢化钠或氰基硼氢化钠。然后，用草酸二甲酯进行反应，二胺171b环化而得到2,3-二酮基哌嗪174。

反应路线43C



如反应路线43C所述，可通过由相应的氨基酸制备而采有上述取代的不对称乙二胺单元(反应路线43C)。由酸部分形成混合酸酐(氯代甲酸异丁酯)，随后还原(硼氢化钠)，得到氨基醇中间体。将醇部分以甲磺酰氯进行衍生，转化成叠氮化物(叠氮化钠)，并用氢气还原，产生适宜的保护的乙二胺。

反应路线44



如反应路线44所示，喹唑啉179可这样制备：用THF中的超氢化物(Super Hydride)还原酸175，得到醇176。然后，使醇176再在甲酰胺中于约180℃下进行反应，得到环化的化合物177。然后，再通过与$POCl_3$反应，将环化的化合物177转化成其氯代衍生物178。再采用氨的乙醇溶液或乙酸铵/苯酚，将氯代衍生物178转化成氨基化合物179。

以下的实施例进一步说明本发明化合物的制备过程，它们仅为举例说明而非对本发明的限制。原料和中间体可采用公知的方法制备，例如本文中所述的方法或文献中所述的方法，例如下述文献：R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989。

通过所有这些实施例的检验，本发明的化合物、其制备方法或制剂及其生物活性均更为清楚，这些实施例仅用于说明本发明，并非对本发明保护范围的限制。

实施例1

6-氯苯并[b]噻吩-2-磺酰氯

A. 1-氯-3-(2,2-二甲氧基乙基硫烷基)苯

在0℃下，向3-氯苯硫酚(2.4 g，16.6 mmol)的THF (200 mL)溶液中加入溴乙醛二甲基乙缩醛(2.8 g，16.6 mmol)。向溶液中加入氢化钠(60%无机油分散液，0.70 g，17.4 mmol)。将反应混合物搅拌16小时，然后，加入饱和氯化铵(水溶液)使反应停止。将溶液用乙酸乙酯稀释。将有机层用饱和氯化钠(水溶液)洗涤。有机层用硫酸镁干燥，过滤并浓缩。粗品产物用柱色谱纯化，用己烷洗脱。获得标题化合物(3.7 g，15.9 mmol)，为一种油。^{1}H NMR ($CDCl_3$，300MHz) δ 7.32 (m，1H)，7.25 (m，1H)，7.12 (m，1 H)，4.47 (m，1H)，3.07 (s，3H)，3.02 (s，3H)。

B. 4-氯苯并[b]噻吩和6-氯苯并[b]噻吩

将包含多磷酸(8 g)和氯苯(50 mL)的溶液加热回流。将包含1-氯-3-(2,2-二甲氧基乙基硫烷基)苯(2.7 g，11.6 mmol)的氯苯(5 mL)溶液滴加至回流的多磷酸溶液中。6小时后，将溶液冷却至室温。将溶液用二氯甲烷稀释，和用水和饱和氯化钠(水溶液)洗涤。有机层用硫酸镁干燥，过滤并浓缩。粗品产物用柱色谱纯化，用己烷洗脱，，得到标题化合物(2.4 g，9.0 mmol)，为一种1:1的异构体混合物。^{1}H NMR ($CDCl_3$，300MHz) δ 7.88 (m，1H)，7.75 (m，2H)，7.42 (m，2H)。MS (EI)：m/z 168，170 (M+)，Cl 花样。

C. 4-氯苯并[b]噻吩-2-磺酰氯和6-氯苯并[b]噻吩-2-磺酰氯

在-78℃下，向4-氯-苯并[b]噻吩和6-氯苯并[b]噻吩(11.8 g, 88.1 mmol)在400 mL THF中的溶液中加入正丁基锂(55 mL, 1.6M 己烷溶液, 88.1 mmol)。15分钟后，通过套管将溶液加至预冷却(-78℃)的SO_2(200 g)在100 mL THF中的溶液中。加完后，将溶液升温至室温。0.5小时后，将溶液浓缩。将残余物悬浮于己烷(400 mL)中，冷却至0℃。向溶液中加入SO_2Cl_2(12.5 g, 92.5 mmol)。搅拌15分钟后，将溶液浓缩。将残余物溶解于乙酸乙酯中。有机溶液用饱和氯化铵(水溶液)，水和饱和氯化钠(水溶液)洗涤。有机层用硫酸镁干燥，过滤并浓缩。将粗品产物溶解于二氯甲烷并用硅胶填料过滤。粗品产物用柱色谱纯化，用己烷洗脱，，得到标题化合物以及4-氯苯并[b]噻吩-2-磺酰基氯，为白色固体。

4-氯苯并[b]噻吩-2-磺酰氯：^{1}H NMR ($CDCl_3$, 300MHz) δ 8.32 (m, 1H), 7.81 (m, 1H), 7.53 (m, 2H)。

6-氯苯并[b]噻吩-2-磺酰基氯：^{1}H NMR ($CDCl_3$, 300MHz) δ 8.11 (s, 1H), 7.88 (m, 2H), 7.50 (m, 1 H)。

实施例2

5′-氯-[2,2']联噻吩基-5-磺酰氯

A. 5-氯-[2,2']联噻吩

标题化合物由2-氯-噻吩制备，按照下述方法：Bull. Chem. Soc. 日本, 1979, 1126. 粗品产物用柱色谱纯化，进行梯度洗脱：5%乙酸乙酯/己烷至10%乙酸乙酯/己烷洗脱，得到一种白色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.24 (m, 1 H), 7.11 (d, 1 H), 7.03 (dd, 1 H), 6.94 (d, 1 H), 6.83 (d, 1 H)。MS (EI) [M+] =200, 202, Cl 花样。

B. 5'-氯-[2,2']联噻吩-5-磺酰氯

按照实施例1部分C所述制备标题化合物，采用5-氯[2,2']联噻吩代替6-氯-苯并[b]噻吩。粗品产物用柱色谱纯化，进行梯度洗脱：5%

乙酸乙酯/己烷至10%乙酸乙酯/己烷洗脱，得到一种白色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.76 (d, 1H), 7.14 (d, 1H), 7.09 (d, 1H), 6.92 (d, 1 H)。MS (EI): m/z 298, 300 (M+), Cl 花样。

实施例3

2-(5-氯-噻吩-2-基)-乙烯磺酰氯

A. 2-(5-氯-噻吩-2-基)-乙烯磺酸乙酯

将正丁基锂(53.1 mL, 2.5M 己烷溶液)滴加至甲磺酸乙酯(12.9 mL, 0.12 mol)的THF (300 mL)溶液中(-78℃下)。将反应混合物搅拌15分钟，然后，滴加入氯代膦酸乙酯(9.9 mL, 0.07 mol)。将溶液在-78℃下搅拌30分钟，然后，加热至50℃搅拌1小时。然后，将反应混合物冷却至-78℃和搅拌1小时，然后，滴加入5-氯噻吩甲醛(7.1 mL, 0.07 mol)。将反应混合物过夜缓慢升温至RT。将水(30 mL)加至混合物中，并搅拌15分钟，然后，真空浓缩。将残余物吸收于二氯甲烷中，用水，盐水洗涤，用硫酸镁干燥，过滤并浓缩至干。粗品产物用柱色谱纯化，用5%乙酸乙酯/己烷洗脱，得到标题化合物(11.3 g, 0.04 mol)，为一种油。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.51 (d, 1H), 7.10 (d, 1 H), 6.91 (d, 1H), 6.42 (d, 1H), 4.20 (q, 2H), 1.40 (t, 3H)。

B. 2-(5-氯-噻吩-2-基)-乙烯磺酰氯

室温下，将四丁基碘化铵(16.3 g, 44.2 mmol)加至2-(5-氯-噻吩-2-基)-乙烯磺酸乙酯(11.3 g, 40.2 mmol)的丙酮(100 mL)溶液中。将混合物加热至回流和搅拌过夜，然后，冷却至RT和真空浓缩。将残余物吸收于二氯甲烷中，然后，用水和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩至干，得到一种油(18.74 g, 40.2 mmol)，其不经纯化即可用于下一步骤。在0℃下，将磺酰氯(7.1 mL, 88.5 mmol)加至三苯膦(21.g, 86.42 mmol)的二氯甲烷溶液中。然后，除去冰浴，加入来自上述反应的产物(18.74 g, 40.2 mmol)。2小时后，将反应混合物进行真空浓缩和将产物用柱色谱纯化，用10%乙酸乙酯/己烷洗脱，

得到标题化合物(6.4 g, 26.3 mmol), 为一种黄白色固体。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, 1 H), 7.23 (d, 1H), 7.00 (d, 1H), 6.91 (d, 1H)。

实施例4

3-氯苄基氨磺酰基儿茶酚

向3-氯苄基胺(0.14 g, 1.0 mmol)的3 mL DMF溶液中加入三乙胺(0.10 g, 1.5 mmol)。将溶液冷却至0℃。加入儿茶酚硫酸酯(0.172 g, 1.0 mmol)。将溶液升温至室温。2.5小时后, 加入30 mL的乙酸乙酯。将溶液用5%盐酸, 水和饱和氯化钠洗涤。有机层用硫酸镁干燥, 过滤并浓缩, 得到标题化合物(0.30 g, 0.97 mmol)。^{1}H NMR (d_6 DMSO, 300 MHz) δ 9.94 (s, 1H), 8.82 (m, 1H), 7.41 (m, 4H), 7.19 (d, 1H), 7.10 (m, 1H), 6.95 (d, 1H), 6.79 (m, 1H), 4.32 (AB, 2H)。

实施例5

2-溴甲基-6-氯苯并[b]噻吩

A. 6-氯苯并[b]噻吩-2-甲醛

在-78℃下, 向6-氯苯并[b]噻吩(1.0 g, 5.93 mmol)的THF (60 mL)溶液中加入1.6 M n-BuLi的THF (3.9 mL, 6.23 mmol)溶液。10分钟后, 加入0.5 mL的DMF。将溶液搅拌0.5小时, 然后, 将其升温至室温。将溶液倒入饱和氯化铵溶液中。将溶液用乙醚稀释, 分层。有机层用水和饱和氯化钠洗涤。有机层用硫酸镁干燥, 过滤并浓缩。获得标题化合物, 为一种白色固体。MS (EI): m/z 196 (M+)。

B. 6-氯苯并[b]噻吩-2-基)甲醇

在0℃下, 向6-氯苯并[b]噻吩-2-甲醛的THF溶液中加入$NaBH_4$。1小时后, 将溶液用饱和氯化铵和乙醚稀释。有机层用水和饱和氯化钠洗涤, 用硫酸镁干燥, 过滤并浓缩。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1 H), 7.60 (d, 1 H), 7.40 (m, 2H), 4.91 (AB, 2H)。

C. 2-溴甲基-6-氯苯并[b]噻吩

向6-氯苯并[b]噻吩-2-基-甲醇(0.2 g, 1.01 mmol)的THF (10 mL)溶液中加入三苯膦(0.34 g, 1.31 mmol)。接着加入CBr_4(0.42g, 1.26 mmol)。3小时后，将溶液浓缩。将产物用柱色谱纯化，进行梯度洗脱：5%乙酸乙酯/己烷至10%乙酸乙酯/己烷. 获得产物，为一种白色固体(0.25 g, 0.53 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1 H), 7.62 (d, 1 H), 7.40 (m, 2H), 4.76 (s, 2H)。

实施例6

5-溴甲基-5'-氯-[2,2']联噻吩

A. (5'-氯-[2,2']联噻吩-5-基)-甲醇

在0℃下，向5-氯-[2,2']联噻吩基(3.00 g, 14.9 mmol)的30 mL THF溶液中滴加入正丁基锂(9.8 mL的1.6M己烷溶液, 15.7 mmol)。再滴加入DMF (2.30 mL, 30 mmol)，将所得溶液加热回流1小时。将溶液用水稀释和用乙醚萃取。有机层用水和饱和氯化钠溶液洗涤，然后，用硫酸镁干燥，过滤并浓缩。将粗品醛溶解于40 mL的无水甲醇中，分批加入硼氢化钠(0.85 g, 22.5 mmol)。将混合物在室温下搅拌10分钟，然后，用水停止反应。将混合物用乙醚稀释和分层。有机层用水洗涤，然后，用硫酸镁干燥，过滤并浓缩，得到标题化合物(2.23 g, 9.66 mmol)其可不经纯化用于下一步骤。^{1}H NMR ($CDCl_3$, 300MHz) δ 6.95 (d, 1 H), 6.90 (m, 2H), 6.86 (d, 1 H), 4.82 (s, 2H), 1.88 (bs, 1 H)。

B. 5-溴甲基-5'-氯-[2,2']联噻吩

向(5'-氯-[2,2']联噻吩-5-基)-甲醇(2.23 g, 9.66 mmol)的65 mL二氯甲烷溶液中加入溴三甲基硅烷(3.82 mL, 29.0 mmol)。4小时后，将溶液真空浓缩。粗品产物在己烷中搅拌并过滤。将滤液浓缩，获得标题化合物(1.67 g, 5.69 mmol)为一种绿色固体。^{1}H NMR ($CDCl_3$,

300MHz) δ 7.00 (d, 1 H), 6.94 (m, 2H), 6.85 (d, 2H), 4.71 (s, 2H)。

实施例7

7-溴甲基-4-氯喹唑啉

A. 7-甲基-3H-喹唑啉-4-酮

将2-氨基-4-甲基苯甲酸(31.6 g, 206 mmol)的甲酰胺(60mL)溶液加热至130℃并搅拌1小时，然后，在175℃搅拌3小时。将溶液倒入500 mL的冰水中。所得固体经过滤收集和再进行减压干燥。获得标题化合物(26.2 g, 170 mmol)，为一种白色固体。MS (EI): m/z 159 (M+)。

B. 4-氯-7-甲基-喹唑啉

向7-甲基-3H-喹唑啉-4-酮(10.6 g, 69 mmol)的甲苯(350mL)溶液中加入三乙胺(17.5 g, 173 mmol)，再加入加入氧氯化磷(12.3 g, 80 mmol)。将所得溶液加热至80℃。4小时，将溶液冷却至室温。将反应混合物倒入500 mL的水中。分层和有机层用水，饱和碳酸氢钠和饱和氯化钠洗涤，用硫酸镁干燥，过滤并浓缩。所得粗品产用乙酸乙酯进行重结晶纯化。获得标题化合物，为一种白色固体(10g, 56 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.02 (s, 1H), 8.16 (d, 1H), 7.87 (s, 1 H), 7.55 (d, 1H), 2.62 (s, 3H)。

C. 7-溴甲基-4-氯喹唑啉

向4-氯-7-甲基喹唑啉 (7.0 g, 39 mmol)的四氯化碳(140 mL)溶液中加入N-溴琥珀酰亚胺(8.0 g, 45 mmol)和苯甲酰基过氧化物(0.8 g, 3.3 mmol)。将溶液回流8小时。此后，将溶液过滤。将滤液浓缩和将残余物与乙醚搅拌，得到标题化合物，为一种米黄色固体(5.1 g, 20 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.10 (s, 1H), 8.30 (d, 1H), 8.10 (s, 1H), 7.82 (d, 1 H), 4.68 (s, 2H)。MS (EI): m/z 237 (M+)。

实施例8

3-溴甲基-7-氯-1H-喹啉-2-酮

A. N-(3-氯苯基)-2-甲基-3-苯基丙烯酰胺

在0℃下，向3-氯苯胺(0.98 mL, 9.3 mmol)的二氯甲烷(25 mL)溶液中加入吡啶(0.78mL, 9.5 mmol)。向所得溶液中滴加α-甲基肉桂酸氯化物(1.6 g, 9.3 mmol)的二氯甲烷(8 mL)溶液。3小时后，将溶液浓缩。粗品产物用柱色谱纯化，用5%乙酸乙酯/己烷至10%乙酸乙酯/己烷洗脱。获得标题化合物，为一种固体(2.5 g, 9.2 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 1 H), 7.73 (s, 1 H), 7.46 (m, 1 H), 7.33 (m, 6H), 7.22 (m, 1 H), 7.03 (m, 1H), 2.13 (s, 3H)。

B. 7-氯-3-甲基-1H-喹啉-2-酮

向N-(3-氯苯基)-2-甲基-3-苯基丙烯酰胺(2.5 g, 9.2 mmol)的氯苯(50 mL)溶液中加入氯化铝(6.2 g, 46 mmol)。将溶液加热至120℃。4小时后，将溶液倒入冰上。将溶液过滤。有机层用1N盐酸，水和饱和氯化钠洗涤。粗品产物用柱色谱纯化，用2%甲醇/二氯甲烷洗脱。获得标题化合物，为一种白色固体(1.5 g, 7.74 mmol)。^{1}H NMR (d6-DMSO, 300 MHz) δ 11.82 (bs, 1H), 7.73 (s, 1H), 7.52 (m, 1H), 7.21 (m, 2H), 2.08 (s, 3H)。

C. 3-溴甲基-7-氯-1H-喹啉-2-酮

按照实施例7部分C所述制备标题化合物，替换7-氯-3-甲基-1H-喹啉-2-酮成7-甲基-4-氯喹唑啉。获得标题化合物，为一种白色固体。^{1}H NMR (d_6-DMSO, 300 MHz) δ 12.00 (bs, 1H), 8.17 (s, 1H), 7.72 (d, 1H), 7.29 (m, 2H), 4.58 (s, 2H)。

实施例9

6-溴甲基-2-氯-喹啉

A. 6-甲基-1H-喹啉-2-酮

按照下述方法由对甲苯胺和肉桂酰氯制备标题化合物：Synthesis 1975, 739。将获得的粗品产物在乙醚/己烷中研制，并过滤，得到标题化合物，为一种米色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.60 (bs, 1H), 7.82 (d, 1H), 7.41 (s, 1 H), 7.30 (d, 1H), 7.18 (d, 1H), 6.45 (d, 1H), 2.30 (s, 3H)。

B. 2-氯-6-甲基喹啉

将6-甲基-1H-异喹啉-2-酮(14.6 g, 91.7 mmol)在氧氯化磷(160 mL)中在60℃下加热搅拌17小时。将混合物冷却至室温，然后，浓缩成一种米色残余物。将残余物用冰水稀释和通过缓慢地加入10N的氢氧化钠将pH值调节至约8。在水溶液中和过程中沉淀出粗品产物，将固体过滤，用水洗涤和干燥。将固体用甲醇进行重结晶，得到标题化合物(12.0 g, 67.5 mmol)，为一种米色固体。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, 1H), 7.92 (d, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.33 (d, 1H), 2.53 (s, 3H)。

C. 6-溴甲基-2-氯-喹啉

将N-溴琥珀酰亚胺(12.9 g, 72.5 mmol)和苯甲酰基过氧化物(0.33 g, 1.30 mmol)加至2-氯-6-甲基-喹啉(12.0 g, 67.5 mmol)的四氯化碳(300 mL)溶液中。将混合物加热回流6小时。此时，将所得混合物冷却至室温，过滤，用二氯甲烷洗涤并真空浓缩。粗品残余物在50%乙酸乙酯/己烷中重结晶，得到标题化合物(8.80 g, 34.3 mmol)，为一种米色晶状固体。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H), 8.02 (d, 1H), 7.83 (s, 1 H), 7.77 (dd, 1 H), 7.40 (d, 1 H), 4.65 (s, 2H)。MS (EI): m/z 256, 258 (M+), Cl 花样。

实施例10

3-溴甲基-1,7-二氯-2H-异喹啉

A. 3-(4-氯苯基)-2-甲基-丙烯酰基叠氮化物

在0℃下，向3-(4-氯苯基)-2-甲基-丙烯酸(11.2 g，57 mmol)的500 mL丙酮溶液中加入三乙胺(9.6 mL，68 mmol)，再加入加入氯代甲酸乙酯(6.2 mL，63 mmol)。将溶液升温至室温。2小时后，加入叠氮化钠(5.6 g，86 mmol)的35 mL的水溶液。加完后，将溶液搅拌2小时。将溶液用水(100 mL)稀释。所得固体经过滤收集，给出标题化合物，为一种白色固体(11.1 g，50mmol)。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.67 (s，1 H)，3.38 (m，4H)，2.10 9s，3H)。

B. 7-氯-3-甲基-2H-异喹啉基-1-酮

将3-(4-氯苯基)-2-甲基-丙烯酰基叠氮化物(11.0 g，50 mmol)溶解于80 mL的二苯基醚中。在210℃下，将溶液滴加至三丁基胺(11.8 mL，50mmol)的170 mL的二苯基醚中。4小时后，将溶液冷却至50℃和用1.5 L己烷稀释。将所得固体经过滤收集，给出标题化合物，为一种白色固体(7.2 g，37 mmol)。^{1}H NMR (d_6-DMSO，300 MHz) δ 11.4 (bs，1 H)，8.02 (s，1 H)，7.67 (d，1H)，7.55 (d，1H)，6.34 (s，1H)，2.18 (s，3H)。

C. 1,7-二氯-3-甲基-异喹啉基

将7-氯-3-甲基-2H-异喹啉基-1-酮(7.1 g，36.7 mmol)的100 mL氧氯化磷溶液加热至100℃。5小时后，将溶液浓缩至干。将残余物溶解于二氯甲烷中。将溶液用水洗涤。有机层用硫酸镁干燥，过滤并浓缩。粗品产物用柱色谱纯化，进行梯度洗脱：3%乙酸乙酯/己烷至5%乙酸乙酯/己烷。获得标题化合物，为一种白色固体(6.0g，28 mmol)。^{1}H NMR ($CDCl_3$，300 MHz)δ8.23 (s，1 H)，7.68 (m，1 H)，7.63 (m，1 H)，7.40 (s，1 H)，2.64 (s，3H)。

D. 3-溴甲基-1,7-二氯-2H-异喹啉

按照实施例7部分C所述制备标题化合物，替换1,7二氯-3-甲基-异喹啉基成4-氯-7-甲基喹唑啉。^{1}H NMR ($CDCl_3$，300 MHz) δ 8.29 (s，

1 H), 7.82 (m, 1H), 7.76 (m, 2H), 4.68 (s, 2H)。

实施例11.3-溴甲基-7-氯异喹啉

A. 7-氯-3-甲基-异喹啉

在75℃下，向1,7-二氯-3-甲基-异喹啉(0.50 g, 2.36 mmol)(实施例10，部分C，在5.5 mL的9:1乙酸:水中的溶液中加入锌(0.23 g, 3.54 mmol)。75分钟后，将溶液冷却至室温。将溶液用4:1乙酸乙酯:二氯甲烷溶液稀释。向溶液中加入100mL的1N氢氧化钠溶液。将含水溶液用4:1乙酸乙酯:二氯甲烷萃取。合并的有机层用饱和氯化钠溶液洗涤。有机层用硫酸镁干燥，过滤并浓缩。粗品产物用柱色谱纯化，进行梯度洗脱：5%乙酸乙酯/己烷至15%乙酸乙酯/己烷。获得标题化合物，为一种白色固体(0.36 g, 1.97 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1 H), 7.89 (s, 1 H), 7.61 (d, 1 H), 7.55 (d, 1H), 7.44 (s, 1H) 2.68 (s, 3H)。MS (EI) : m/z 177, 179 (M+), Cl 花样。

B. 3-溴甲基-7-氯异喹啉

按照实施例7，部分C，所述制备标题化合物，替换7-氯-3-甲基-异喹啉基成4-氯-7-甲基喹唑啉。^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.18 (s, 1 H), 7.97 (s, 1H), 7.75 (m, 2H), 7.67 (m, 1H), 4.71 (s, 2H)。

实施例12

2-溴甲基-6-氯萘

A. 6-氯-3,4-二氢-1H-萘-2-酮

在-20℃下，向(4-氯苯基)-乙酰氯(17.3 g, 92 mmol)的50 mL的二氯甲烷溶液中滴加入氯化铝(24.4 g, 184 mmol)的200 mL二氯甲烷溶液。20分钟后，乙烯(g)鼓泡通过溶液30分钟。将溶液在10℃下搅拌15分钟。将反应混合物倒入300 g冰中。分层。有机层用水，饱和碳酸氢钠和饱和氯化钠洗涤。有机层用硫酸镁干燥，过滤并浓缩。所得固

体用戊烷研制(2x20mL)。然后，将固体干燥，得到标题化合物，为一种固体(15.2 g，84.2 mmol)。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.28 (m，2H)，7.06 (m，1H)，3.52 (s，2H)，3.04 (m，2H)，2.56 (m，2H)。

B. 6-氯-2-甲基-1,2，3,4-四氢萘-2-醇

在-45℃下，向$TiCl_4$ (95 mL，1 M在甲苯中)溶液中加入CH_3MgBr (4.2 mL，3M THF溶液)。将溶液搅拌20分钟。此后，在15分钟内滴加入6-氯-3,4-二氢-1H-萘-2-酮(11.3 g，63 mmol)的80 mL的二氯甲烷溶液。将反应混合物在-45℃下搅拌15分钟。将溶液升温至0℃。2小时后，将溶液用水和二氯甲烷稀释。有机层用硫酸镁干燥，过滤并浓缩。获得标题化合物，为一种油状物(11.3 g，57.5 mmol)。

^{1}H NMR ($CDCl_3$，300 MHz) δ 7.10 (m，2H)，6.97 (m，1H)，3.02 (m，2H)，2.80 (s，3H)，1.85 (m，2H)，1.80 (m，2H)。

C. 2-氯-6-甲基萘

将6-氯-2-甲基-1,2,3,4-四氢萘-2-醇(11.3 g，57.5 mmol)和Ph_3COH (16.5 g，63 mmol)的80 mL TFA溶液搅拌2.5天。此后，将溶液浓缩至干。将残余物溶解于二氯甲烷中。有机层用水，饱和碳酸氢钠和饱和氯化钠洗涤。有机层用硫酸镁，过滤并浓缩。粗品产物用柱色谱纯化，用己烷洗脱。获得标题化合物，为一种白色固体(4.05 g，22.9 mmol)。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.78 (s，1 H)，7.69 (m，2H)，7.58 (s，1 H)，7.50 (m，2H)，2.49 (s，3H)。

D. 2-溴甲基-6-氯萘

按照实施例7，部分C所述制备标题化合物，替换2-氯6-甲基萘成4-氯-7-甲基喹唑啉。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.82 (m，2H)，7.78 (s，1H)，7.76 (m，2H)，7.52 (d，1 H)，7.42 (d，1H)，4.62 (s，2H)。

实施例13

2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈

A. 2-(二苯亚甲基-氨基)-4-甲基-苯甲腈

向2-氨基-4-甲基苯甲腈(20 g, 151 mmol)的1000mL的二氯乙烷溶液中加入二苯甲酮亚胺(30g, 166mmol)。将溶液回流48小时。此后，将溶液冷却至室温。将溶液用饱和碳酸氢钠，水和饱和氯化钠洗涤。有机层用硫酸镁干燥，过滤并真空浓缩。将产物用叔丁基醚进行重结晶而进一步纯化，获得标题化合物(25.5g, 118mmol)，为一种黄色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.88 (m, 2H), 7.42 (m, 3H), 7.32 (m, 7H), 6.79 (d, 1H), 6.58 (s, 1 H), 2.23 (s, 3H)。

B. 2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈

向2-(二苯亚甲基-氨基)-4-甲基-苯甲腈(11,2g, 37.8mmol)的500mL的CCl_4溶液中加入N-溴琥珀酰亚胺(7.06g, 39.7mmol)和苯甲酰基过氧化物(0.92g, 3.8mmol)。将溶液加热至回流16小时。此后，将溶液过滤，将有机溶液真空浓缩。将残余物用柱色谱纯化，进行梯度洗脱：20%叔丁基醚/己烷至25%叔丁基醚/己烷。获得一种油状产物，其包含所需单溴化物、二溴化物和未反应的原料的混合物。将混合物通过质子NMR进行测定，发现其纯度为60-75%。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (m, 2H), 7.42 (m, 9H), 6.92 (d, 1H), 6.81 (s, 1H), 4.29 (s, 2H)。

实施例14

7-溴甲基-4-氯喹啉

A. 7-甲氧羰基-4-氯喹啉

在一密封管中，将在100 mL 80%硫酸中的4-氯-7-三氟甲基喹啉(5.0 g, 21.6 mmol)的加热至200℃并搅拌24小时。将溶液冷却，倒入水中，和用氢氧化钠中和至pH3-4。收集沉淀出的固体，用水洗涤和溶解于2N氢氧化钠中。水溶液用乙酸乙酯洗涤，然后，酸化至pH3-4。

收集沉淀，用水洗涤和真空下过夜干燥，得到7-羧基-4-氯喹啉，为一种固体(5.1 g，24.6 mmol)。将部分产物(2.0 g，9.6 mmol)用无水THF (200 mL)和DMF (2 mL)和2 M草酰氯的二氯甲烷(14.5 mL，29 mmol)溶液处理。将所得悬浮液在室温下搅拌2小时，然后，用甲醇(10 mL)处理。搅拌30分钟，将溶液浓缩和残余物吸收于二氯甲烷中。将溶液用饱和碳酸氢钠洗涤和干燥(硫酸钠)并浓缩，得到标题化合物，为一种固体(2.1 g，9.5 mmol)。MS m/z: M^+ =221; ^{1}H NMR ($CDCl_3$，300 MHz) δ 8.6 (s，1 H)，8.2 (s，1 H)，7.9 (d，1 H)，7.65 (d，1 H)，7.45 (s，1 H)，3.95 (s，3H)。

B. 7-羟基甲基-4-氯喹啉

将7-甲氧羰基-4-氯喹啉(2.1 g，9.5 mmol)溶解于无水THF (25 mL)和无水醚(200 mL)中。将溶液在干冰/丙酮浴中冷却，并在1M氢化铝锂的THF(11.0 mL，11 mmol)溶液中处理。将溶液升温(大约-45℃)20分钟和用乙酸乙酯停止反应。将溶液用醚(100 mL)稀释和依次用水(36 mL)，15%氢氧化钠(36 mL)和水(36 mL)处理。将混合物过滤和蒸发，得到标题化合物，为一种残余物(2.0 g，9.7 mmol)，将其真空干燥无需进一步纯化即可使用。MS m/z: M^+ =193; ^{1}H NMR ($CDCl_3$，300 MHz) δ 8.65 (d，1H)，8.15 (d，1H)，8.0 (d，1H)，7.6 (d，1H)，7.45 (d，1 H)，4.8 (s，2H)。

C. 7-溴甲基-4-氯喹啉

将7-羟基甲基-4-氯喹啉(0.2 g，0.97 mmol)用48 %HBr处理，加热至120℃搅拌1小时。将所得溶液用冰冷却，用水稀释和用乙酸乙酯和碳酸氢钠处理直至pH试纸呈碱性。分层和有机层用水洗涤，干燥(硫酸钠)并浓缩，得到7-溴甲基-4-氯喹啉(0.23 g，0.9 mmol)。MS m/z: M^+ =255; ^{1}H NMR ($CDCl_3$，300 MHz) δ 8.75 (d，1H)，8.25 (d，1H)，8.1 (s，1H)，7.7 (d，1H)，7.5 (d，1H)，4.7 (s，2H)。

实施例15

7-溴甲基-4-氯噌啉

A. 4-甲基-2-硝基苯基乙酮

将4-氯-3-硝基甲苯(7.5 g, 48.4 mmol)用硝基乙烷(15.2 mL, 200 mmol)的乙酸乙酯(100 mL)和DBU(21 mL, 145 mmol)溶液处理，在室温下搅拌过夜。将溶液真空浓缩，用甲醇稀释，用30%过氧化氢(25 mL)和10%碳酸氢钠(25 ml)处理，和在室温下搅拌过夜。将反应混合物进行真空浓缩，用5%盐酸酸化和用二氯甲烷萃取。有机层干燥(硫酸钠)和进行色谱处理(35%乙酸乙酯/己烷)，得到标题化合物(7.2 g, 40.2 mmol)。MS m/z: M^+ =279; ^1H NMR ($CDCl_3$, 300MHz) δ 7.8 (s, 1 H), 7.48 (d, 1 H), 7.32 (d, 1 H), 2.5 (s, 3H), 2.4 (s, 3H)。

B. 2-氨基-4-甲基苯基乙酮

将4-甲基-2-硝基苯基乙酮(5.0 g, 28 mmol)的甲醇(100 mL)溶液用甲酸铵(9.6 g, 140 mmol)和5%钯/炭(1.5 g)处理。将混合物加热至60℃并搅拌6小时，然后，在室温下搅拌16小时。将反应混合物用硅藻土过滤，将滤液真空浓缩。将浓缩液用碳酸氢钠处理，并在水和乙酸乙酯间分配。分出有机层，用硫酸钠干燥并浓缩，得到粗品标题化合物(4.5 g, 30.2 mmol)，其不经纯化即可使用。MS m/z: M^+=149; ^1H NMR ($CDCl_3$, 300MHz) δ 8.05 (d, 1H), 7.4 (d, 1H), 7.25 (s, 1H), 2.8 (s, 3H), 2.45 (s, 3H)。

C. 7-甲基-1-H-噌啉-4-酮

将2-氨基-4-甲基苯基乙酮(5.0 g, 33.6 mmol)的浓盐酸(100 mL)溶液分批用亚硝酸钠(5.7 g, 82.6 mmol)的水(~ 10 mL)溶液处理。所得溶液在60℃下搅拌2小时，冷却至室温和用饱和乙酸钠(-200 mL)溶液处理。分批加入固体乙酸钠直至用pH试纸测试溶液为碱性。搅拌后，沉淀出标题化合物，经收集和干燥，得到标题化合物的白色固体(2.3 g, 14.3 mmol)。MS m/z: $[M+H]^+$ =161; ^1H NMR ($CDCl_3$, 300MHz)

δ 8.1 (d, 1H), 7.85 (s, 1 H), 7.45 (s, 1H) 7.3 (d, 1H), 2.55 (s, 3H)。

D. 4-氯-7-甲基噌啉

将7-甲基-1-H-噌啉-4-酮(1.3 g, 8.1 mmol)用约80 mL的氯苯处理并加热直至固体溶解。将所得溶液冷却并用吡啶(0.16 mL, 2 mmol)和$POCl_3$ (1.13 mL, 12.2 mmol)处理。将溶液加热至回流1小时，然后，浓缩至干。将残余物进行色谱处理(20 %乙酸乙酯/己烷)，得到标题化合物，为一种黄褐色固体(约1g, 5.6 mmol)。MS m/z (M^+=178)；^{1}H NMR ($CDCl_3$, 300MHz) δ 9.3 (s, 1H), 8.35 (s, 1H), 8.1 (d, 1 H), 7.7 (d, 1H), 2.68 (s, 3H)。

E. 7-溴甲基-4-氯噌啉

将4-氯-7-甲基噌啉(0.6 g, 3.37 mmol)的四氯化碳(30 mL)溶液用N-溴琥珀酰亚胺(0.64 g, 3.4 mmol)和催化剂量的70 %苯甲酰基过氧化物(0.22 g, 0.63 mmol) 处理。将溶液过夜加热至80℃，然后，过滤。将滤液进行真空浓缩和所得残余物进行色谱处理(20 %乙酸乙酯/甲氯)，得到标题化合物(0.3 g, 1.2 mmol)和一些未反应的原料(0.1 g, 0.56 mmol)。MS m/z: $[M+H]^+$=257; ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.35 (s, 1 H), 8.55 (s, 1 H), 8.2 (d, 1 H), 8.85 (d, 1 H), 4.75 (s, 2H)。

实施例16

6-溴甲基-3-氯-1-(甲苯-4-磺酰基)-1H-吲哚

A. 1H-吲哚-6-甲酸甲酯

向6-吲哚甲酸(0.91 g, 5.67 mmol)在33 mL的2:1 THF/甲醇中的溶液中，加入(三甲基甲硅烷基)重氮甲烷(5.0 mL, 2.0M己烷溶液, 10.0 mmol)。将混合物搅拌3小时，并真空浓缩，得到标题化合物(0.87 g, 4.97 mmol)。粗品产物不经进一步纯化即可用于下一步骤。^{1}H NMR

($CDCl_3$, 300 MHz) δ 8.70 (bs, 1 H), 8.20 (s, 1 H), 7.82 (dd, 1 H), 7.67 (d, 1 H), 7.45 (m, 1 H), 6.60 (m, 1 H), 3.95 (s, 3H)。

B. 3-氯-1H-吲哚-6-甲酸甲酯

在1.5小时内，向1H-吲哚-6-甲酸甲酯(5.86 g, 33.5 mmol)的30 mL二氯甲烷溶液中分批加入N-氯琥珀酰亚胺(0.58, 4.33 mmol)。将混合物搅拌2小时，然后，用水稀释。分层和有机相用水和饱和氯化钠溶液洗涤。有机层用硫酸镁干燥，过滤并真空浓缩，得到标题化合物(5.74 g, 27.3 mmol)。粗品产物不经进一步纯化即可用于下一步骤。^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (bs, 1H), 8.19 (s, 1 H), 7.90 (dd, 1H), 7.69 (d, 1 H), 7.36 (d, 1H), 3.97 (s, 3H)。

C. 3-氯-1-(甲苯-4-磺酰基)-1H-吲哚-6-甲酸甲酯

在-78℃下，向3-氯-1H-吲哚-6-甲酸甲酯(3.00 g, 17.1 mmol)在40 mL THF中滴加入LDA (8.55 mL, 2.0M己烷溶液, 17.1 mmol)。将溶液在-78℃下搅拌30分钟，滴加入对甲苯磺酰基氯(3.43 g, 18.0 mmol)在15 mL THF中的溶液，将所得溶液在-78℃下搅拌3小时。将混合物升温至0℃，用饱和碳酸氢钠溶液中止反应和用水和乙醚稀释。分层。有机相用饱和碳酸氢钠溶液，水和饱和氯化钠溶液洗涤，然后，用硫酸镁干燥，过滤和浓缩。粗品残余物用快速柱色谱纯化，进行梯度洗脱：10%乙酸乙酯/己烷至30%乙酸乙酯/己烷，得到标题化合物(3.64 g, 10.0 mmol)。^1H NMR ($CDCl_3$, 300MHz) δ 8.70 (s, 1H), 8.01 (dd, 1 H), 7.80 (d, 2H), 7.70 (s, 1 H), 7.60 (d, 1 H), 7.38 (m, 2H), 4.00 (s, 3H), 2.49 (s, 3H)。

D. [3-氯-1-(甲苯-1-磺酰基)-1H-吲哚-6-基]-甲醇

在-78℃下，向3-氯-1-(甲苯-4-磺酰基)-1H-吲哚-6-甲酸甲酯(3.10 g, 8.53 mmol)的50 mL甲苯溶液中滴加入DIBAL (13.8 mL, 1.5M甲苯溶液, 20.8 mmol)。将混合物在-78℃下搅拌2小时，然后，升温

至室温和搅拌2小时。加入甲醇使反应混合物中止反应，用饱和酒石酸二钠溶液洗涤。水层用乙醚萃取。合并后的有机相用饱和酒石酸二钠溶液，水和饱和氯化钠溶液洗涤。然后，有机相用无水硫酸镁干燥，过滤并浓缩，得到标题化合物(2.88 g)。粗品产物不经进一步纯化即可用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), 7.79 (d, 2H), 7.56 (s, 1H), 7.53 (d, 1H), 7.31 (d, 1H), 7.25 (d, 2H), 4.84 (s, 2H), 2.37 (s, 3H), 1.88 (bs, 1H)。

E. 6-溴甲基-3-氯-1-(甲苯-4-磺酰基)-1H-吲哚

在0℃下，向[3-氯-1-(甲苯-1-磺酰基)-1H-吲哚-6-基]-甲醇(0.45 g, 1.34 mmol)的13 mL的乙醚溶液中加入三溴化磷(0.04 mL, 0.40 mmol)。将混合物在0℃下搅拌15分钟，然后在室温下搅拌2小时。向混合物中加入水/冰中止反应，用乙醚稀释。分层，有机相用饱和碳酸氢钠溶液，水和饱和氯化钠溶液洗涤。有机层用无水硫酸镁干燥，过滤并浓缩，得到标题化合物(0.47 g, 1.18 mmol)，为一种油。粗品产物不经进一步纯化即可用于下一步骤中。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1 H), 7.79 (d, 2H), 7.59 (s, 1 H), 7.50 (d, 1H), 7.35 (d, 1H), 7.27 (m, 2H), 4.66 (s, 2H), 2.39 (s, 3H)。

实施例17

2-(3-溴-(E)-丙烯基)-5-氯-噻吩

A. 3-(5-氯-噻吩-2-基)-(E)-丙烯酸甲酯

向5-氯-2-噻吩-甲醛(5.10 g, 34.8 mmol)的100 mL的无水二氯甲烷溶液中加入(三苯基亚正磷基(亚正膦基))乙酸甲酯(11.8 g, 35.3 mmol)。将得到的褐绿色混合物在室温下搅拌19小时。将混合物用硅藻土垫过滤，真空浓缩和用己烷研制。滤出白色沉淀(三苯膦氧化物)，将滤液浓缩。粗品残余物用快速柱色谱纯化，进行梯度洗脱：5%乙酸乙酯/己烷至10%乙酸乙酯/己烷，得到标题化合物(6.20 g, 30.6 mmol)，为一种黄色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.65 (d, 1H), 7.05 (d,

1 H), 6.89 (d, 1H), 6.10 (d, 1H), 3.80 (s, 3H).

B. 3-(5-氯-噻吩-2-基)-丙-2-(E)-烯-1-醇

在0℃下，向3-(5-氯-噻吩-2-基)-(E)-丙烯酸甲酯(5.00 g, 24.7 mmol)的80 mL的二氯甲烷溶液中缓慢加入DIBAL(36.2 mL, 1.5M甲苯溶液, 54.3 mmol)。将混合物在0℃下搅拌15分钟，然后，加入6 mL的甲醇中止反应。将混合物升温至室温，用水/冰稀释和搅拌15分钟.将混合物用硅藻土垫过滤和用二氯甲烷洗涤。分层和水层用二氯甲烷萃取。合并后的有机相用饱和氯化钠溶液，用无水硫酸钠干燥，过滤并浓缩。将残余物用快速柱色谱纯化，进行梯度洗脱：15%乙酸乙酯/己烷至25%乙酸乙酯/己烷洗脱，得到标题化合物(4.18 g, 23.9 mmol)，为一种油。^{1}H NMR (CDC) 300 MHz) δ 6.77 (d, 1H), 6.71 (d, 1H), 6.60 (d, 1H), 6.10 (m, 1H), 4.30 (d, 2H), 1.79 (bs, 1H).

C. 2-(3-溴-(E)-丙烯基)-5-氯-噻吩

在0℃下，向3-(5-氯-噻吩-2-基)-丙-2-(E)-烯-1-醇(4.18 g, 23.9 mmol)的140 mL的乙醚溶液中加入三溴化磷(1.34 mL, 14.3 mmol)的10 mL的乙醚溶液。将混合物在0℃下搅拌45分钟，然后在室温下搅拌1.5小时。向混合物中加入水/冰中止反应和用乙醚稀释稀释。分层和有机相用水洗涤直至中和(3x)和，再用饱和氯化钠溶液洗涤一次。有机层用无水硫酸镁干燥，过滤并浓缩，得到标题化合物(5.46 g, 23.0 mmol)，为一种油。粗品物质在冷冻器中贮藏时固化，可不经进一步纯化用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80 (m, 2H), 6.65 (d, 1H), 6.10 (m, 1H), 4.10 (d, 2H).

实施例18

3-(4-溴-呋喃-2-基)-(E)-丙烯醛

向4-溴-2-糠醛(0.5 g, 2.86 mmol)的30 mL的无水二氯甲烷溶液中加入(tri苯基亚正膦基)乙醛(0.87 g, 2.86 mmol)。所得混合物在

室温下搅拌16小时。将粗品混合物进行真空浓缩和残余物用快速柱色谱纯化，用二氯甲烷洗脱，得到标题化合物(0.15 g，0.75 mmol)，为一种白色固体。^{1}HNMR ($CDCl_3$，300 MHz) δ 9.62 (d，1H)，7.59 (s，1H)，7.18 (d，1H)，6.81 (s，1H)，6.60 (m，1H)。

实施例19

乙酸3-(6-甲氧基-吡啶-3-基)-(E)-烯丙基酯

在0℃下，向3-(6-甲氧基-吡啶-3-基)-丙-2-(E)-烯-1-醇(0.39 g，2.36 mmol，如实施例17所述制备17，采用6-甲氧基-吡啶-3-甲酯(J. Org. Chem. 1990，72))的8 mL的二氯甲烷溶液中加入三乙胺(0.66 mL，4.72 mmol)，DMAP (0.05 g，0.40 mmol)和Ac_2O(0.33 mL，3.54 mmol)。将混合物在0℃下搅拌45分钟，然后在室温下搅拌16小时。将混合物用乙醚稀释和用1N盐酸，水，饱和碳酸氢钠溶液和饱和氯化钠溶液洗涤。有机层用无水硫酸镁干燥，过滤并浓缩。将残余物用快速柱色谱纯化，进行梯度洗脱：10%乙酸乙酯/己烷至20%乙酸乙酯/己烷洗脱，得到标题化合物(0.25 g，1.21 mmol)，为一种油。^{1}H NMR ($CDCl_3$，300 MHz) δ 8.12 (d，1H)，7.68 (dd，1 H)，6.72 (d，1H)，6.60 (d，1H)，6.18 (dt，1H)，4.73 (d，2H)，3.95 (s，3H)，2.10 (s，3H)。

实施例20

2-(3-溴-丙-1-炔基)-5-氯-噻吩

A. 3-(5-氯-噻吩-2-基)-丙-2-炔-1-醇

将氮气(g)鼓泡通过5-溴-2-氯-噻吩(1.00 g，5.06 mmol)的8 mL的哌啶溶液。5分钟后，向溶液中加入炔丙醇(0.32 mL，5.56 mmol)，四(三苯基膦)钯(0)(0.06 g)和碘化铜(催化量)。在密封的玻璃容器中，将混合物在80℃下加热搅拌1小时。此时，将混合物冷却和用乙酸乙酯/乙醚稀释。有机层用3N盐酸，水，饱和碳酸氢钠溶液和饱和氯化钠溶液洗涤。将有机层干燥，过滤并浓缩。粗品残余物用快速柱色谱纯化，进行梯度洗脱：10%乙酸乙酯/己烷至20%乙酸乙酯/己烷洗脱，得到标

题化合物(0.8 g, 0.46 mmol)，为一种油。^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.99 (d, 1H), 6.80 (d, 1H), 4.49 (s, 2H), 1.90 (bs, 1H)。EI MS, $[M]^+$=172, 174 (Cl 花样)。

B. 2-(3-溴-丙-1-炔基)-5-氯-噻吩

此标题化合物按照实施例17，部分C所述制备，采用3-(5-氯-噻吩-2-基)-丙-2-炔-1-醇代替3-(5-氯-噻吩-2-基)-丙-2-(E)-烯-1-醇。粗品产物不经进一步纯化即可用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, 1H), 6.80 (d, 1H), 4.98 (d, 2H)。

实施例21

2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯

A. 5-氯-2-甲基-吲哚-1-甲酸叔丁酯

将包含5-氯-2-甲基吲哚(4.0 g, 24.1 mmol)和DMAP(295 mg, 2.42 mmol)的无水THF (100 mL)溶液冷却至0℃。将包含$(Boc)_2O$(5.27 g, 24.1 mmol)的无水THF (100 mL)溶液在20分钟内加入。将反应混合物在0℃下搅拌2小时，然后，在室温下搅拌16小时。将反应混合物浓缩和粗品残余物进行快速硅胶色谱纯化(2%乙酸乙酯/己烷至5%乙酸乙酯/己烷)，得到5.2 g (81 %)的标题化合物，为一种浅黄色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.57 (s, 3H), 6.24 (t, J =0.9 Hz, 1H), 7.16 (dd, J =8.8, 2.1 Hz, 1H), 7.38 (d, J =2.1 Hz, 1H), 8.01 (d, J =8.8 Hz, 1H) ppm; MS (EI) : m/z 265 (M^+)。

B. 2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯

将包含5-氯-2-甲基-吲哚-1-甲酸叔丁酯(3.0 g, 11.3 mmol), NBS (1.33 g, 11.3 mmol)和苯甲酰基过氧化物(0.4 g, 1.13 mmol)在CCl_4(100 mL)中的溶液在80℃下加热搅拌3小时。然后，再加入另一份NBS (0.65 g, 5.65 mmol)和苯甲酰基过氧化物(0.2 g, 0.56 mmol)，并将将反应混合物再加热3小时。冷却至室温后，将反应混合物过滤。

将滤液浓缩成一种褐色油，将其用己烷研制，除去残余的琥珀酰亚胺，过滤，并浓缩。形成的油(4.5 g，> 100%)不经进一步纯化直接用于下一反应。^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 9H), 4.88 (s, 2H), 6.63 (s, 1 H), 7.27 (dd, J =9.0, 2.0 Hz, 1 H), 7.46 (d, J =2.0 Hz, 1 H), 8.09 (d, J =9.0 Hz, 1 H) ppm; MS (EI): m/z 343 (M^+)。

实施例22

3-溴甲基-5-碘-2-甲氧基-吡啶

A. 5-碘-3-甲基-2-甲氧基-吡啶

在0℃下，向包含2-溴-5-碘-3-甲基-吡啶(4.80 g, 16.0 mmol)的DMSO (15 mL)溶液中加入甲醇钠的甲醇溶液(3.33 M, 5.3 mL, 17.7 mmol)。将溶液升温至室温，然后，在70℃下加热搅拌1小时。将反应混合物用乙醚(300 mL)和水 (200 mL)稀释，分层。有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品产物用硅胶柱色谱纯化(己烷/乙醚, 19:1)，得到2.86 g (71%)的标题化合物，为一种白色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.90 (s, 3H), 7.60 (d, J =2.1 Hz, 1H), 8.14 (d, J =2.1 Hz, 1H) ppm; MS (EI): m/z 249 (M^+)。

B. 3-溴甲基-5-碘-2-甲氧基-吡啶

将包含5-碘-3-甲基-2-甲氧基-吡啶(1.00 g, 4.00 mmol)和NBS (0.78 g, 4.40 mmol)的四氯化碳(20 mL)溶液升温至回流。每小时以5 mg的量(0.03 mmol)加入AIBN。3小时后，将反应混合物冷却，然后，真空浓缩。将残余物溶解于乙酸乙酯(150 mL)中和依次用硫代硫酸钠水溶液(100 mL)，水(100 mL)，盐水洗涤，然后，用无水硫酸钠干燥，过滤并浓缩。粗品产物用硅胶柱色谱进行纯化(己烷/乙醚, 19: 1)，得到0.72 g (55%)的标题化合物，为一种白色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.38 (s, 2H), 7.83 (d, J =2.2 Hz, 1 H), 8.27 (d, J =2.2 Hz, 1 H) ppm; MS (EI): m/z 327 (M^+)。

实施例23

5-溴甲基-6-甲氧基-烟酸甲酯

A. 6-甲氧基-5-甲基-烟酸甲酯

将包含5-碘-3-甲基-2-甲氧基-吡啶(10.0 g, 40.0 mmol), 三乙胺(8.0 g, 80.0 mmol)和$(Ph_3P)_4PdCl_2$(2.80 g, 4.00 mmol)的1:1DMF/甲醇(100 mL)溶液冷却至0℃。将一氧化碳鼓泡进入冷却溶液中大约5分钟, 将反应混合物密封在一氧化碳的气罐中。将反应混合物升温至室温, 然后, 搅拌16小时。将反应混合物进行真空浓缩和将残余物在水 (300 mL)和乙酸乙酯(300 mL)间分配, 分层。有机相用盐水, 用无水硫酸钠干燥, 过滤并浓缩。粗品产物用硅胶柱色谱纯化(己烷/乙醚, 19: 1)得到4.10 g (57%)的标题化合物, 为一种白色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.88 (s, 3H), 4.00 (s, 2H), 7.96 (d, J =2.2 Hz, 1H), 8.65 (d, J =2.2 Hz, 1H) ppm; MS (ISP周线): m/z 182 (M+H)。

B. 5-溴甲基-6-甲氧基-烟酸甲酯

将包含6-甲氧基-5-甲基-烟酸甲酯(4.00 g, 22.1 mmol), NBS (5.11 g, 28.7 mmol)和AIBN (0.90 g, 5.5 mmol)的四氯化碳(100 mL)溶液升温至回流。在5小时后, 将反应混合物冷却, 然后, 真空浓缩。将残余物溶解于乙酸乙酯(500 mL)中, 依次用硫代硫酸钠水溶液(300 mL), 水(100 mL), 盐水洗涤, 然后, 用无水硫酸钠干燥, 过滤并浓缩。粗品产物用硅胶柱色谱纯化(己烷/乙醚, 9:1)得到3.10 g (54%)的标题化合物, 为一种白色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.07 (s, 3H), 4.46 (s, 2H), 8.19 (d, J =2.2 Hz, 1 H), 8.79 (d, J =2.2 Hz, 1H) ppm; MS (EI): m/z 259 (M^+)。

实施例24

5-氯-2-噻吩基氧基乙酸

A. 2-羟基-噻吩

将噻吩(42g, 500mol)溶解于醚(250mL)中。向溶液中加入正丁基锂(200mL, 2.5N 己烷溶液, 500mmol), 加入速度保持温和回流。加完后, 将溶液搅拌0.5小时。然后, 将溶液冷却至-78℃, 滴加入硼酸三乙酯(102 g, 700mL)。将溶液搅拌3小时。撤除冷浴, 在迅速搅拌下加入130mL, 30%过氧化氢2滴。加完后, 将溶液再回流20分钟。然后将溶液冷却至0℃和酸化至pH=3, 采用6N盐酸。将所得溶液用乙醚萃取。有机溶液用10%硫酸亚铁铵, 水和饱和氯化钠洗涤。将溶液用硫酸镁干燥, 过滤并真空浓缩, 获得标题化合物(32g, 320mol)为一种油状物。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.60 (m, 1 H), 6.35 (m, 1H), 4.12 (d, 2H)。

B. 2-噻吩基氧基乙酸乙酯

向2-羟基-噻吩(32g, 320 mmol)的氯仿(500mL)溶液中加入溴代乙酸乙酯(53.4 g, 320 mmol)。向所得溶液加入包含n-Bu_4NHSO_4 (25g, 74mmol)和氢氧化钠(15.8g, 394 mmol)的水(500mL)溶液。将溶液剧烈搅拌, 采用机械搅拌。将反应混合物搅拌12小时。此后, 分层。水层用氯仿萃取。合并的有机层用水和饱和氯化钠洗涤。有机层用硫酸镁干燥, 过滤并真空浓缩。所得粗品产物用柱色谱纯化, 进行梯度洗脱: 30%二氯甲烷:己烷至60%二氯甲烷:己烷, 获得标题化合物(11.5g, 62mmol), 为一种油。^{1}H NMR ($CDCl_3$, 300MHz) δ 6.68 (dd, 1 H), 6.60 (d, 1 H), 6.22 (d, 1 H), 4.62 (s, 2H), 4.30 (q, 2H), 1.31 (t, 3H)。

C. 5-氯-2-噻吩基氧基乙酸乙酯

向2-噻吩基氧基乙酸乙酯(1.1g, 5.9mmol)的乙酸(15mL)溶液中加入N-氯琥珀酰亚胺(0.78g, 5.9mmol)。将溶液搅拌1.5小时。此后, 将溶液浓缩。将所得油状物溶解于乙醚和用1 N氢氧化钠, 水和饱和氯化钠洗涤。有机层用硫酸镁干燥, 过滤并真空浓缩。标题化合物(1.26g, 5.7mmol)为一种油状物。^{1}H NMR ($CDCl_3$, 300MHz) δ 6.52 (d, 1 H),

6.06 (d, 1 H), 4.60 (s, 2H), 4.24 (q, 2H), 1.31 (t, 3H).

D. 5-氯-2-噻吩基氧基乙酸

向5-氯-2-噻吩基氧基乙酸乙酯(0.39g, 1.77mmol)的9mL, 1:1:1甲醇: THF:水的混合物中的溶液中加入乙酰胺(0.38g, 9.0 mmol)。将溶液搅拌16小时。此后,将溶液浓缩成1/3体积。将所得溶液酸化至pH=3,采用1N 盐酸。将水溶液用二氯甲烷萃取。有机层用硫酸镁干燥,过滤并真空浓缩。获得标题化合物(0.32g, 1.66mmol),为一种白色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 6.50 (d, 1 H), 6.07 (d, 1 H), 4.66 (s, 2H).

实施例25

3-(5-氯-噻吩-2-基)-(E)-丙烯酸

在0℃下, 3-(5-氯-噻吩-2-基)-(E)-丙烯酸甲酯(0.60 g, 2.96 mmol)在15 mL的1:1:1 THF/甲醇/水的混合物中加入氢氧化锂一水合物(0.62 g, 14.7 mmol)。将混合物在0℃下搅拌1小时,然后在室温下搅拌1小时并真空浓缩。将残余物用乙酸乙酯稀释,用1N盐酸洗涤。水层用乙酸乙酯萃取,合并后的有机相用水洗涤(2x),干燥,过滤并浓缩,得到标题化合物(0.54 g, 2.86 mmol),为一种白色固体。粗品物质可不经进一步纯化用于下一步骤。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.65 (d, 1H), 7.05 (d, 1H), 6.90 (d, 1H), 6.10 (d, 1H).

实施例26

3-(4-氯-噻吩-2-基)-(E)-丙烯酸

A. 4-氯-2-噻吩-甲醛

在0℃下,在几分钟内,分批向2-噻吩-甲醛(6.33 g, 56.4 mmol)的100 mL的氯仿溶液中加入三氯化铝(16.8 g, 126 mmol)。在分液漏斗中,在0℃下,向100 mL的四氯化碳中鼓泡通入氯气(4.00 g),然后,在0℃下缓慢地加入前一种混合物。将所得混合物在0℃下搅拌45分钟,

然后，升温至室温和搅拌过夜。16小时后，在0℃下，将反应混合物缓慢地倒入6N盐酸中，然后，在室温下搅拌2小时。分层。水层用氯仿萃取。合并的有机层用水和饱和氯化钠溶液洗涤，然后，用硫酸镁干燥，过滤并浓缩。粗品产物用柱色谱纯化，用10%乙酸乙酯/己烷洗脱，得到标题化合物(6.70 g，45.9 mmol)。^{1}H NMR ($CDCl_3$，300 MHz) δ 9.87 (s，1 H)，7.64 (s，1 H)，7.63 (s，1 H)。

B. 3-(4-氯-嘧吩-2-基)-(E)-丙烯酸甲酯

此标题化合物按照实施例1部分A所述制备，采用4-氯-2-噻吩-甲醛。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.69 (d，1 H)，7.15 (s，1 H)，7.11 (s，1H)，6.25 (d，1 H)，3.82 (s，3H)。

C. 3-(4-氯-噻吩-2-基)-(E)-丙烯酸

此标题化合物按照实施例1，部分B所述制备，采用3-(4-氯-噻吩-2-基)-(E)-丙烯酸甲酯。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.77 (d，1H)，7.19 (d，2H)，6.25 (d，1H)。

实施例27

(5-氯-噻吩-2-基)-乙酸

A. [2-(5-氯-噻吩-2-基)-1-二甲基氨基乙烯基]膦酸二乙醚

向氢化钠(0.25 g，6.25 mmol，60%矿物油悬浮液)的10 mL THF悬浮液中缓慢地加入二甲基氨基亚甲基二膦酸四乙酯(2.03 g，6.14 mmol，按照以下文献制备：Psaume，Montury，and Cosmetic Comm. 1982，12，415)的10 mLTHF溶液。在搅拌1小时后，加入5-氯-2-噻吩甲醛(0.90 g，6.14 mmol)的10 mL THF溶液。将形成的混合物在回流下加热1小时，然后冷却至室温。将反应混合物在乙醚与水间分配。有机层依次用1N盐酸，水和饱和氯化钠洗涤，然后，用硫酸镁干燥，过滤并浓缩。粗品产物用快速柱色谱纯化，进行梯度洗脱：40%乙酸乙酯/己烷至50%乙酸乙酯/己烷洗脱，得到标题化合物(1.52 g，4.69

mmol)，为一种油。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 1 H), 6.95 (d, 1 H), 6.82 (d, 1H), 4.15 (m, 4H), 2.62 (s, 6H), 1.60 (t, 6H)。

B. (5-氯-噻吩-2-基)-乙酸

将[2-(5-氯-噻吩-2-基)-1-二甲基氨基乙烯基]膦酸二乙酯(1.52 g, 4.69 mmol)和30 mL 6N盐酸的混合物加热回流2小时。在冷却至室温后，加入冰水，将混合物在乙醚和水间分配。有机层用水(2x)洗涤，用硫酸镁干燥，过滤并浓缩，得到标题化合物(0.62 g, 3.51 mmol)，为一种褐色固体。粗品产物可不经进一步纯化用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (bs, 1 H), 7.79 (d, 1H), 6.71 (d, 1H), 3.81 (s, 2H)。

实施例28

3-(5-氯-噻吩-2-基)-丙酸

A. 3-(5-氯-噻吩-2-基)-丙醛

向$Pd(OAc)_2$ (0.12 g, 0.53 mmol)，碳酸氢钠(0.52 g, 6.19 mmol)和碘化钠(0.28 g, 1.87 mmol)在5 mL的HMPA中的混合物中加入5-溴-2-氯-噻吩(1.00 g, 5.06 mmol)和烯丙醇(1.03 mL, 15.2 mmol)。将混合物加热至90℃和搅拌16小时。将反应混合物冷却至室温，用乙醚稀释和用水洗涤。有机层用硫酸镁干燥，过滤并真空浓缩。粗品残余物用快速柱色谱进行纯化，进行梯度洗脱：10%乙醚/己烷至20%乙醚/己烷，得到产物(0.18 g, 1.03 mmol)，为一种油。^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, 1H), 6.71 (d, 1H), 6.58 (d, 1H), 3.07 (t, 2H), 2.81 (t, 2H)。

B. 3-(5-氯-噻吩-2-基)-丙酸

在0℃下，将1 mL的水中的硝酸银(117 mg, 0.69 mmol)加至1.36 mL的1N氢氧化钠中，搅拌5分钟。向褐色的悬浮液中加入3-(5-氯-噻吩-

2-基)-丙醛(60 mg, 0.34 mmol), 并将所得混合物在2小时内升温至室温。将沉淀过滤和用热水(2x)洗涤。合并的水层用6 N盐酸酸化, 用乙酸乙酯萃取(2x)。合并的有机层用水洗涤(2x), 然后, 用硫酸镁干燥, 过滤并真空浓缩, 得到标题化合物(50 mg, 0.26 mmol), 为一种米色固体。粗品产物可不经进一步纯化用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.72 (d, 1 H), 6.60 (d, 1 H), 3.07 (t, 2H), 2.71 (t, 2H)。

实施例29

3-氟苯氧基-乙酸

A. 3-氟苯氧基-乙酸乙酯

在0℃下, 向3-氟苯酚(1.2g, 11.8mmol)的20mL的DMF溶液中加入氢化钠(0.47g, 10.7mmol)。搅拌10分钟, 滴加入溴代乙酸乙酯(1.2g, 10.7 mmol)溶液。将反应混合物升温至室温和搅拌16小时。向反应混合物中加入饱和氯化铵溶液(水溶液)。将所得混合物用乙酸乙酯和水稀释。分层。有机层用水和饱和氯化钠(水溶液)洗涤。有机层用硫酸镁干燥, 过滤并浓缩, 得到产物(2g, 10mmol), 为一种油。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.22 (m, 1 H), 6.65 (m, 3H), 4.61 (s, 2H), 4.27 (q, 2H), 1.24 (t, 3H)。

B. 3-氟苯氧基-乙酸

向3-氟苯氧基-乙酸乙酯(2g, 10mmol)在24mL, 甲醇:水:THF的1:1:1溶液中的溶液中加入氢氧化锂一水合物(2.25g, 54mmol)。将溶液搅拌16小时。此后, 将溶液减压浓缩至1/3体积。 将剩余的溶液酸化至pH=3, 采用1N盐酸(水溶液)。将水溶液用乙酸乙酯萃取。将有机层用饱和氯化钠(水溶液)洗涤。有机层用硫酸镁干燥, 过滤并浓缩, 得到产物(1.65g, 9.7mmol), 为一种白色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 9.8 (bs, 1H), 7.28 (m, 1H), 6.69 (m, 3H), 4.70 (s, 2H)。

实施例30

2-氯吡啶-3-基氨基-乙酸

向3-氨基-2-氯吡啶(1.0g, 7.8mmol)的20mL的甲醇溶液中加入乙醛酸(0.86mL, 50wt%水溶液, 7.8mmol)。搅拌10分钟, 加入$NaCNBH_3$(1.54 g, 23mmol)溶液。将反应混合物搅拌16小时。然后, 减压浓缩。将所得残余物溶解于水中将溶液酸化至pH=3, 用1N盐酸(水溶液)。将溶液用乙酸乙酯/二氯甲烷(2:1)萃取。有机层用硫酸镁干燥, 过滤并浓缩。获得产物, 为一种白色固体(0.95g, 5.1 mmol)。^{1}H NMR (d_6-DMSO, 300MHz) δ 12.7 (bs, 1H), 7.62 (m, 1H), 7.44 (m, 1 H), 6.90 (m, 1 H), 5.8 (bs, 1H), 3.95 (AB, 2H)。4.70 (s, 2H)。

实施例31

5-氯噻吩-2-基-硫烷基乙酸

A.噻吩-2-基-硫烷基乙酸乙酯

向噻吩-2-硫醇(1.49g, 116mmol)的40mL的乙腈溶液中加入溴代乙酸乙酯(2.14g, 167mol),再加入加入碳酸钾(3.54g, 138mmol)。将溶液搅拌16小时。此后, 将溶液过滤。将溶液蒸发, 得到产物, 为一种油(2.4g, 118mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.37 (m, 1H), 7.21 (m, 1H), 6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H)。MS (EI): m/z 202 (M^+)。

B. 5-氯噻吩-2-基硫烷基乙酸

向噻吩-2-基-硫烷基乙酸乙酯(0.52g, 2.6mmol)的25 mL的二氯甲烷溶液中加入N-氯琥珀酰亚胺(0.35g, 2.6mmol)。将溶液搅拌10分钟。此后, 加入1滴TFA。将溶液搅拌16小时。然后, 将反应混合物用25 mL的二氯甲烷稀释。所得溶液用1 N氢氧化钠和饱和氯化钠溶液洗涤。有机层用硫酸镁干燥, 过滤并浓缩。获得所得产物, 为一种油, 经测定其包含45%所需产物。然后, 将油溶解于60 mL的1:1:1THF:甲醇:水中。向溶液中加入氢氧化锂一水合物(1.26g, 30mol)。将溶液搅拌

16小时。此后，将溶液酸化至pH=3，采用1N盐酸。水溶液用水和饱和氯化钠溶液洗涤。将溶液用乙酸乙酯/二氯甲烷(2:1)萃取。有机层用硫酸镁干燥，过滤并浓缩。所得粗品产物用柱色谱纯化，用20%甲醇:乙醚洗脱，得到产物，为一种白色固体(0.4g，1.9mmol)。MS (EI)：m/z 208，210 (M^+)，Cl 花样。

实施例32

5'-氯-[2,2']联嘧吩-5-甲酸

A. 5'-氯-[2,2']联嘧吩-5-甲醛

在-78℃下，向5-氯-[2,2']联嘧吩(1.06 g，5.28 mmol)的12 mL的THF溶液中加入正丁基锂(4.4 mL，1.6M 己烷溶液，6.99 mmol)。15分钟后，加入DMF (0.97 mL，14 mmol)，将所得溶液升温至0℃。15分钟后，将溶液用乙酸乙酯稀释，和用饱和碳酸氢钠溶液中止反应。有机溶液用水和饱和氯化钠溶液洗涤，然后，用硫酸镁干燥，过滤并浓缩。粗品产物用快速柱色谱进行纯化，进行梯度洗脱：10%乙醚/己烷至20%乙醚/己烷，得到标题化合物(0.89 g，3.89 mmol)，为一种白色固体。^{1}H NMR ($CDCl_3$，300 MHz) δ 9.87 (s，1 H)，7.70 (d，1 H)，7.20 (d，1 H)，7.15 (d，1H)，6.91 (d，1H)。

B. 5'-氯-[2,2']联嘧吩-5-甲酸

此标题化合物按照实施例28，部分B所述制备，采用5'-氯-[2,2']联嘧吩-5-甲醛。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.69 (d，1 H)，7.09 (d，1 H)，7.06 (d，1 H)，6.89 (d，1 H)。EI MS，$[M]^+$=243,245 (Cl 花样)。

实施例33

7-氯-异喹啉-3-甲酸

A. 7-氯-异喹啉-3-甲醛

将20mL的80%硫酸加至7-氯-3,3-二溴甲基异喹啉(0.69g，

2.06mmol)中，加热至150℃搅拌16小时。然后将溶液冷却至室温，用40 mL的水稀释。将所得溶液用1N氢氧化钠碱化至pH=11。将水溶液用二氯甲烷萃取。有机溶液用水和饱和氯化钠溶液洗涤。有机层用硫酸镁干燥，过滤和浓缩，得到产物，为一种油(0.25g, 1.3 mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 10.0 (s, 1H), 9.30 (s, 1 H), 8.36 (s, 1 H), 8.07 (s, 1 H), 7.95 (d, 1H), 7.78 (d, 1H)。MS (EI): m/z 191, 193 (M^+), Cl 花样。

B. 7-氯-异喹啉-3-甲酸

在0℃下，向4.5 mL的1N氢氧化钠溶液中加入硝酸银(0.31 g, 1.8mmol)的3 mL水溶液，再加入7-氯-异喹啉基-3-carb醛(0.25g, 1.3mmol)的3 mL的乙醇溶液。将溶液在0℃下搅拌10分钟，然后，在室温下搅拌3小时。将溶液酸化至pH=3，采用1H盐酸。将所得溶液用氯仿萃取。有机层用硫酸镁干燥，过滤并浓缩，得到产物，为一种白色固体(0.2g, 0.96mmol)。^{1}H NMR (CD_3OD, 300MHz) δ 9.18 (s, 1H), 8..63 (s, 1 H), 8.18 (m, 1H), 7.80 (m, 2H)。6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H)。MS (EI): m/z 208, 210 (M^+), Cl 花样。

实施例34

2-乙酰基氨基-3-(5-氯-噻吩-2-基)-丙烯酸

A. 4-(5-氯-噻吩-2-基亚甲基)-2-甲基-4H-噁唑-5-酮

将5-氯噻吩-2-甲醛(1.00 g, 6.82 mmol), N-乙酰基甘氨酸(0.96 g, 8.18 mmol), NaOAc (0.67 g, 8.18 mmol)的Ac_2O(5 mL)混合物升温回流16小时。将反应混合物冷却至室温和用氢氧化钠(0.5 M, 100 mL)水溶液和二氯甲烷(100 mL)稀释。分层和有机相用碳酸氢钠水溶液，盐水洗涤，用无水硫酸钠干燥，过滤并浓缩，得到1.5 g (100%)的标题化合物，为一种无色油，其可不经纯化用于下一反应。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 6.94 (d, J =4.0 Hz, 1 H), 7.21

(s, 1 H), 7.26 (d, J =4.0 Hz, 1 H) ppm。

B. 2-乙酰基氨基-3-(5-氯-噻吩-2-基)-丙烯酸

在室温下，向包含4-(5-氯-噻吩-2-基亚甲基)-2-甲基-4H-噁唑-5-酮(1.5 g, 6.82 mmol)的甲醇(18 mL)溶液中加入1.0 M氢氧化钠(12.0 mL, 12 mmol)。3小时后，将反应混合物用水(100 mL)和二氯甲烷(100 mL)稀释，分层。碱性的水层用二氯甲烷洗涤，然后，采用1.0M盐酸(20 mL)酸化，经布氏漏斗收集，得到粗品固体。真空干燥，得到1.2 g (75%)的标题化合物，为一种浅褐色固体，其可不经纯化而使用。^{1}H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H), 7.14 (d, J =4.01 Hz, 1H), 7.38 (d, J =4.01 Hz, 1H), 7.63 (s, 1H), 9.28 (s, 1H), 12.73 (br s, 1 H) ppm; MS (EI): m/z 245 (M^+)。

实施例35

2-乙酰基氨基-3-(5-氯-噻吩-2-基)-丙酸

在室温下，向包含2-乙酰基氨基-3-(5-氯-噻吩-2-基)-丙烯酸(1.00 g, 4.08 mmol)和碳酸钾(1.70 g, 12.1 mmol)的DMF (20 mL)溶液中加入MeI (0.87 g, 6.12 mmol)。2小时后，将反应混合物用水(100 mL)和乙酸乙酯(100 mL)稀释，分层。水层用乙酸乙酯(50 mL)萃取，和合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩，得到0.92 g (83%)的甲基酯，其不经进一步纯化即可使用。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.77 (s, 3H), 6.86 (d, J =4.02 Hz, 1 H), 6.99 (m, 1 H), 7.05 (d, J =4.02 Hz, 1 H), 7.64 (s, 1 H) ppm。

在小的Parr® 容器中装入甲醇(50 mL)中的粗品酯(0.85 g, 3.13 mmol)和$(Ph_3P)_3RhCl$ (0.10 g, 0.10 mmol)。向容器施以50 PSI H_2压和在室温下搅拌7小时。然后，将反应混合物过滤并浓缩，得到所需化合物，其不经纯化即可使用。MS (EI): m/z 261 (M^+)。

将上面制备的饱和酯溶解于1:1:1水/THF/甲醇(15 mL)溶液中。加

入氢氧化锂一水合物(0.14 g, 3.23 mmol)，将多相混合物搅拌16小时。将反应混合物用水(100 mL)和乙酸乙酯(100 mL)稀释，和分层。水层用乙酸乙酯萃取(50 mL)，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩，得到0.62 g (81 %)的标题化合物，为一种无色油。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.30 (m, 2H), 4.81 (m, 1 H), 6.45 (br d, J =6.45 Hz, 1 H), 6.58 (d, J =3.68 Hz, 1 H), 6.71 (d, J =3.68 Hz, 1 H), 9.79 (br s, 1H) ppm; MS (EI): m/z 247 (M^+)。

实施例36

3-(6-氨基-吡啶-3-基)-丙烯酸

A. N-(5-溴-吡啶-2-基)- 乙酰胺

将三乙胺(17.7mL, 75 mmol)加至2-氨基-5-溴吡啶(5.0 g, 29 mmol)和乙酸(7.1 mL, 75 mmol)的混合物中。将溶液加热并回流48小时。此后，将溶液浓缩。将残余物溶解于水中，用1N氢氧化钠调节pH值至10. 过滤收集固体。粗品产物用沸水进行重结晶，得到标题化合物(2.6 g 12.0 mmol)，为一种白色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (1H, bs), 8.42 (s, 1H), 8.01 (m, 2H), 2.05 (s, 3H)。

B. 3-(6-乙酰基氨基-吡啶-3-基)-丙烯酸

向N-(5-溴-吡啶-2-基)-乙酰胺(1.26 g, 5.86 mmol)和三正丁基胺在二甲苯(10 mL)中的溶液中加入$Pd(OAc)_2$(1.4 mg, 0.006 mmol)和三苯膦(15.4mg, 0.06 mmol)。然后在5分钟内滴加入丙烯酸(0.48 mL, 7.03 mmol)。将混合物加热至回流5小时。将溶液冷却至室温。将混合物用水稀释和用1N盐酸调节pH至4。将溶液用乙酸乙酯/二氯甲烷(2:1)萃取。对所得悬浮液过滤，得到标题化合物(0.80 g, 3.88 mmol)，为一种白色固体。MS (离子喷雾) 207, (M+H)。

C. 3-(6-氨基-吡啶-3-基)-丙烯酸

向3-(6-乙酰基氨基-吡啶-3-基)-丙烯酸(0.80 g, 3.88 mmol)的乙醇(10 mL)溶液中加入1N氢氧化钠(20mL)。将溶液加热至回流。16小时后，将溶液浓缩成1/3体积。将水溶液用水稀释和酸化至pH=2，采用6N盐酸。将溶液浓缩至干。将残余物溶解于甲醇中。将溶液过滤。将有机溶液浓缩。粗品产物进行RP-HPLC纯化，进行梯度洗脱：5%乙腈/水(0.1%TFA)至30%乙腈/水(0.1%TFA)，得到产物，为一种白色固体(0.54 g, 1.93 mmol)。^{1}H NMR (300 MHz, CD_3OD) δ 8.34 (d, 1H), 8.07 (s, 1 H), 7.54 (d, 2H), 7.06 (d, 1 H), 6.47 (d, 1H)。MS (离子喷雾) 165, (M+H)。

实施例37

4-氯-苄基异氰酸酯

在0℃下，向三光气(0.54 g, 1.85 mmol)的10 mL的无水二氯甲烷溶液中滴加入白色沉淀形式的4-氯-苄基胺(0.61 mL, 5.00 mmol)。再立即加入在5 mL二氯甲烷中的三乙胺(1.39 mL, 10.0 mmol)，将所得混合物在0℃下搅拌5分钟，然后在室温下搅拌3小时。将混合物进行真空浓缩和用乙酸乙酯研制。滤出白色沉淀(三乙胺盐酸盐)，将滤液浓缩。分离出标题化合物(6.20 g, 30.6 mmol)，为一种粗品黄色残余物，其不经进一步纯化即采用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, 2H), 7.25 (d, 2H), 4.50 (s, 2H)。

实施例38

5-氯-噻吩-2-羰基叠氮化物

向5-氯-2-噻吩-甲酸(5.00 g, 30.7 mmol)的130 mL丙酮溶液中加入三乙胺(4.29 mL, 30.7 mmol)。将混合物冷却至0℃，加入氯代甲酸乙酯(3.23 mL, 33.8 mmol)。将混合物在0℃下搅拌1小时，加入叠氮化钠(3.40 g, 52.3 mmol)。将混合物在0℃下搅拌2小时后，然后，倒入300 mL的冰水中，水层用二氯甲烷(2x)萃取。合并后的有机相用水(2x)和盐水洗涤，然后，干燥，过滤并浓缩。粗品残余物用快速柱色

谱纯化，用10%乙酸乙酯/己烷洗脱，得到标题化合物(3.00 g，16.0 mmol)，为一种白色固体。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.67 (d，1 H)，6.99 (d，1H)。

实施例39

4-硝基-2,3,5,6-四氯吡啶

将五氯吡啶(80 g，320 mmol)用苄基胺(104 mL，96 mmol)处理，溶解于二噁烷(1L)中，回流16小时。将反应混合物冷却至室温，滤出沉淀出的白色固体。将滤液浓缩至褐色残余物，用4%乙酸乙酯的己烷溶液(3x 250 mL)，。 得到4-苄基氨基-2,3,5,6-四氯吡啶，为一种米黄色固体(40 g，124 mmol)。将该产物溶解于氯仿(400 mL)中，在冰浴中冷却，用三氟乙酸(500 mL)和30%过氧化氢(100 mL)处理。将反应混合物过夜升温至室温再用三氟乙酸(500 mL)和30%过氧化氢(100 mL)处理。搅拌24小时后，将反应混合物用水(1L)处理。分离出下面的有机层，水层用氯仿萃取。将合并的有机层浓缩成固体残余物，再溶解于乙酸乙酯/己烷(30 mL)中。除去悬浮的橙色固体，将滤液负载于硅胶快速柱上。柱子用己烷洗脱，收集标题化合物，为一种白色固体(15.6 g，60 mmol)。EI MS m/z 260，262，264 [M^+]。

实施例40

4-(叔丁基氧基羰基)-哌嗪-2-酮

将4-(苄氧基羰基)-哌嗪-2-酮(2.2 g，9.4 mmol)，Boc酸酐(2.5 g，11.3 mmol)溶解于甲醇(100 mL)中，用5%Pd/C处理，在氢气氛(30 PSI)下振摇16小时。将反应器内容物用硅藻土过滤，将滤液浓缩，得到4-(叔丁基氧基羰基)-2-氧代哌嗪(1.9 g，9.4 mmol)，其不经纯化即可使用。EI MS m/z 200，M^+；^{1}H NMR ($CDCl_3$，300 MHz) δ 6.17 (br，1 H)，4.20 (s，2H)，3.55 (t，2H)，3.38 (m，2H)，1.48 (s，9H)。

实施例41

2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯

A. N-Cbz-O-甲基丝氨酸-氨基乙醛二甲基乙缩醛

向N-Cbz-O-甲基丝氨酸(10.8g, 41.8mmol)的500mL的二氯甲烷溶液中加入三乙胺(12.7 g, 125mol)。将溶液冷却至0℃, 加入TBTU (13.5g, 42mmol), 氨基乙醛二甲基乙缩醛(4.83g, 46mmol)。将溶液搅拌16小时。将溶液用500mL的乙醚稀释。所得溶液用水, 1N硫酸氢钾和饱和氯化钠洗涤。获得标题化合物(13.7g, 41.8mmol), 为一种白色泡沫状物。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.40 (m, 5H), 6.55 (bs, 1H), 5.66 (bs, 1 H), 5.32 (m, 1H), 5.13 (s, 2H), 4.32 (m, 2H), 3.79 (dd, 1 H), 3.44 (m, 2H), 3.40 (m, 9H)。

B. N-Cbz-2-氧代-3-(S)-甲氧基甲基-(4, 5-二氢)哌嗪

向N-Cbz-O-甲基丝氨酸-氨基乙醛二甲基乙缩醛(1 3.7g, 41.8mmol)的300mL的甲苯溶液中加入TsOH·H_2O(0.80g, 4.2mmol)。将溶液加热至60℃。5小时后, 将溶液用乙醚稀释。所得有机溶液用水, 饱和碳酸氢钠和饱和氯化钠洗涤。有机层用硫酸镁干燥, 过滤并真空浓缩。所得粗品产物用柱色谱纯化, 进行梯度洗脱: 10%乙酸乙酯:二氯甲烷至20%乙酸乙酯:二氯甲烷。获得标题化合物(1 0.7g, 38mmol), 为一种白色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H), 6.45,6.30 (d, 1 H转动异构体), 5.61, 5.50 (d, 1 H转动异构体), 5.20 (s, 2H), 4.92, 4.83 (bs, 1 H转动异构体), 3.63 (m, 3H), 3.32, 3.20 (s, 1 H转动异构体)。

C. 2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯

向N-Cbz-2-氧代-3-(S)-甲氧基甲基-(4, 5-二氢)哌啶(10.7g, 38mmol)的50mL的甲醇溶液中加入Pt/C (1gm, 10wt%)。将反应混合物上方的气体用氢气代替。24小时后, 将溶液过滤, 将滤液用甲醇洗涤。将收集的有机溶液真空浓缩。所得粗品产物用柱色谱纯化, 进行梯度洗脱: 2%甲醇/二氯甲烷至5%甲醇/二氯甲烷, 获得标题化合物(6.0g,

22mmol)，为一种白色固体。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.35 (m, 5H), 6.42 (bs, 1H), 5.20 (AB, 2H), 4.58 (m, 1 H), 4.18 (m, 1H), 3.95 (m, 1H), 3.50 (m, 4H), 3.27 (s, 3H)。

实施例42

2-丁基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-正亮氨酸替换CbzO-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300mHz) δ 7.32 (m, 5H), 5.13 (AB, 2H), 4.60 (m, 1H), 4.13 (m, 1 H), 3.38 (m, 2H), 3.23 (m, 2H), 1.90 (m, 1 H), 1.66 (m, 1 H), 1.29 (m, 4H), 0.89 (m, 3H)。MS (离子喷雾) m/z 291, (M+H)。

实施例43

2-乙基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-2-氨基-丁酸替换Cbz-O-甲基丝氨酸。^{1}H NMR ($CDCl_3$, 300mHz) δ 7.37 (m, 5H), 6.55 (bs, 1H), 5.10 (AB, 2H), 4.57 (m, 1H), 4.24 (m, 1H), 3.42 (m, 1H), 3.26 (m, 2H), 2.20 (m, 1H), 1.81 (m, 1H), 0.96 (m, 3H)。

实施例44

2-丙基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-正缬氨酸替换CbzO-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300mHz) δ 7.32 (m, 5H), 7.00 (bs, 1H), 5.12 (AB, 2H), 4.58 (m, 1H), 4.21 (m, 1H), 3.40 (m, 1H), 3.19 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 1.37 (m, 2H), 0.91 (m, 3H)。MS (离子喷雾) m/z 277, (M+H)。

实施例45

2-乙氧基甲基-3-氧基-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-O-乙基-丝氨酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 5H), 6.96 (bs, 1H), 5.17 (AB, 2H), 4.58 (m, 1H), 4.18 (m, 1H), 4.03 (m, 1 H), 3.66 (m, 2H), 3.44 (m, 3H), 3.27 (s, 1H), 1.06 (m, 3H)。MS (离子喷雾) m/z 293, (M+H)。

实施例46

2-甲基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-丙氨酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.34 (m, 5H), 7.02 (bs, 1H), 5.17 (AB, 2H), 4.65 (m, 1H), 4.17 (m, 1H), 3.42 (m, 1H), 3.23 (m, 2H), 1.41 (d, 3H)。MS (EI) m/z 248, (M^+)。

实施例47

2-苄基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-苯基丙氨酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.22 (m, 10H), 7.00 (bs, 1H), 5.10 (AB, 2H), 4.10 (m, 1H), 3.27 (m, 2H), 3.10 (m, 2H), 2.55 (m, 2H)。MS (EI) m/z 324, (M^+)。

实施例48

2-(1-甲氧基乙基)-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-O-甲基苏氨酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.52 (bs, 1 H), 7.22 (m, 5H), 5.12 (AB, 2H), 4.33 (m, 1H), 4.05 (m, 2H), 3.60 (m, 1H), 3.14 (s, 3H), 3.10 (m, 1H), 2.82 (m, 1H), 1.10 (d, 3H)。MS (离子喷雾) m/z 293, (M+H)。

实施例49

2,2-二甲基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-2-氨基-异丁酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H), 6.52 (bs, 1 H), 5.12 (s, 2H), 3.72 (m, 2H), 3.33 (m, 2H), 1.68 (s, 3H), 1.64 (s, 3H)。MS (EI) m/z 262, (M^+)。

实施例50

2-异丙基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-缬氨酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.36 (m, 5H), 5.88 (bs, 1H), 5.10 (s, 2H), 4.35 (m, 1H), 3.44 (m, 1H), 3.27 (m, 2H), 2.31 (m, 1H), 1.00 (d, 3H), 0.94 (d, 2H)。

实施例51

2-异丁基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-亮氨酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.35 (m, 5H), 6.50 (m, 1H), 5.15 (s, @ ;H), 4.18 (m, 1H), 3.42 (m, 2H), 3.21 (m, 2H), 1.50 (m, 3H), 0.90 (m, 6H)。

实施例52

2-(2-甲氧基乙基)-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用Cbz-O-甲基-高丝氨酸替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.32 (m, 5H), 6.85 (bs, 1H), 5.14 (s, 2H), 4.75 (m, 2H), 4.20 (m, 2H), 3.42 (m, 1H), 3.21 (m, 3H), 2.12 (m, 4H)。

实施例53

2-甲氧基甲基-5-甲基-3-氧代-哌嗪-1-甲酸苄酯

按照实施例41制备标题化合物，用2-氨基丙醛二甲基乙缩醛替换Cbz-O-甲基-丝氨酸。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.42 (m, 5H), 6.96 (bs, 1 H), 5.12 (AB, 2H), 4.52 (m, 1H), 4.21 (m, 1H), 3.92 (m, 1H), 3.58 (m, 2H), 3.22 (s, 3H), 3.10 (m, 1H), 0.95 (m, 3H)。

实施例54

3-(R)-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸苄酯

A. 2-叔丁氧羰基氨基-3-(叔丁基-二甲基-硅烷氧基)-丙酸

在室温下，将叔丁基二甲基氯硅烷(32.3 g, 0.214 mol)的THF (50 mL)溶液经套管滴加至BOC丝氨酸(20.0g, 0.098 mol)，咪唑(15.3 g, 0.224 mol)的THF (360 mL)溶液中。将所得浆液搅拌2.5小时后，真空除去溶剂。将粗品产物溶解于甲醇(180 mL)中，在室温下，缓慢地加入5N氢氧化钠(58 mL)。将混合物搅拌3小时后，用水(180 mL)稀释，此后，水层用乙醚(180 mLx2)洗涤。水层用2N盐酸酸化至pH 4-5，用乙醚萃取。有机层用饱和碳酸氢钠，盐水洗涤，然后，用硫酸镁干燥，过滤并浓缩至干。获得粗品产物(12.67g, 0.040 mol)，其不经进一步纯化即可用于下一步骤中。^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.35 (bs, 1H), 4.30 (bs, 1H), 4.13 (dd, 1H), 3.80 (dd, 1H), 1.45 (s, 9H), 0.98 (s, 9H), 0.10 (s, 6H)。EI MS, $[M+H]^+$=320。

B. [2-(叔丁基-二甲基-硅烷氧基)-1-(甲氧基-甲基-氨基甲酰基)-乙基]-氨基甲酸叔丁酯

在室温下，将N,N-二甲基氨基吡啶(2.60 g, 21.3 mmol)，BOP试剂(18.15 g, 41.0 mmol)加至2-叔丁氧羰基氨基-3-(叔丁基-二甲基-硅烷氧基)-丙酸(12.37 g, 38.7 mmol)，二异丙基乙基胺(8.1 mL, 46.4 mmol)，N,O-二甲基羟基胺盐酸盐(4.53 g, 46.4 mmol)的THF (260 mL)溶液中。将所得悬浮液在室温下过夜搅拌，然后，浓缩至干。将残余物用乙酸乙酯稀释，用饱和氯化铵，饱和碳酸氢钠和盐水洗涤。有机层用硫酸镁干燥，过滤并真空浓缩，得到粗品产物，将其用

快速色谱进行纯化，用10-30%乙酸乙酯/己烷洗脱，得到标题化合物(11.86 g，30.37 mmol)，为一种油。^{1}H NMR ($CDCl_3$，300 MHz) δ 5.35 (bd，1 H)，4.71 (bs，1 H)，3.78-3.85 (m，2H)，3.72 (s，3H)，3.20 (s，3H)，1.42 (s，9H)，0.90 (s，9H)，0.05 (s，6H)。

C. [1-(叔丁基-二甲基-硅烷氧基甲基)-2-氧代-乙基]-氨基甲酸叔丁酯

在-5℃至0℃下，将[2-(叔丁基-二甲基-硅烷氧基)-1-(甲氧基-甲基-氨基甲酰基)-乙基]-氨基甲酸叔丁酯(11.86，30.37 mmol)的乙醚(100 mL)溶液滴加至1.0M LAH的乙醚(35.5 mL)溶液中。将所得混合物搅拌2.5小时后，缓慢地加入硫酸氢钾水溶液。将反应混合物搅拌30分钟，然后，用饱和氯化铵，饱和碳酸氢钠和盐水洗涤。有机层用硫酸镁干燥，过滤并真空浓缩，得到粗品产物，将其进行快速色谱纯化，用30%乙酸乙酯/己烷洗脱，得到标题化合物(6.04 g，19.9 mmol)，为一种油。^{1}H NMR ($CDCl_3$，300 MHz) δ 9.65 (s，1H)，5.30 (bs，1H)，4.20 (m，1 H)，3.65 (4.90 (m，2H)，1.48 (s，9H)，0.90 (s，9H)，0.05 (s，6H)。离子喷雾 MS，$[M+H]^+$=304。

D. [2-叔丁氧羰基氨基-3-(叔丁基-二甲基-硅烷氧基)-丙基氨基]-乙酸甲酯

将氰基硼氢化钠(2.63 g，41.9 mmol)加至[1-(叔丁基-二甲基-硅烷氧基甲基)-2-氧代-乙基]-氨基甲酸叔丁酯(6.04 g，19.9 mmol)，甘氨酸甲基酯盐酸盐(2.75 g，32.9 mmol)的甲醇(500 mL)溶液中。将混合物在室温下搅拌2天，然后，浓缩至干。粗品产物进行快速色谱纯化，用1-5%甲醇/二氯甲烷洗脱，得到标题化合物(3.06，8.12 mmol)，为无色油状物。^{1}H NMR ($CDCl_3$，300 MHz) δ 5.00 (bs，1 H)，3.75 (s，3H)，3.60-3.70 (m，4H)，3.40 (d，1 H)，2.80 (dd，1 H)，2.68 (dd，1 H)，1.40 (s，9H)，0.90 (s，9H)，0.05 (s，6H)。离子喷雾 MS，$[M+H]^+$=377。

E. (苄氧基羰基-[2-叔丁氧羰基氨基-3-(叔丁基-二甲基-硅烷氧基)-丙基]-氨基)-乙酸甲酯

在室温下，将氯代甲酸苄酯(1.4 mL, 9.81 mmol)滴加至N,N-二甲基氨基吡啶(1.09 g, 8.93 mmol)，[2-叔丁氧羰基氨基-3-(叔丁基-二甲基-硅烷氧基)-丙基氨基]-乙酸甲酯(3.06 g, 8.12 mmol)的二氯甲烷溶液中。将所得混合物搅拌过夜，然后，浓缩至干。粗品产物进行快速色谱纯化，用1%甲醇/二氯甲烷洗脱，得到标题化合物(3.52 g, 6.89 mmol)，为无色油状物。离子喷雾 MS, $[M+H]^+$=511。

F. 3-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸苄酯

在室温下，将(苄氧基羰基-[2-叔丁氧羰基氨基-3-(叔丁基-二甲基-硅烷氧基)-丙基]-氨基)-乙酸甲酯(3.52 g, 6.89 mmol)在50%TFA/二氯甲烷(40 mL)中搅拌40分钟。将反应混合物进行真空浓缩，粗品产物进行快速色谱纯化，用1%甲醇/二氯甲烷洗脱，得到标题化合物(1.1 g, 2.9 mmol)，为无色油状物。离子喷雾 MS, $[M+H]^+$=379。

实施例55

5-氧代-哌嗪-1,3 (R或S)-二甲酸1-苄基酯3-甲基酯

在室温下，将N,N-二甲基氨基吡啶(0.43 g, 3.5 mmol)，氯代甲酸苄酯(0.55 g, 3.8 mmol)加至6-氧代哌嗪-2-甲酸甲酯(0.50 g, 3.2 mmol) (Aebischer, B., Helv. Chim. Acta 1989, 72, 1043-1051)的二氯甲烷溶液中。1小时后，将反应混合物倒入乙酸乙酯中，用饱和碳酸氢钠和盐水洗涤，然后，用硫酸镁干燥，过滤并浓缩至干，得到一种固体(0.90 g, 3.1 mmol)，其不经纯化即可用于下一步反应。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (bs, 5 H), 6.32 (bs, 1 H), 5.15 (s, 2H), 4.00-4.30 (m, 3H), 4.23 (s, 3H), 3.70-3.80 (m, 2H)。MS (EI) m/z 292 (M^+)。

实施例56

(S)-5-氧代-哌嗪-1,3-二甲酸1-烯丙基酯3-甲基酯

在0℃下，向包含(S)-6-氧代哌嗪-2-甲酸甲酯(1.32 g, 8.35 mmol)(Aebischer方法制备)的无水二氯甲烷(30 mL)溶液中加入三乙胺(1.26 g, 12.5 mmol)，再加入氯代甲酸烯丙酯(1.20 g, 10.0 mmol)。1小时后，将反应混合物倒至二氯甲烷/水(200 mL)的1:1混合物中，采用1N盐酸酸化，分层。有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行硅胶色谱处理(二氯甲烷至1%甲醇/二氯甲烷)，得到1.22 g (60%)的实施例35的产物，为一种粘稠油。^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (bs, 1H), 5.90 (m, 1 H), 5.26 (m, 2H), 4.61 (m, 2H), 4.05-4.26 (m, 3H), 3.80 (s, 3H), 3.72 (m, 2H); MS (ISP周线): m/z 243 (M+H)。

实施例57

(2S,6R)-4-(2,6-二甲基)-3-氧代-哌嗪-1-甲酸苄酯和

实施例58

(2S,6S)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

A. (2RS, 1S)-[1-(2-羟基-丙基氨基甲酰基)-乙基]-氨基甲酸叔丁酯

将N-(叔丁氧羰基)-1-丙氨酸(10.0 g, 52.8 mmol)溶解于150 mL的THF中。在加入三乙胺(11.0 ml, 79.2 mmol)后，将溶液冷却至0℃。缓慢加入氯代甲酸异丙酯的甲苯(1M)(52.8 ml, 52.8 mmol)溶液，再加入(2RS) 1-氨基-2-丙醇(6.1 ml, 79.2 mmol)。过夜搅拌，将混合物用1N氢氧化钠和，1N盐酸洗涤。浓缩有机溶剂，得到(2RS, 1S)-[1-(2-羟基-丙基氨基甲酰基)-乙基]-氨基甲酸叔丁酯(9.92 g, 76%yield)，为一种澄清油。

B. (1S)-[1-(2-氧代-丙基氨基甲酰基)-乙基]-氨基甲酸叔丁酯

将二甲基硫(7.16 ml, 100.8 mmol)加至草酰氯(4.41 ml, 50.4 mmol)的126 mL的二氯甲烷溶液中(-78℃下)。将混合物搅拌15分钟，滴

加入(2RS, 1S)-[1-(2-羟基-丙基氨基甲酰基)-乙基]-氨基甲酸叔丁酯(9.92 g, 40.32 mmol)的100 mL的二氯甲烷溶液。在-78℃下搅拌15分钟，将反应混合物用三乙胺(28 mL, 381 mmol)中止反应，升温至室温。除去挥发性溶剂，将残余物进行快速柱色谱纯化(SiO_2, 60%乙酸乙酯/己烷)。分离出产物(1S)-[1-(2-氧代-丙基氨基甲酰基)-乙基]-氨基甲酸叔丁酯(5.93 g, 60 %)，为一种白色固体。MS $C_{11}H_{20}N_2O_4$ MS m/z: 245。

C: (3S,5RS)-3,5-二甲基-哌嗪-2-酮

将(1S)-[1-(2-氧代-丙基氨基甲酰基)-乙基]-氨基甲酸叔丁酯(5.93 g, 24.3 mmol)在30 %三氟乙酸的二氯甲烷(100 mL)溶液中搅拌3小时。真空除去溶剂。将残余物溶解于50 mL的甲醇中，转移至标准瓶中。加入钯/炭(10 %, 1.0 g)。将混合物在压力下氢化24小时。过滤除去催化剂；真空除去甲醇，得到(3S,5RS)-3,5-二甲基-哌嗪-2-酮，其可不经纯化直接用氨基甲酸苄酯进行保护。

D: (2S,6RS)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

向(3S,5RS)-3,5-二甲基-哌嗪-2-酮(24.3 mmol)的100 mL的二氯甲烷溶液中加入三乙胺(8.45 mL, 60.75 mmol)，N-(苄氧基羰基氧基)琥珀酰亚胺(12.1 g, 48.6 mmol)。过夜搅拌，除去二氯甲烷，粗品混合物进行色谱处理(50 %乙酸乙酯/己烷)，分离出(2S,6RS)-2,6二甲基-3-氧代-哌嗪-1-甲酸苄酯(3.3 g, 三步的收率52 %)，为一种白色粉末。MS $C_{14}H_{18}N_2O_3$ MS m/z: 263。

E. (2S,6R)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯，(2S,6S)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

两种独立的异构体[(2S,6R)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯，(2S,6S)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯]可通过柱色谱分离，采用 (2S,6RS)-2,6-二甲基-3-氧代-哌嗪-1羧酸苄酯作原料，其

也可直接组合使用或如下所示分离其衍生物。

实施例59

(2S,6R)-4-(2, 4-二甲氧基-苄基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

A. (2S,2S)-N-(2, 4-二甲氧基-苄基)-N-(2-羟基-丙基)-2-(2,2,2-三氟乙酰基氨基)丙酰胺

向(2S)-2-(2,2,2-三氟乙酰基氨基)-丙酸(15.3 g, 53.4 mmol)的120 mL的二氯甲烷浆液中加入三乙胺(5.6 mL, 40.0 mmol)。将多相混合物冷却至0℃, 缓慢地加入氯代甲酸异丙酯(27 mL, 27.0 mmol)。在室温下搅拌20分钟, 加入(2S)-1-(2,4-二甲氧基苄基氨基)-丙-2-醇(6.0 g, 26.7 mmol, 由相应醛、氨基醇经还原胺化获得)的5mL的二氯甲烷溶液。将所得混合物搅拌过夜。加入乙酸乙酯(500 mL), 有机溶液用1N盐酸(50 mL)和1N氢氧化钠(50 mL)洗涤。乙酸乙酯用硫酸镁干燥, 过滤, 浓缩。将所得残余物进行硅胶色谱处理(25%乙酸乙酯/己烷), 得到(2S,2S)-N-(2,4-二甲氧基苄基)-N-(2-羟基-丙基)-2-(2,2,2-三氟乙酰基氨基)-丙酰胺(6.29g, 60%收率), 为一种澄清油。MS $C_{17}H_{23}F_3N_2O_5$ MS m/z: 393。

B. (3S,5R)-1-(2,4-二甲氧基-苄基)-3,5-二甲基-4-三氟乙酰基-哌嗪-2-酮

将(2S,2S)-N-(2,4-二甲氧基-苄基)-N-(2-羟基丙基)-2-(2,2,2-三氟乙酰基氨基)-丙酰胺(3.64 g, 9.29 mmol)溶解于25 mL的四氢呋喃中。加入磷酸三苯酯(3.65 g, 14.0 mmol), 并将所得混合物冷却至0℃, 再缓慢加入偶氮二甲酸二乙酯(2.2 mL, 14 mmol)。将所得混合物搅拌过夜。将反应混合物浓缩, 残余物用柱色谱纯化(SiO_2,25%乙酸乙酯/己烷)。分离出所需产物(3S,5R)-1-(2,4二甲氧基-苄基)-3,5-二甲基-4-三氟乙酰基-哌嗪-2-酮(1.5 g, 43%收率), 为一种澄清油。

C. (3S,5R)-1-(2,4-二甲氧基-苄基)-3,5-二甲基-哌嗪-2-酮

将(3S,5R)-1-(2,4-二甲氧基-苄基)-3,5-二甲基-4-三氟乙酰基-哌嗪-2-酮(575 mg, 1.54 mmol)溶解于30 mL的甲醇和3 mL的水中。向溶液中加入碳酸钾(883 mg, 6.4 mmol),将反应混合物回流1.5小时,浓缩。用乙酸乙酯(3x 50 mL)萃取水层。除去乙酸乙酯,得到粗品胺(387 mg, 91 %收率),为一种澄清油。$C_{15}H_{22}N_2O_3$ MS m/z: 279。

D. (2S,6R)-4-(2,4-二甲氧基-苄基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

将三乙胺(0.4 mL, 2.8 mmol), N-(苄氧基羰基氧基)-琥珀酰亚胺(1.04 g, 4.2 mmol)加至上述粗品胺(387 mg, 1.4 mmol)的15 mL的二氯甲烷溶液中。将反应混合物搅拌过夜。在浓缩后,将残余物进行硅胶色谱处理(30%乙酸乙酯/己烷),得到(2S,6R)-4(2,4-二甲氧基-苄基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(450 mg, 78 %收率),为一种澄清油。

E. (2S,6R)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

将(2S,6R)-4-(2,4-二甲氧基-苄基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(1.13 g, 2.74 mmol)溶解于20 mL的乙腈中。加入过硫酸钾(2.2 g, 8.23 mmol),磷酸钠(2.3 g, 16.5 mmol)的12 mL的水溶液,并将所得混合物加热至95-100℃并搅拌2小时。在冷却至室温后,用乙酸乙酯(200 mL)萃取水层,用硫酸镁干燥。将残余物过滤和浓缩后进行色谱处理(SiO_2, 60%乙酸乙酯/己烷),得到(2S,6R)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(480 mg, 67 %收率),为黄色油状物。

实施例60

(2S,6RS)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

将(2S,6RS)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(380 mg, 1.45 mmol)溶解于10 mL的THF和1 mL的DMF中。在0℃下加入氢化钠(60%, 72 mg, 3.14 mmol), 在室温下搅拌30分钟, 再加入7溴甲基-4-氯-喹啉(257 mg, 1.0 mmol)。将反应混合物搅拌4小时。将乙酸乙酯加至混合物中, 将反应混合物用3 mL的水中止反应。分层, 用乙酸乙酯(2x 30 ml)萃取, 再用硫酸镁干燥。将残余物过滤和浓缩后进行硅胶色谱处理(60%乙酸乙酯/己烷), 得到(2S,6RS)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代哌嗪-1-甲酸苄酯(417 mg, 95 %收率)。$C_{22}H_{20}ClN_3O_3$ MS m/z: 438, 440。

实施例61

(3S,5RS)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮和

实施例62

(3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮和

实施例63

(3S,5S)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮

将(2S,6RS)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(417 mg, 1.0 mmol)吸收于7 mL的乙腈中, 加入碘代三甲基硅烷(0.43 mL, 3.0 mmol)。将所得混合物在室温下搅拌1小时, 再用甲醇(1 mL)中止反应。将残余物浓缩后吸收于2N盐酸(3 mL)中, 用乙醚(2x 30 mL)萃取。将水层浓缩至干, 将残余物用异丙醇和乙醚重结晶, 得到一种(3S,5RS)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮的混合物(1: 4), 为一种黄色固体(290 mg)。采用快速柱色谱分离出两种差向异构体(SiO_2, 1%三乙胺/3%甲醇/二氯甲烷)。$C_{16}H_{18}ClN_3O$ MS m/z: 304, 306。少量异构体(3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮为(3S,5R)-1-(4氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮, 而主要的异构体为(3S,5S)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮。或者, (3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮, (3S,5S)-1-(4-氯-喹啉-7-基

甲基)-3,5-二甲基-哌嗪-2-酮可由如下所述相同的化学，分别由纯(2S,6S)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯，(2S,6RS)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯制备.

或者，合成(3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮

A. (2S,6R)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

将(2S,6R)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(750 mg，2.86 mmol)溶解于20 mL的THF和2 mL的DMF中。在0℃下加热氢化钠(60%，142.6 mg，6.20 mmol)。将反应混合物在室温下搅拌30分钟，再加入7-溴甲基-4-氯-喹啉 (952 mg，3.72 mmol)。在搅拌4小时后，反应完成。向混合物中加入乙酸乙酯(200 mL)，将反应混合物用3 mL的水中止反应。分层，用乙酸乙酯(2x 30 mL)进行萃取，用硫酸镁干燥。将残余物经过滤和浓缩后进行硅胶色谱处理(60%乙酸乙酯/己烷)，得到(2S,6R)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(1.04 g，83 %)。

B. (3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮

将33 %的溴化氢的乙酸(10 mL)溶液加至(2S,6R)-4-(4-氯-喹啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(1.04 g，2.38 mmol)中。将反应混合物在室温下搅拌1小时。将反应混合物用乙酸乙酯稀释，剧烈搅拌以使产物从溶液中沉淀出来。滗析出乙酸乙酯，沉淀用硅胶柱进行纯化(1%三乙胺/3%甲醇/二氯甲烷)，得到582 mg(81%收率)的(3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮，为一种白色固体。

实施例64

(3S,5S)-1-(4-氯-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮和

实施例65

(3S,5R)-1-(4-氯-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮和

将上面获得的粗品(3S,5R)-1-(4-氯-喹啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮(69 mg, 0.20 mmol)溶解于1mL DMF中。加入碳酸钾(76 mg, 0.60 mmol), 再加入2-(3-溴丙烯基)-5-氯-噻吩(56 mg, 0.24 mmol)。将反应混合物搅拌过夜。滤除碳酸钾,将粗品产物纯化。通过制备薄层色谱(80%乙酸乙酯/己烷)分离出两种差向异构体,得到主要的差向异构体(3S,5R)-1-(4-氯-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮,和次要差向异构体(3S,5S)-1-(4-氯-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮(7 mg, 7.5%)。

实施例66

4-(2-氧代哌嗪-1-基甲基)苯甲脒

A. 4-(4-氰基苄基)-3-氧代哌嗪-1-甲酸苄酯

在0℃下, 向3-氧代哌嗪-1-甲酸苄酯(3.0 g, 12.8 mmol)和4-溴甲基甲苯基腈(2.76 g, 14.1 mmol)在135mL的THF和15mL的DMF中的溶液中加入60%氢化钠(0.49 g, 12.8 mmol)的矿物油分散液。5小时后,将溶液用氯化铵和乙酸乙酯稀释。有机层用水和饱和氯化钠洗涤。有机层用硫酸镁干燥,过滤和浓缩。将粗品产物用硅胶柱色谱纯化,用20%乙酸乙酯/二氯甲烷洗脱。获得标题化合物,为一种白色固体(4.01 g, 11.4 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 2H), 7.39 (m, 7H), 5.14 (s, 2H), 4.68 (s, 2H), 4.27 (s, 2H), 3.73 (s, 2H), 3.30 (m, 2H)。

B. 4-(4-脲基(carbamimidoyl)苄基)-3-氧代-哌嗪-1-甲酸苄酯

将4-(4-氰基苄基)-3-氧代哌嗪-1-甲酸苄酯(2.4 g, 6.87 mmol)在30 mL吡啶和3 mL三乙胺中的溶液用硫化氢饱和。将形成的混合物密

封，搅拌16小时。此后，将溶液浓缩。将残余物溶解于30 mL的丙酮中，加入甲基碘(19.4 g，137 mmol)。将溶液回流2小时。此后，将溶液浓缩。将残余物溶解于甲醇(40 mL)中，加入乙酸铵(5.0 g，65 mol)。将溶液回流3小时。此后，将溶液浓缩。将粗品产物通过RP-HPLC纯化，用乙腈至60%乙腈/水(0.1 %TFA)进行梯度洗脱。将适当收集的馏分进行冷冻干燥，得到产物，为一种白色泡沫物。MS (FAB) m/z 367，(M+H)。

C. 4-(2-氧代哌嗪-1-基甲基)苯甲脒

向4-(4-脲酰基苄基)-3-氧代哌嗪-1-甲酸苄酯(2.0 g，5.0 mmol)在40 mL的甲醇和4 mL的乙酸中的溶液中加入10% Pd/C (0.4 g)。将反应气氛变成氢气氛。4小时后，将溶液用硅藻土垫过滤。将有机层浓缩。所得粗品产物进行RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1 %TFA)至40%乙腈/水(0.1%TFA)。获得标题化合物，为一种白色泡沫物。^{1}H NMR (d^6-DMSO，300 MHz) δ 9.3 (bs，4H)，9.1 (bs，2H)，7.83 (d，2H)，7.42 (d，2H)，4.78 (s，2H)，3.80 (s，2H)，3.44 (m，2H)，3.32 (m，2H)。

实施例67

1-(2-氨基喹啉-6-基甲基)哌嗪-2-酮

A. 4-(2-氯-喹啉-6-基甲基)-3-氧代-哌嗪-1-甲酸苄酯

在0℃下，向3-氧代哌嗪-1-甲酸苄酯(4.65 g，19.8 mmol)，6-溴甲基-2-氯喹啉(5.40 g，21.0 mmol)在80 mL，3:1的THF:DMF混合物中加入氢化钠(0.81 g，20.2 mmol，60%无机油分散液)。将所得混合物在0℃下搅拌1小时，然后在室温下搅拌18小时。将反应混合物用饱和氯化铵溶液中止反应，然后，用乙酸乙酯稀释。有机层用依次用1N盐酸，水，饱和碳酸氢钠和饱和氯化钠洗涤，然后，用硫酸镁干燥，过滤并浓缩。粗品产物在乙醚/己烷/乙酸乙酯中研制，过滤，得到标题化合物(6.96 g，17.0 mmol)，为一种白色固体。^{1}H NMR ($CDCl_3$，300

MHz) δ 8.08 (d, 1 H), 8.00 (d, 1 H), 7.69 (s, 1 H), 7.63 (dd, 1 H), 7.41 (d, 1 H), 7.35 (s, 5H), 5.15 (s, 2H), 4.78 (s, 2H), 4.28 (s, 2H), 3.70 (m, 2H), 3.32 (bs, 2H)。

B. 4-(2-苯氧基喹啉-6-基甲基)-3-氧代哌嗪-1-甲酸苄酯

将苯酚(15.1 g, 160 mmol), 4-(2-氯喹啉-6-基甲基)-3氧代哌嗪-1-甲酸苄酯(6.60 g, 16.1 mmol)的混合物在70℃下熔化在一起，直至获得均匀的混合物。加入氢氧化钾(3.15 g, 56.1 mmol)，将所得混合物在120℃下过夜加热。24小时后，将褐色/黑色残余物冷却至室温，用二氯甲烷稀释，与1N氢氧化钠(100 mL)一起搅拌30分钟。分层，水层用二氯甲烷萃取。合并的有机层用1N氢氧化钠，饱和氯化钠洗涤，用硫酸钠干燥，过滤并浓缩。获得粗品标题化合物(6.92 g, 14.8 mmol)，为一种米色泡沫物，不经进一步纯化即可用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, 1H), 7.76 (d, 1 H), 7.63 (s, 1H), 7.50 (dd, 1H), 7.42 (m, 2H), 7.34 (m, 6H), 7.25 (m, 2), 7.09 (d, 1H), 5.14 (s, 2), 4.75 (s, 2H), 4.27 (s, 2H), 3.66 (m, 2H), 3.30 (bs, 2H)。

C. 4-(2-氨基喹啉-6-基甲基)-3-氧代哌嗪-1-甲酸苄酯

将乙酸铵(18.7 g, 242 mmol), 4-(2-苯氧基喹啉-6-基甲基)-3-氧代哌嗪-1-甲酸苄酯(6.92 g, 14.8 mmol)的混合物在150℃下过夜加热。21小时后，，再加入3 g乙酸铵，继续加热。5小时后，将混合物冷却至室温，用二氯甲烷稀释，与1N氢氧化钠(100 mL)一起搅拌30分钟。分层，水层用二氯甲烷萃取。合并的有机层用1N氢氧化钠，饱和氯化钠洗涤，用硫酸钠干燥，过滤并浓缩。获得标题化合物的粗品混合物(5.50 g, 14.1 mmol)，为一种米色泡沫物，不经进一步纯化即可用于下一步骤。大部分组分 (4-(2-氨基喹啉-6-基甲基)-3-氧代哌嗪-1-甲酸苄酯): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.45 (d, 1H), 7.35 (s, 5H), 6.74 (d, 1 H),

5.14 (s, 2H), 4.79 (bs, 2H), 4.71 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H)。少部分组分(3-氧代-4-(2-氧代-1,2-二氢喹啉-6-基甲基)哌嗪-1-甲酸苄酯): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, 1 H), 7.48 (m, 2H), 7.37 (m, 6H), 6.70 (d, 1H), 5.14 (s, 2H), 4.66 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H)。

D. 1-(2-氨基喹啉-6-基甲基)哌嗪-2-酮

向4-(2-氨基喹啉-6-基甲基)-3-氧代哌嗪-1-甲酸苄酯, 3-氧代-4-(2-氧代-1,2-二氢-喹啉-6-基甲基)哌嗪-1-甲酸苄酯(5.50 g, 14.1 mmol)在100 mL的10:1甲醇/HOAc的混合物的溶液中加入催化剂量的10%钯/活性炭。将多相混合物在室温下在氢气气氛下氢化18小时。将反应混合物用硅藻土垫过滤, 用甲醇洗涤, 将滤液进行真空浓缩。产物的粗品混合物进行RP-HPLC纯化, 进行梯度洗脱: 2%乙腈/水(0.1%TFA)至20%乙腈/水(0.1%TFA), 适宜的产物馏分进行真空浓缩, 得到1-(2-氨基喹啉-6-基甲基)-哌嗪-2-酮二三氟乙酸酯(2.64 g, 5.45 mmol), 为主要产物, 为一种白色固体。^{1}H NMR (d^6-DMSO, 300 MHz) δ 8.78 (bs, 2H), 8.31 (d, 1 H), 7.80 (s, 1 H), 7.66 (m, 2H), 7.08 (d, 1 H), 4.70 (s, 2H), 3.84 (s, 2H), 3.46 (bs, 4H)。MS m/z 256, [M$^+$]。元素分析计算, 带有0.25摩尔的水, 计算值: C=44.25%, H=3.82%, N=11.47%, 实测值C=44.23%, H=3.76%, N=11.23%。

少量的副产物6-(2-氧代-哌嗪-1-基甲基)-1H-喹啉-2-酮(0.62 g, 1.28 mmol)也通过RP-HPLC分离, 为一种白色固体^{1}H NMR (d_6-DMSO, 300 MHz) δ 11.76 (bs, 1H), 9.30 (bs, 2H), 7.85 (d, 1H), 7.55 (s, 1H), 7.42 (d, 1H), 7.28 (d, 1H), 6.50 (d, 1H), 4.60 (s, 2H), 3.80 (s, 2H), 3.38 (bs, 4H)。MS m/z 257, [M$^+$]. 元素分析计算值, 带有0.25摩尔的水, 计算值C=43.72%, H=3.68%, N=8.50%, 实测值C=43.70%, H=3.62%, N=8.61%。

实施例68

1-(1-氨基异喹啉-6-基甲基)哌嗪-2-酮

此标题化合物按照实施例67所述制备，由6-溴甲基-1-氯异喹啉代替溴甲基-2-氯喹啉。^{1}H NMR (d_6-DMSO, 300 MHz) δ (9.18 (bs, 2H), 8.53 (d, 1H), 7.81 (s, 1H), 7.63 (m, 2H), 7.14 (d, 1H), 4.77 (s, 2H), 3.88 (s, 2H), 3.50 (m, 4H)。

实施例69

2-(2-氧代哌嗪-1-基甲基)吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

A. 3-碘代吡啶-4基胺

将碘化钾(19.48 g, 117.4 mmol), 碘(18.37 g, 72.3 mmol)的水(77 mL)溶液中经分液漏斗滴加至回流中的4-氨基吡啶(9.21 g, 97.8 mmol), 碳酸钠(6.12 g, 57.7 mmol)的水(35 mL)溶液中。加完后，将混合物回流下搅拌2小时，然后，冷却至室温，用乙酸乙酯萃取。合并的有机层用饱和硫代硫酸钠溶液(3x)和盐水洗涤，然后，用硫酸镁干燥，过滤并浓缩，得到标题化合物(8.37 g, 38.0 mmol)和痕量的二碘代化合物，为一种黄色/橙色固体。该物质不经进一步纯化即可用于下一步骤中。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.10 (d, 1H), 6.55 (d, 1H), 4.60 (bs, 2H)。

B. (3-碘吡啶-4-基)-氨基甲酸叔丁酯

将二叔丁基重碳酸酯(20.7 g, 94.8 mmol)加至3-碘吡啶-4-基胺(19.0 g, 86.4 mmol)的THF (86 mL)溶液中。所得溶液在室温下搅拌2小时，然后，浓缩。将残余物用乙酸乙酯稀释，用饱和碳酸氢钠溶液和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩。将残余物用柱色谱纯化，用1 %乙酸乙酯/二氯甲烷洗脱，得到标题产物，少量的BOC-保护的二碘化合物。将混合物用乙醚/己烷研制，除去不想要的化合物，留下标题化合物在溶液中。对固体进行过滤，将滤液浓缩，得到标题化合物(18.95 g, 59.2 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1 H), 8.35 (d, 1H), 8.1 (d, 1H), 7.0 (bs, 1H), 1.55 (s, 9H).

C. 3-氧代-4-丙-2-炔基哌嗪-1-甲酸苄酯

在0℃下，将氢化钠(0.82 g，23.0 mmol，60%无机油分散液)加至4-苄氧基羰基哌嗪-2-酮(5.13 g，21.9 mmol)的THF/DMF(75 mL，3/1 v/v)溶液中。将混合物搅拌5分钟，然后，滴加入炔丙基溴(3.7 mL，41.5 mmol)。将所得溶液搅拌1小时，然后，升至室温，再搅拌2小时。将反应混合物用饱和氯化铵溶液中止反应，然后用乙酸乙酯稀释，用水(4x)和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩至干。将残余物用柱色谱纯化，用5%甲醇/二氯甲烷洗脱，得到产物(5.96 g，21.9 mmol)，为一种白色固体。^{1}H NMR ($CDCl_3$，300 MHz) δ 7.3 (m，5H)，5.12 (s，2H)，4.25 (s，2H)，4.16 (s，2H)，3.75 (m，2H)，3.47 (m，2H)，2.22 (s，1 H)。

D. 2-(4-苄氧基羰基-2-氧代哌嗪-1-基甲基)吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

在室温下，将$Pd(PPh_3)_2Cl_2$ (0.29 g，0.41 mmol)，碘化铜(0.05 g，0.25 mmol)，三乙胺(4.6 mL，32.9 mmol)加至3-氧代-4-丙-2-炔基哌嗪-1-甲酸苄酯(2.24 g，8.23 mmol)，(3-碘吡啶-4-基)-氨基甲酸叔丁酯(2.63 g，8.23 mmol)的DMF (30 mL)溶液中。将混合物加热至100℃，搅拌1.5小时。将反应混合物冷却至50℃，加入DBU (2.5 mL，16.5 mmol)。30分钟后，将溶液冷却至室温，用乙酸乙酯稀释，用饱和氯化铵，水和盐水洗涤。有机层用硫酸镁干燥，过滤并真空浓缩。所得固体用柱色谱纯化，进行梯度洗脱：2%甲醇/二氯甲烷至5%甲醇/二氯甲烷，得到产物(2.93 g，6.31 mmol)，为一种白色固体。^{1}H NMR ($CDCl_3$，300 MHz) δ 8.75 (s，1 H)，8.4 (d，1 H)，7.85 (d，1H)，7.35 (m，5H)，6.38 (s，1 H)，5.2 (s，2H)，5.00 (s，2H)，4.29 (s，2H)，3.85 (m，2H)，3.52 (m，2H)，1.7 (s，9H)。离子喷雾 MS，$[M+H]^+$=465。

E. 2-(2-氧代哌嗪-1-基甲基)吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

将钯黑(1.1 g, 10.3 mmol)加至2-(4-苄氧基羰基-2-氧代-哌嗪-1-基甲基)吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(1.7 g, 3.7 mmol)的甲酸/甲醇(45 mL, 4.4%溶液)溶液中。40分钟后，用硅藻土滤出催化剂，用甲醇洗涤。将滤液进行真空浓缩除去甲醇，将所得溶液用二氯甲烷稀释，用饱和碳酸氢钠和盐水洗涤。将有机层用硫酸镁干燥，过滤并浓缩至干，所得固体用柱色谱纯化，进行梯度洗脱：5%甲醇/二氯甲烷-10%甲醇/二氯甲烷洗脱，得到产物(0.8 g, 2.5 mmol)，为一种浅黄色泡沫状固体。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1 H), 8.40 (d, 1 H), 7.9 (d, 1 H), 6.48 (s, 1H), 4.98 (s, 2H), 3.7 (s, 2H), 3.51 (t, 2H), 3.40 (t, 2H), 1.91 (bs, 1 H), 1.70 (s, 9H)。

实施例70

2-(5-(±)-甲氧基羰基-2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

A. 2-苄氧基羰基氨基-3-(丙-2-炔基氨基)-丙酸甲酯

将炔丙基溴(1.6 mL, 14.4 mmol)加至3-氨基-2苄氧基羰基氨基-丙酸甲酯盐酸盐(4.0 g, 13.9 mmol)，三乙胺(4.1 mL, 29.4 mmol)的THF (46 mL)溶液中。将所得混合物加热至50℃，搅拌过夜，然后，冷却至室温并真空浓缩。粗品残余物用二氯甲烷稀释，用饱和碳酸氢钠和盐水洗涤，然后，有机层用硫酸镁干燥，过滤并真空浓缩。将粗品产物(4.0 g)不经纯化即可用于下一步骤。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.30 (m, 5H), 5.75 (bs, 1 H), 5.20 (s, 2H), 4.45 (bs, 1 H), 3.80 (s, 3H), 3.75 (m, 1 H), 3.31 (s, 2H), 3.08 (dd, 1H), 2.98 (dd, 1H), 2.20 (t, 1H)。EI MS, $[M+H]^+$=291。

B. 2-苄氧基羰基氨基-3-(溴乙酰基-丙-2-炔基-氨基)-丙酸甲酯

在室温下，将DCC (2.27 g, 11.0 mmol)和溴乙酸(1.48 g, 10.7 mmol)加至2-苄氧基羰基氨基-3-(丙-2-炔基氨基)-丙酸甲酯(3.10 g,

10.7 mmol)的二氯甲烷溶液中。将混合物搅拌过夜，然后，用乙醚稀释，滤出沉淀出来的白色固体，将滤液浓缩，得到一种黄色油状物。将粗品产物进行色谱纯化，进行梯度洗脱：40%乙酸乙酯/己烷至50%乙酸乙酯/己烷，得到标题化合物(2.1g, 5.12 mmol)，为一种油。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.70 (d, 1H), 5.10 (s, 2H), 4.63 (m, 1H), 4.15 (d, 2H), 4.00 (m, 1H), 3.80 (s, 3H), 3.75 (s, 2H), 3.70 (dd, 1 H), 2.27 (bs, 1 H)。离子喷雾 MS, $[M+H]^+$=411, 413, Br花样。

C. 5-氧代-4-丙-2-炔基-哌嗪-1,2-二甲酸1-苄基酯2-甲基酯

在0℃下，将氢化钠(0.20 mg, 4.9 mmol)加至2-苄氧基羰基氨基-3-(溴乙酰基-丙-2-炔基-氨基)-丙酸甲酯(2.0 g, 4.8 mmol)的THF (50 mL)溶液中。将溶液搅拌40分钟，然后，用饱和氯化铵溶液中止反应。将反应混合物进行真空浓缩，然后，用二氯甲烷稀释，用盐水洗涤。干燥有机层，过滤并真空浓缩。粗品产物进行色谱纯化，用50%乙酸乙酯/己烷洗脱，得到标题化合物(1.4 g, 4.1 mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.20 (s, 2H), 5.10 (m, 1H), 4.30 (dd, 1 H), 4.25 (d, 2H), 4.08 (m, 1H), 4.00 (dd, 1 H), 3.78 (dd, 1H), 3.78 (s, 3H), 2.25 (t, 1 H)。

D. 2-(5-(±)-甲氧基羰基-2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1 H), 8.41 (d, 1 H), 7.90 (d, 1 H), 6.42 (s, 1 H), 5.00 (AB, 2H), 3.85-3.93 (m, 2H), 3.78 (s, 3H), 3.70-3.81 (m, 3H), 1.65 (s, 9H)。离子喷雾 MS, $[M+H]^+$=389。

实施例71

2-(2-(±)-甲氧基羰基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶

-1-甲酸叔丁酯

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (s, 1 H), 8.43 (d, 1 H), 7.90 (d, 1 H), 6.48 (s, 1 H), 5.63 (d, 1 H), 4.40 (d, 1H), 4.20 (m, 1 H), 3.78 (s, 3H), 3.70 (d, 1H), 3.52 (d, 1H), 3.33 (dd, 1 H), 2.92 (s, 1H), 1.55 (s, 9H)。[on spray MS, $[M+H]^+$=389。

实施例72

1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮

A. 4-(4-氯喹唑啉-7-基甲基)-3-氧代哌嗪-1-甲酸叔丁酯

在0℃下，向3-氧代哌嗪-1-甲酸叔丁酯(3.93 g, 19.6 mmol)，7-溴甲基-4-氯喹唑啉(实施例7)(5.0 g, 19.6 mmol)在150 mL的THF和15 mL的DMF中的溶液中加入60%氢化钠的矿物油悬浮液(0.79 g, 19.6 mmol)。将溶液在0℃下搅拌0.5小时然后，升温至室温。4小时后，将溶液倒入饱和氯化铵溶液中。分层，有机层用水和饱和氯化钠洗涤，用硫酸镁干燥，过滤并浓缩。获得标题化合物，为一种白色固体(5.1 g, 13.4 mmol)。MS (FAB) m/z 377, 379, (M+H)，氯化物花样。

B. 4-(4-氨基喹唑啉-7-基甲基-3-氧代哌嗪-1-甲酸叔丁酯

将4-(4-氯喹唑啉-7-基甲基)-3-氧代哌嗪-1-甲酸叔丁酯(1.84 g, 4.9 mmol)的120 mL的乙醇溶液用氨气饱和。向所得溶液中加入乙酸(0.03 mL)。将溶液加热至回流。16小时后，将溶液浓缩。将所得固体溶解于二氯甲烷，滤除无机盐，将有机溶液浓缩。所得固体用乙酸乙酯研制。获得标题化合物，为一种白色固体(1.59 g, 4.5 mmol)。MS (FAB) m/z 356, (M+H)。

C. 1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮

在0℃下，将4-(4-氨基喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸叔丁酯(1.92 g, 5.4 mmol)的乙酸乙酯(200 mL)溶液用HCl气体饱和。将溶液在0℃下搅拌4小时。此后，将溶液浓缩。获得标题化合物，为

一种白色固体(1.79 g, 5.4 mmol)。^{1}H NMR (d^6-DMSO, 300 MHz) δ 9.9 (bs, 3H), 9.7 (bs, 2H), 8.8 (s, 1 H), 8.46 (d, 1 H), 7.72 (s, 1 H), 7.61 (d, 1 H), 4.78 (s, 2H), 3.83 (s, 2H), 3.4 (m, 4H)。

实施例73

1-(4-氨基-噻吩并[2,3-d]嘧啶-6-基甲基)-哌嗪-2-酮

A. 1-(4-氨基-噻吩并[2,3-d]嘧啶-6-基甲基)-3-氧代-哌嗪-1-甲酸叔丁酯

此标题化合物按照实施例72, 部分A所述制备, 用6溴甲基-4-氯噻吩并[2,3-d]嘧啶代替7-溴甲基-4-氯喹唑啉。再如实施例72, 部分B处理, 获得标题化合物。^{1}H NMR (CD_3OD, 300 MHz) δ 8.22 (s, 1H), 7.35 (s, 1H), 5.48 (s, 2H), 4.10 (s, 2H), 3.60 (m, 2H), 3.40 (m, 2H), 1.45 (s, 9H)。MS (离子喷雾), 364, (M+H)。

B. 1-(4-氨基-噻吩并[2,3-d]嘧啶-6-基甲基)-哌嗪-2-酮

如实施例72, 部分C所述, 通过处理1-(4-氨基-噻吩并[2,3-d]嘧啶-6-基甲基)-3-氧代-哌嗪-1-甲酸叔丁酯获得标题化合物。MS (EI), 2634, (M^+)。

实施例74

4-[3-(2-氧代-哌嗪-1-基)-丙基]-哌啶-1-甲酸叔丁酯

A. 4-[3-(1-叔丁氧羰基-哌啶-4-基)-丙基]-3-氧代-哌嗪-1-甲酸苄酯

此标题化合物按照实施例72, 部分A所述制备, 用3-氧代哌嗪-1-甲酸苄酯代替3-氧代哌嗪-1-甲酸叔丁酯, 4-(3-溴丙基)-哌啶-1-甲酸叔丁酯代替7-溴甲基-4氯喹唑啉。获得标题化合物, 为一种白色泡沫物。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.38 (m, 5H), 5.12 (s, 2H), 4.18 (m, 4H), 3.73 (m, 2H), 3.33 (m, 4H), 2.66 (m, 2H), 1.58 (m, 6H), 1.42 (s, 9H), 1.38 (m, 3H)。

B. 4-[3-(2-氧代-哌嗪-1-基)-丙基]-哌啶-1-甲酸叔丁酯

如实施例67，部分D所述处理4-[3-(1-叔丁氧羰基-哌啶-4-基)-丙基]-3-氧代-哌嗪-1-甲酸苄酯，得到标题化合物，为一种油。

实施例75

1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮

A. 2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯

向2-氧代-3-(S)-甲氧基甲基哌啶(5.36g，19.3mmol)(实施例41)在200mL的10:1 THF：DMF中的溶液中加入2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(12.6g，60%纯度，19.3mmol)(实施例13制备)。将溶液冷却至0℃。向溶液中加入氢化钠(0.77g，60%矿物油分散液，19.3mmol)。将溶液搅拌16小时。此后，加入1N盐酸直至pH=1。将溶液搅拌1小时。此后，将溶液用乙酸乙酯稀释。有机层用水和饱和氯化钠洗涤。有机层用硫酸镁干燥，过滤并真空浓缩。所得粗品产物用柱色谱纯化，进行梯度洗脱，20%乙酸乙酯/二氯甲烷-40%乙酸乙酯/二氯甲烷，获得标题化合物(6.8g，16.7mmol)，为一种白色固体。^{1}H NMR ($CDCl_3$，300MHz) δ 7.34 (m，5H)，6.61 (m，2H)，5.13 (AB，2H)，4.76 (m，1H)，4.40 (AB，2H)，4.08 (m，5H)，3.74 (m，2H)，3.32 (m，1 H)，3.30 (s，3H)，3.10 (m，1H)。

B. 4-(4-氨基-喹唑啉-7-基甲基)-2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯

向2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯(6.8g，16.7mmol)的100mL的乙醇溶液中加入三嗪(2.2g，26.4mmol)，乙酸(1.6g，26.4mmol)。将溶液加热至回流。36小时后，将溶液浓缩。所得粗品产物用柱色谱纯化，进行梯度洗脱：2%甲醇/二氯甲烷-5%甲醇/二氯甲烷，获得标题化合物(5.8g，13.3mmol)，为一种白色固体。

^{1}H NMR ($CDCl_3$, 300MHz) δ 8.55 (s, 1H), 7.72 (m, 2H), 7.48 (m, 1H), 7.35 (m, 5H), 6.40 (bs, 2H), 5.16 (AB, 2H), 5.06 (m, 1H),4.72 (m, 1H), 4.59 (m, 1H), 4.09 (m, 2H), 3.74 (m, 2H), 3.44 (m, 1H), 3.30 (s, 3H), 3.12 (m, 1H). MS (离子喷雾) m/z 436, (M+H).

C. 1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮

向2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯（5.8g, 13.3ml）的50ml乙酸溶液中滴加20ml 30% HBr的AcOH溶液。搅拌溶液1小时，浓缩溶液。用柱色谱纯化所得粗产物，用CH_2Cl_2:MeOH:NH_4OH(20:5:1)洗脱。得到白色固体标题化合物（2.0g, 6.6mmol）。^{1}H NMR (d^6-DMSO, 300MHz) δ 8.60 (s, 1H), 7.72 (m, 2H),7.48 (d, 1H), 5.60 (bs, 2H), 4.72 (AB, 2H), 3.87 (m, 2H), 3.71 (m, 1H), 3,42 (m, 1H), 3.40 (s, 3H), 3.19 (m, 2H), 3.02 (m, 1H). MS (离子喷雾) m/z 302, (M+H).

实施例76

1-(4-氨基喹唑啉-7-基甲基)-3-丁基哌嗪-2-酮

按实施例75所述制备标题化合物，用实施例42的2-丁基-3-氧代-哌嗪-1-甲酸苄酯替代2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。

^{1}H NMR (CD_3OD, 300MHz) δ 8.35 (s, 1H), 8.09 (d, 1H), 7.54 (s, 1H), 7.41 (d, 1H), 4.74 (s, 2H), 3.43 (m, 2H), 3.28 (m, 1H), 3.09 (m, 1H), 2.95 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.39 (m, 4H), 0.93 (m, 3H). MS (离子喷雾) m/z 314, (M+H).

实施例77

1-(4-氨基喹唑啉-7-基甲基)-3-乙基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-乙基-3氧代-哌嗪-1-甲酸苄酯(实施例43)代替2-甲氧基甲基-3-氧代哌嗪-1-甲酸苄酯。^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1H), 8.11 (d, 1H), 7.57 (s, 1H), 7.42 (d, 1H), 4.78 (s, 2H), 3.40 (m, 2H), 3.29 (m, 1H), 3.11 (m, 1H), 2.98 (m, 1 H), 2.00 (m, 1 H), 1.77 (m, 1 H), 1.20 (m, 3H)。MS (离子喷雾) m/z 286, (M+H)。

实施例78

1-(4-氨基喹唑啉-7-基甲基)-3-丙基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-丙基-3氧代-哌嗪-1-

甲酸苄酯(实施例44)代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。^{1}H NMR(CD_3OD, 300MHz) δ 8.36(s, 1H), 8.13(d, 1H), 7.60(s, 1H), 7.47(d, 1H), 4.78(s, 2H), 3.44(m, 2H), 3.30(m, 1H), 3.11(m, 1H), 2.97(m, 1H), 1.98(m, 1H), 1.72(m, 1H), 1.50(m, 2H), 0.97(m, 3H)。MS(离子喷雾)m/z 300,(M+H)。

实施例79

1-(4-氨基-喹唑啉-7-基甲基)-3-乙氧基甲基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-乙氧基甲基-3-氧代-哌嗪-1-甲酸苄酯(实施例45)代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。^{1}H NMR (CD_3OD, 300MHz) δ 8.34 (s, 1 H), 8.07 (d, 1 H), 7.53 (s, 1 H), 7.40 (d, 1 H), 4.79 (AB, 2H), 3.90 (m, 1 H), 3.72 (m, 1 H), 3.68 (m, 1H), 3.52 (m, 2H), 3.36 (m, 2H), 3.20 (m, 1H), 3.00 (m, 1H), 1.92 (m, 3H)。MS (离子喷雾) m/z 316, (M+H)。

实施例80

1-(4-氨基-喹唑啉-7-基甲基)-3-甲基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-甲基-3氧代-哌嗪-1-甲酸苄酯(实施例46)代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。^{1}H NMR (CD_3OD, 300MHz) δ 8.36 (s, 1 H), 8.11 (d, 1H), 7.57 (s, 1H), 7.44 (d, 1 H), 4.79 (AB, 2H), 3.58 (m, 1H), 3.47 (m, 1H), 3.31 (m, 1H), 3.12 (m, 1 H), 3.00 (m, 1 H), 1.41 (d, 3H)。MS (离子喷雾) m/z 272, (M+H)。

实施例81

1-(4-氨基-喹唑啉-7-基甲基)-3-苄基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-苄基-3-氧代-哌嗪-1-甲酸苄酯(实施例47)代替2-甲氧基甲基-3-氧代哌嗪-1-甲酸苄酯。^{1}H NMR (CD_3OD, 300MHz) δ 8.35 (s, 1 H), 8.09 (d, 1 H), 7.57 (s,

1 H), 7.38 (d, 1H), 7.27 (m, 5H), 4.74 (AB, 2H), 3.76 (m, 1 H), 3.47 (m, 1 H), 3.30 (m, 3H), 3.08 (m, 1 H), 2.96 (m, 1 H)。MS (离子喷雾) m/z 348, (M+H)。

实施例82

1-(4-氨基-喹唑啉-7-基甲基)-3-(1-甲氧基乙基)-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-(1-甲氧基乙基)-3-氧代-哌嗪-1-甲酸苄酯(实施例48)代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。该化合物以二氢溴酸盐分离。^{1}H NMR (CD_3OD, 300MHz) δ 8.70 (s, 1 H), 8.40 (d, 1 H), 7.88 (s, 1 H), 7.71 (d, 1H), 4.94 (AB, 2H), 4.30 (m, 2H), 3.76 (m, 1H), 3.68 (m, 3H), 3.36 (s, 3H), 1.42 (d, 3H)。MS (离子喷雾) m/z 316, (M+H)。

实施例83

1-(4-氨基-喹唑啉-7-基甲基)-3,3-二甲基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2,2-二甲基-3-氧代-哌嗪-1-甲酸苄酯(实施例49)代替2-甲氧基甲基-3-氧代哌嗪-1-甲酸苄酯。^{1}H NMR (d_6-DMSO, 300MHz) δ 8.34 (s, 1H), 8.12 (d, 1H), 7.72 (bs, 2H), 7.41 (s, 1H), 7.26 (d, 1H), 4.60 (s, 2H), 3.33 (m, 2H), 2.98 (m, 2H), 1.27 (s, 6H)。

实施例84

1-(4-氨基-喹唑啉-7-基甲基)-3-异丙基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-异丙基3-氧代-哌嗪-1-甲酸苄酯(实施例50)代替2-甲氧基甲基-3-氧代哌嗪-1-甲酸苄酯。^{1}H NMR (d_6-DMSO, 300MHz) δ 8.32 (s, 1 H), 8.12 (d, 1 H), 7.66 (bs, 2H), 7.42 (s, 1 H), 7.27 (d, 1 H), 4.60 (AB, 2H), 3.23 (m, 2H), 3.05 (m, 1 H), 2.79 (m, 1 H), 2.34 (m, 1 H), 0.92 (s, 3H), 0.80 (s, 3H)。

实施例85

1-(4-氨基-喹唑啉-7-基甲基)-3-异丁基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-异丁基-3氧代-哌嗪-1-甲酸苄酯(实施例51)代替2-甲氧基甲基-3-氧代哌嗪-1-甲酸苄酯。^{1}H NMR (d^6-DMSO, 300MHz) δ 8.65 (s, 1H), 7.70 (m, 2H), 7.48 (m, 1H), 5.61 (m, 2H), 4.82 (m, 1H), 4.65 (m, 1H), 3.52 (dd, 1H), 3.37 (m, 1H), 3.18 (m, 2H), 2.98 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.59 (m, 2H), 0.95 (m, 6H)。

实施例86

1-(4-氨基-喹唑啉-7-基甲基)-3-(2-甲氧基乙基)-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-(2-甲氧基乙基)-3-氧代-哌嗪-1-甲酸苄酯(实施例52)代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。^{1}H NMR (d^6-DMSO, 300MHz) δ 8.32 (s, 1H), 8.13 (d, 1H), 7.70 (bs, 2H), 7.42 (s, 1H), 7.28 (m, 1H), 4.60 (m, 2H), 3.32 (m, 8H), 3.11 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H)。

实施例87

1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-6-甲基-哌嗪-2-酮

此标题化合物按照实施例75所述制备，用2-甲氧基甲基-5-甲基-3-氧代-哌嗪-1-甲酸苄酯(实施例53)代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。^{1}H NMR (CD_3OD, 300MHz) δ 8.72 (s, 1H), 8.32 (d, 1H), 7.78 (m, 2H), 5.11 (m, 1 H), 4.81 (m, 1H), 4.42 (m, 1H), 4.13 (m, 1 H), 4.04 (m, 1H), 3.74 (m, 2H), 3.52 (m, 1H), 3.43 (s, 3H), 1.34 (d, 3H)。

实施例88

(3S,5RS)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮

A. (2S,6RS)-4-[3-(二苯甲基-氨基)-4-氰基-苄基]-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

在0℃下，向(2S,6RS)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(1.98 g, 7.56 mmol)在20 mL的四氢呋喃和2 mL的DMF中的溶液中加入氢化钠(60%, 289 mg, 12.6 mmol)。将反应混合物在室温下搅拌1小时，加入2-二苯亚甲基-氨基)-4-溴甲基-苯甲腈(4.24 mg, 11.34 mmol)(实施例13)。室温下搅拌过夜后，除去四氢呋喃。将残余物吸收于乙酸乙酯中。过量的氢化钠用5 mL水中止反应，随后进行常规水处理。粗品产物进行硅胶色谱处理(50%乙酸乙酯/己烷)，得到(2S,6RS)-4-[3-(二苯甲基-氨基)-4-氰基-苄基]-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(2.6 g, 65%)。$C_{35}H_{32}N_4O_3$ MS m/z : 557。

B. (2S,6RS)-4-(3-氨基)-4-氰基-苄基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

将(2S,6RS)-4-[3-(二苯甲基-氨基)-4-氰基-苄基]-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(2.6 g, 5.21 mmol)溶解于100 mL的乙酸乙酯中，冷却至0℃。滴加入12N盐酸(0.5 ml, 6.0 mmol)溶液。在30分钟内完成脱保护。将反应混合物用10 %碳酸氢钠洗涤。乙酸乙酯层用硫酸镁干燥，过滤，浓缩。将所得残余物进行快速柱色谱纯化(SiO_2, 60%乙酸乙酯/己烷)，得到产物(2S,6RS)-4-(3-氨基)-4-氰基-苄基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(2.03 g, 99 %)。

C. (2S,6RS)-4-(4-氨基-喹唑啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯

将冰醋酸(0.9 ml, 15.54 mmol)，1,3,5-三嗪(840 mg, 10.36 mmol)加至(2S,6RS)-4-(3-氨基-4-氰基-苄基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(2.03 g, 5.18 mmol)的乙醇溶液中。将所得混合物过夜加热回流。用乙酸乙酯代替乙醇，用饱和碳酸氢钠(5 mL)洗涤。

乙酸乙酯层用硫酸镁干燥，过滤和浓缩。将所得残余物进行快速柱色谱纯化(SiO_2，20%甲醇/二氯甲烷)，得到产物(2S,6RS)-4-(4-氨基-喹唑啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(1.85 g，85%)，为一种黄色固体。$C_{23}H_{25}N_5O_3$ MS m/z：420。

D. (3S,5RS)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮

将钯/炭(10 %，700 mg)加至(2S,6RS)-4-(4-氨基-喹唑啉-7-基甲基)-2,6-二甲基-3-氧代-哌嗪-1-甲酸苄酯(1.62 g，3.87 mmol)在20 mL的甲醇和2 mL的乙酸溶液中。将反应混合物在氢气氛下搅拌8小时。滤除钯，经旋转蒸发除去挥发性溶剂。将粗品产物(1.7 g，95 %)分离，为一种白色固体。在硅胶上分离两种差向异构体(1%三乙胺/15%甲醇/二氯甲烷)。次要差向异构体为(3S,5R)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮，主要差向异构体为(3S,5S)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮。

实施例89

1-(4-氯喹啉-7-基甲基)-哌嗪-2-酮

将4-(苄氧基羰基)-哌嗪-2-酮(苄氧基羰基)-哌嗪-2-酮(1.1 g，4.6 mmol)溶解于THF (50 mL)中，在冰浴中冷却，用四丁基碘化铵(0.18 g，mmol)和60%氢化钠(0.24 g，6.0 mmol)处理。将反应混合物在0℃下搅拌30分钟，然后，用7-溴甲基-4-氯喹啉(1.2 g，4.6 mmol)(实施例14)的THF (50 mL)溶液滴加处理。将所得溶液在0℃下搅拌2小时后，用氯化铵溶液中止反应并浓缩。用乙酸乙酯稀释，再用水洗涤；有机层用硫酸钠干燥，浓缩。将残余物进行色谱处理(4%甲醇/二氯甲烷)，得到固体4-(苄氧基羰基)-1-(4-氯喹啉-7-基甲基)-哌嗪-2-酮(1.2 g，2.9 mmol)。将一部分该产物(0.75 g，1.8 mmol)溶解于乙腈(20 mL)中，再用碘代三甲基硅烷(0.78 mL，5.4 mmol)在室温下处理3小时。用甲醇中止反应，并浓缩至干。加入甲醇，重复浓缩四次。将最后的残余物吸收于2M的盐酸中；将溶液用乙醚洗涤并浓缩。

将残余物在异丙醇和乙醚中重结晶，得到标题化合物(0.63 g, 2.3 mmol) MS m/z: M^+ =275; ^{1}HNMR (CD_3OD, 300 MHz) δ 9.1 (d, 1H), 8.5 (d, 1 H), 8.2-8.3 (m, 2H), 8.0 (d, 1H), 5.2 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H)。

实施例90

1-(4-氯噌啉-7-基甲基)-哌嗪-2-酮

将4-(叔丁基氧基羰基)-哌嗪-2-酮(0.6 g, 3.0 mmol)(实施例40)溶解于THF (80 mL)中，在冰浴中冷却，用四丁基碘化铵(0.23 g, 0.62 mmol)和60%氢化钠(0.12 g, 3.0 mmol)处理。将反应混合物在℃下搅拌40分钟，然后，用7-溴甲基-4-氯噌啉(10.7g, 2.7 mmol)(实施例15)的THF (20 mL)溶液滴加处理。将所得溶液在2小时内升温至室温。将溶液蒸发至干，将残余物吸收于乙酸乙酯和10% 碳酸氢钠水溶液中。分离出有机层，用水洗涤，干燥(硫酸钠)，浓缩。将残余物进行色谱处理(乙酸乙酯)，得到标题化合物(0.6 g, 1.6 mmol)。将一部分该产物(0.21 g, 1.26 mmol)溶解于THF (约4 mL)，用HCl在乙酸乙酯(50 mL)中的饱和溶液在室温下下处理2小时。将溶液过滤并浓缩成残余物(0.14 g, 0.4 mmol)。MS m/z: M^+=275; ^{1}H NMR (CD_3OD, 300 MHz) δ 9.15 (d, 1H), 8.5 (d, 1H), 8.25 (s, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 5.0 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H)。

实施例91

1-(4-氯喹啉-7-基甲基)-3-(S)-甲基哌嗪-2-酮

将4-(苄氧基羰基)-3-(S)-甲基哌嗪-2-酮(1.0 g, 4.0 mmol)(实施例46)溶解于THF (60 mL)中，在冰浴中冷却，用四丁基碘化铵(0.10 g, 0.27 mmol)和60%氢化钠(0.18 g, 4.4 mmol)处理。将反应混合物在0℃下搅拌30分钟 ，然后，用7-溴甲基-4-氯喹啉(1.12 g, 4.4 mmol)(实施例14)的THF (5 mL)溶液滴加处理。将所得溶液在大约 1

小时内升温至室温，用碳酸氢钠溶液中止反应，浓缩。将残余物在乙酸乙酯和水间分配；有机层用硫酸钠干燥并浓缩。将残余物进行色谱处理(5％甲醇/二氯甲烷)，得到固体4-(苄氧基羰基)-1-(4-氯喹啉-7-基甲基)-3-(S)-甲基-哌嗪-2-酮(1.32 g，3.1 mmol)。将一部分该产物(0.10 g，0.23 mmol)溶解于乙腈(6 mL)中，用碘代三甲基-硅烷(0.1 mL，0.75 mmol)在室温下处理2小时。此反应用甲醇中止并浓缩至干。加入甲醇，重复浓缩6次。将最后的残余物吸收于2M 盐酸中；将溶液用乙醚并浓缩，得到标题化合物。MS m/z：M^+=289；^{1}H NMR (CD_3OD，300 MHz) δ 9.2 (d，1 H)，8.6 (d，1 H)，8.2-8.3 (m，2H)，8.0 (d，1 H)，5.1 (q，1 H)，4.3-4.4 (m，1H)，3.8-4.0 (m，2H)，3.6-3.8 (m，3H)，1.75 (d，3H)。

实施例92

1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮

A. 4-(叔丁基氧基羰基)-1-(2-氨基乙基)-哌嗪-2-酮

将4-(叔丁基氧基羰基)-哌嗪-2-酮(8.0 g，40 mmol)(实施例40)溶解于THF (160 mL)中，在冰浴中冷却，用60％氢化钠(1.9 g，48 mmol)处理。将反应混合物搅拌40分钟，然后，用四丁基碘化铵(0.35 g，0.95 mmol)和溴乙腈(3.4 mL，48 mmol)处理。2小时后，用水中止反应，浓缩成较小的体积，用二氯甲烷萃取(3x)。将合并的有机萃取液浓缩，残余物进行色谱处理(50 ％乙酸乙酯/己烷)，得到4-(叔丁基氧基羰基)-1-氰基甲基-哌嗪-2-酮(5.2 g，21.7 mmol)。将该产物溶解于乙醇(140 mL)中，用铂氧化物(0.83 g)在50 PSI氢气下处理24小时。滤除催化剂，将溶液浓缩，得到4-(叔丁基氧基羰基)-1-(2-氨基乙基)-哌嗪-2-酮(5.2 g，21.6 mmol)。^{1}H NMR ($CDCl_3$，300 MHz) δ 4.08 (s，2H)，3.62 (m，2H)，3.44 (t，2H)，3.38 (t，2H)，2.89 (t，2H)。

B. 4-(叔丁基氧基羰基)-1-[2-(2,3,5,6-四氯吡啶-4-基氨基)-乙基]-哌嗪-2-酮

将4-(叔丁基氧基羰基)-1-(2-氨基乙基)-哌嗪-2-酮(叔丁基氧基羰基)-1-(2-氨基乙基)-哌嗪-2-酮(4.0 g, 16 mmol)溶解于二氯甲烷(150 mL), 用4-硝基-2,3,5,6-四氯-吡啶(4.8 g, 18 mmol)和N-甲基吗啉(4.0 mL, 36 mmol)处理。将反应混合物搅拌5小时后, 浓缩, 残余物进行色谱纯化(50%乙酸乙酯/己烷), 得到标题化合物(4.8 g, 10.5 mmol)。Fab MS m/z: 457,469,461[M+1]$^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.00 (t, 1H), 4.10 (s, 2H), 3.97 (m, 2H), 3.66 (m, 2H), 3.38 (m, 2H)。

C. 1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮

将4-(叔丁基氧基羰基)-1-[2-(2,3,5,6-四氯吡啶-4-基氨基)-乙基-哌嗪-2-酮(3.5 g, 7.6 mmol)溶解于甲醇(20 mL)和0.5 M甲醇钠的甲醇(150 mL, 75 mmol)溶液中。将溶液用Pd/C (0.5 g)处理, 在50 PSI的氢气下搅拌16小时。除去溶剂, 将残余物用二氯甲烷萃取, 过滤。将滤液浓缩, 负载至硅胶快速柱上, 用5%甲醇/二氯甲烷洗脱, 再用氢氧化铵/甲醇/二氯甲烷(1:5:95)洗脱, 再用氢氧化铵/甲醇/二氯甲烷(1:10:70), 得到4-(叔丁基氧基羰基)-1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮, 为一种白色泡沫物(1.5 g, 4.7 mmol)。将该产物(1.5 g, 4.7 mmol)用20%三氟乙酸的二氯甲烷(110mL)溶液在室温下搅拌2小时。将溶液浓缩, 将残余物用饱和碳酸氢钠溶液和氢氧化铵处理直至获得碱性溶液。将溶液施加至硅胶柱上, 用氢氧化铵/甲醇/二氯甲烷(1:10:60)洗脱, 分离出1-[2-(吡啶-4-基氨基)乙基]-哌嗪-2-酮为所需产物无机盐的混合物(估计25 wt%) EI MS m/z: 220, M$^+$; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.07 (d, 2H), 6.96 (d, 2H), 3.77 (s, 2H), 3.65 (m, 6H), 3.44 (t, 2H)。

实施例93

1-[2-{(甲基)-(吡啶-4-基)-氨基}-乙基]-哌嗪-2-酮三氟乙酸盐

将4-(叔丁基氧基羰基)-1-[2-(2,3,5,6-四氯吡啶-4-基氨基)-乙基]-哌嗪-2-酮(0.19 g, 0.41 mmol)(实施例92, 部分B)溶解于DMF (3

ml)中，用60 %氢化钠(20 mg，0.5 mmol)处理。10分钟后，加入甲基碘(0.025 ml，0.40 mmol)，将黄色溶液在室温下搅拌过夜。将溶液用乙酸乙酯稀释，用水洗涤(6x)。有机层用硫酸镁干燥，浓缩成残余物(0.19 g，0.40 mmol)。将残余物溶解于甲醇(2 ml)中，用0.5 M 甲醇钠的甲醇(8 ml，4.0 mmol))溶液处理。将溶液用Pd/C处理，在60 PSI氢气下过夜处理，过滤。将滤液浓缩，用二氯甲烷萃取几次；真空除去溶剂，得到4-(叔丁基氧基羰基)-1-[2-{(甲基)-(吡啶-4-基)-氨基}-乙基]-哌嗪-2-酮，为一种无定形残余物(0.16 g)。EI MS m/z: 335，$[M+1]^+$；^1H NMR ($CDCl_3$，300 MHz) δ 8.21 (d，2H)，6.56 (d，2H)，3.99 (s，2H)，3.60 (t，2H)，3.53 (t，2H)，3.47 (t，2H)，3.28 (t，2H)，2.98 (s，3H)，1.46 (s，9H)。用20%TFA/二氯甲烷(10 mL)在室温下处理上述产物1小时，浓缩后，得到标题化合物，为一种残余物，其可不经进一步纯化即可使用。^1H NMR (CD_3OD，300 MHz) δ 8.14 (d，2H)，7.30 (br，1 H)，7.00 (br，1 H)，3.88-3.67 (m，8H)，3.53 (t，2H)，2.26 (s，3H)。

实施例94

1-[2-(3-甲基吡啶-4-基-氨基)-乙基]-哌嗪-2-酮

A. 4-[2-(3-甲基吡啶-4-基亚氨基)-乙基]-3-氧代-哌嗪-1-甲酸苄酯

将4-(苄氧基羰基)-哌嗪-2-酮(4.7 g，20 mmol)溶解于THF (50 mL)中，用1.5M LDA (20 mL，30 mmol)在0℃下处理。将反应混合物用浓缩的环氧乙烷(3 mL，40 mmol)处理，在室温下搅拌过夜。将混合物用2N盐酸中和，浓缩，用乙酸乙酯萃取。将乙酸乙酯层用水洗涤，浓缩成粗品残余物。再用乙醚对粗品进行萃取，对乙醚层浓缩，得到一种油(1.5 g)。将上述油溶解于二氯甲烷(25 mL)中，在-60℃下，加至2M草酰氯(7.5 mL，15 mmol)和DMSO (2.3 mL，29.7 mmol)的二氯甲烷(25 mL)溶液中。15分钟后，加入三乙胺(2.1 ml，15 mmol)。将混合物在-50℃下搅拌10分钟，然后，在10分钟内升温至室温。用0.5N盐酸中止反应，用二氯甲烷萃取。二氯甲烷层用0.5 N盐酸，盐水(2x)

和水洗涤，浓缩成残余物。将残余物进行色谱纯化(2%甲醇/二氯甲烷)，得到4-氨基-3-甲基吡啶，为一种油(0.5 g，1.6 mmol)。将该油(0.2 g，2 mmol)和(1R)-(-)-10-樟脑磺酸(15 mg)的甲苯(100 ml)溶液采用Dean Stark回流过夜。将混合物浓缩，残余物进行色谱纯化(2-4%甲醇/二氯甲烷)，得到标题亚胺，为一种白色泡沫物(0.20 g，0.54 mol)。离子喷雾 MS m/z: 367，$[M+1]^+$；^1H NMR ($CDCl_3$，300 MHz) δ 8.20 (d，1H)，8.14 (s，1H)，7.35 (s，5H)，6.60 (d，1H)，6.18 (dd，1 H)，5.15 (s，2H)，4.97 (d，1H)，4.30 (s，2H)，3.78 (t，2H)，3.50 (bm，2H)，2.15 (s，3H)。

B. 1-[2-(3-甲基吡啶-4-基-氨基)-乙基]-哌嗪-2-酮

将4-[2-(3-甲基吡啶-4-基亚氨基)-乙基]-3-氧代-哌嗪-1-甲酸苄酯(0.20 g，0.54 mmol)溶解于无水乙醇(20 mL)中，在50 PSI下用10%Pd/C过夜氢化。过滤后，将滤液浓缩。将残余物用Pd黑在5%甲酸/二氯甲烷(10 ml)中处理10分钟。过滤，浓缩，得到粗品残余物，将其进行色谱纯化，采用氢氧化铵/甲醇/二氯甲烷(1:5:95)洗脱，得到标题化合物，为一种澄清的浆液(0.078 g，0.33 mmol)。^1H NMR ($CDCl_3$，300 MHz) δ 8.17 (d，1H)，8.03 (s，1H)，7.35 (s，5H)，6.36 (d，1H)，5.30 (b，1H)，3.74 (t，2H)，3.53 (s，2H)，3.38 (m，4H)，3.08 (t，2H)，2.02 (s，3H)。

实施例95

1-[2-(哒嗪-4-基氨基)-乙基]-哌嗪-2-酮

将1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮(实施例92，部分A)(1.0 g，4.1 mmol)用3,4,5-三氯哒嗪(0.81 g，4.1 mmol)、三乙胺(0.57 mL，4.1 mmol)和THF(25 mL)处理，在密封管中于120℃加热3小时。冷却后，将溶液用乙酸乙酯稀释，用碳酸氢钠水溶液(25 mL)和水洗涤，用硫酸镁干燥。将有机层浓缩，进行色谱处理(5%甲醇/二氯甲烷)，得到异构体混合物(0.8g 20 mmol)。将混合物溶解于0.5M

的甲醇钠的甲醇(200 mL)溶液中，用10% Pd/C (0.5 g)处理，在50PSI氢气下搅拌20小时。将反应混合物过滤；将滤液浓缩成残余物，将残余物进行色谱处理(氢氧化铵/水/甲醇/乙酸乙酯，1:1:2:90)，得到粗品4-(叔丁氧羰基)-1-[2-(哒嗪-4-基氨基)-乙基]-哌嗪-2-酮。将该产物溶解于少量的THF中，用饱和的HCl乙酸乙酯溶液(50 mL)处理。将溶液在室温下搅拌2小时，用乙醚(50 mL)稀释。收集沉淀出的标题化合物，空气干燥(0.5 g, 1.7 mmol)。MS m/z: 367, $[M+1]^+$；^1H NMR (CD_3OD, 300 MHz) δ 8.8 (d, 1H), 8.5 (s, 1 H), 7.4 (d, 1H), 4.1 (s, 2H), 3.5-3.8 (m, 8H)。

实施例96

4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙烯基]-3-氧代-哌嗪-1-甲酸叔丁酯，4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-烯丙基]-3-氧代-哌嗪-1-甲酸叔丁酯

A. 1-烯丙基-4-(叔丁基氧基羰基)-哌嗪-2-酮

将4-(叔丁基氧基羰基)-哌嗪-2-酮(1.0 g, 5.0 mmol)(实施例40)采用实施例92，部分A所述过程用烯丙基溴(0.48 ml, 5.5 mmol)在THF (20 ml)中进行烷基化。在进行色谱处理(50 %乙酸乙酯/己烷)，获得标题化合物(0.92 g, 3.8 mmol)，为一种无色液体。EI MS m/z 240 (M^+)；^1H NMR ($CDCl_3$, 300 MHz) δ 5.80-5.68 (m, 1H), 5.23-5.15 (m, 2H), 4.09 (s, 2H), 4.03 (d, 2H), 3.63 (t, 2H), 3.30 (t, 2H), 1.45 (s, 9H)。

B. 4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙烯基]-3-氧代-哌嗪-1-甲酸叔丁酯，4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-烯丙基]-3-氧代-哌嗪-1-甲酸叔丁酯

将1-烯丙基-4-(叔丁基氧基羰基)-哌嗪-2-酮(0.49 g, 2.0 mmol)用(3-碘-吡啶-4-基)-氨基甲酸叔丁酯(0.64 g, 2.0 mmol)，$Pd(OAc)_2$(14 mg, 0.06 mm油)，P(o-tol)$_3$(37 mg, 0.12 mmol)，三乙

胺(0.56 mmol)在密封管中处理。将混合物在100℃下搅拌过夜，然后，用二氯甲烷稀释，用水(2 x)洗涤。将二氯甲烷层浓缩，将残余物进行色谱处理(5%甲醇/二氯甲烷)，得到两种异构体的混合物(0.40 g，0.92 mmol)。经进一步色谱处理(乙酸乙酯)，将混合物分离成其构成异构体，得到4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙烯基]-3-氧代-哌嗪-1-甲酸叔丁酯(90 mg，0.21 mmol，高R_f值)，4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-烯丙基]-3-氧代-哌嗪-1-甲酸叔丁酯(0.24 g，0.56 mmol，低R_f值)。对前一种：MS m/z 433 (M+1)；^{1}H NMR ($CDCl_3$，300 MHz) δ 8.38 (d，1H)，8.28 (s，1H)，7.93 (d，1 H)，7.48 (d，1H)，6.67 (s，1 H)，5.10 (m，1 H)，4.15 (s，2H)，3.70 (t，2H)，3,46 (t，2H)，3.39 (d，2H)，1.48 (s，9H)，1.45 (s，9H)。对后一种：MS m/z 433 (M+1)；^{1}H NMR ($CDCl_3$，300 MHz) δ 8.39 (s，1H)，8.37 (d，1H)，7.98 (d，1H)，6.77 (s，1H)，6.52 (d，1H)，6.07 (m，1H)，4.23 (d，2H)，4.12 (s，2H)，3，69 (t，2H)，3.40 (t，2H)，1.52 (s，9H)，1.45 (s，9H)。

实施例97

4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙基]-3-氧代-哌嗪-1-甲酸叔丁酯

将实施例96，部分B两种异构体的混合物(0.11 g，0.25 mmol)溶解于甲醇(7 ml)中，用10%Pd/C处理，在氢气气氛下搅拌4小时。过滤，浓缩，得到一种白色泡沫物(80 mg，0.18 mmol)。EI MS m/z 434 (M^+)；^{1}H NMR ($CDCl_3$，300 MHz) δ 8.33 (d，1 H)，8.30 (s，1 H)，8.05 (d，1 H)，4.08 (s，2H)，3.64 (t，2H)，3.50 (t，2H)，3.35 (t，2H)，2.58 (t，2H)，1.90 (m，2H)，1.57 (s，9H)，1.48 (s，9H)。

实施例98

4-(苄氧基羰基)-1-(2-吡咯并[3,2-c] 吡啶-1-基乙基)-哌嗪-2-酮

将4-(苄氧基羰基)-1-(2-羟基乙基)-哌嗪-2-酮(实施例94部分A

所述制备)(0.26 g, 0.94 mmol)的二氯甲烷(6 mL)溶液用三苯膦(0.60 g, 2.3 mmol), 咪唑(0.16 g, 2.3 mmol), 碘(0.47 g, 1.9 mmol)在0℃下处理1.5小时。将反应混合物在水和二氯甲烷间分配; 将有机层浓缩, 残余物进行色谱处理(15 %乙酸乙酯/二氯甲烷), 得到4-(苄氧基羰基)-1-(2-碘乙基)-哌嗪-2-酮(0.24 g, 0.62 mmol)。将吡咯并[3,2-c]吡啶(0.073 g, g, 0.62 mmol)溶解于DMF (3 mL)中, 用60 %氢化钠(0.03 g, 0.74 mmol)和所有来自上一步骤的4-(苄氧基羰基)-1-(2-碘乙基)-哌嗪-2-酮处理; 将反应混合物在室温下搅拌16小时。将反应混合物浓缩至干, 将残余物在水和二氯甲烷间分配。将有机层浓缩, 进行色谱处理(2-5 %甲醇/二氯甲烷), 得到标题化合物(0.028 g, 0.074 mmol)。离子喷雾MS m/z: 379, $[M+1]^+$。

实施例99

(+)-1-(3-氨基-4-氰基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲酯

A. (±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲酯

将包含(±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-2-甲酸甲酯(55 mg, 0.12 mmol)的二氯甲烷(1 mL)溶液冷却至0 C。加入DIPEA (24 mg, 0.18 mmol), 再加入6-氯苯并[b]噻吩-2-磺酰基氯(32 mg, 0.12 mmol) (实施例1)。将反应混合物升温至室温。16小时后, 将反应混合物直接吸收于硅胶上进行色谱处理(二氯甲烷-2%甲醇/二氯甲烷), 得到60 mg (73%)的标题化合物。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (dd, J =12.3, 3.4 Hz, 1 H), 3.50-3.72 (m, 3H), 3.79 (s, 3H), 4.15 (dd, J =12.3, 1.4 Hz, 1H), 4.24 (d, J =16.9 Hz, 1H), 5.41 (d, J =15.3 Hz, 1 H), 6.50 (s, 1 H), 6.76 (dd, J =7.9, 1.4 Hz, 1H), 7.11-7.86 (m, 15H) ppm; MS (ISP周线): m/z 683 (M+H)。

B. (±)-1-(3-氨基-4-氰基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲酯

在0℃下，将浓盐酸(12M，1滴)加至包含(±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代哌嗪-2-甲酸甲酯(60 mg，0.08 mmol)在甲醇(5 mL)中的混合物中。加入THF(2 mL)，再加入第二滴12M盐酸，升温反应混合物至室温。通过将反应混合物倒入1:1二氯甲烷/碳酸氢钠水溶液中使反应中止，分层。水层用二氯甲烷洗涤，合并后的有机相用盐水洗涤，用无水硫酸镁干燥，过滤并浓缩。将粗品残余物进行硅胶色谱处理(二氯甲烷至4%甲醇/二氯甲烷)，得到42 mg (93%)的标题化合物。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98 (dd, J =12, 5, 3.5Hz, 1H), 3.60 (d, J =16.8 Hz, 1H), 3.69 (d, J =15.3 Hz, 1H), 3.79 (s, 3H), 3.98 (m, 1H), 4.21-4.31 (m, 2H), 4.44 (br s, 2H), 5.36 (d, J =15.3 Hz, 1H), 6.47 (dd, J =8.0, 1.4 Hz, 1H), 6.54 (s, 1H), 7.26 (d, J =8.0 Hz, 1H), 7.45 (dd, J =85, 1.8 Hz, 1H), 7.80-7.86 (m, 3H) ppm; MS (ISP周线): m/z 519 (M+H)。

实施例100

(±)-1-(3-氨基-4-氰基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸

将水(5滴)加至包含(±)-1-(3-氨基-4-氰基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲酯(30 mg，0.05 mmol)(实施例99)在1:1THF/甲醇混合物(2 mL)中的溶液中。在室温下，加入氢氧化锂一水合物(7 mg，1.66 mmol)。16小时后，将反应混合物用水稀释，用反相HPLC 纯化[缓冲液A: 水w/0.1 %TFA; 缓冲液B: 乙腈 w/0.1 %TFA; 梯度: 0%B至60%B，30分钟内]，得到10 mg (34%)的标题化合物，为一种白色固体。^{1}H NMR (300 MHz, d_6-DMSO) δ 3.18 (dd, J =12.1, 3.5 Hz, 1H), 3.61 (d, J =16.0 Hz, 1H), 3.77 (d, J =16.0 Hz, 1H), 3.95 (d, J =16.0 Hz, 1H), 4.06 (d, J =12.1 Hz, 1H),

4.14 (m, 1H), 6.40 (d, J =8.0 Hz, 1H), 6.54 (s, 1H), 7.21 (d, J =8.0 Hz, 1H), 7.57 (dd, J =8.6, 1.9 Hz, 1H), 8.06 (d, J =8.6 Hz, 1H), 8.18 (s, 1H), 8.33 (s, 1H) ppm; MS (ISP周线): m/z 505 (M+H)。

实施例101

4-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]苯甲脒

向4-(2-氧代哌嗪-1-基甲基)苯甲脒二三氟乙酸盐(0.38 g, 0.83mmol) (实施例66)的二氯甲烷(5 mL)溶液中加入三乙胺(0.35 mL, 2.6 mmol), 6-氯-苯并[b]噻吩-2-磺酰基氯(0.23 g, 0.85 mmol(实施例1)。6小时后, 将溶液浓缩。将产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1 %TFA)至70%乙腈/水(0.1%TFA)。将收集的沉淀物进行冷冻干燥, 得到标题化合物, 为一种白色固体(0.37 g, 0.65 mmol)。^{1}H NMR (d^6-DMSO, 300MHz) δ 9.33 (bs, 2H), 8.96 (bs, 2H), 8.30 (s, 1H), 8.18 (s, 1H), 8.04 (d, 1H), 7.70 (m, 2H), 7.50 (m, 1 H), 7.28 (m, 2H), 4.55 (s, 2H), 3.86 (s, 2H), 3.44 (m, 2H), 3.22 (m, 2H)。

采用实施例101的方法, 由1-(4-氨基喹唑啉-7-基甲基)-3-乙基-哌嗪-2-酮(实施例77)和适宜的磺酰氯制备下述化合物。

实施例	名称	m/z(M+H)
102	4-[4-(4-甲氧基-苯磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	403
103	4-[4-(5-氯-噻吩并[3,2-b]吡啶-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	463, 465
104	4-[4-(6-氯-噻吩并[2,3-b]吡啶-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	464, 466 Cl花样

105	4-[2-氧代-4-(噻吩并[2,3-c]吡啶-2-磺酰基)-哌嗪-1-基甲基]-苯甲脒	430
106	4-[4-(7-氯-噻吩并[2,3-c]吡啶-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	464，466 Cl花样
107	4-[4-(5'-氯-[2,2']联噻吩-5-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	495，497 Cl花样
108	4-[4-(4-氯-噻吩并[3,2-c]吡啶-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	464，466 Cl花样
109	4-[2-氧代-4-(甲苯-4-磺酰基)-哌嗪-1-基甲基]-苯甲脒	387
110	4-[4-(苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	429
111	4-氨基-3-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	478，480 Cl花样
112	3-[2-氧代-4-(甲苯-4-磺酰基)-哌嗪-1-基甲基]-苯甲脒	387
113	3-[4-(6-氟-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	447
114	3-[4-(4-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	463，465 Cl花样
115	3-[4-(5-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	463，465 Cl花样
116	3-[4-(6-甲氧基-萘-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	453
117	3-{4-[5-(5-硝基-吡啶-2-磺酰基)-噻吩-2-磺酰基]-2-氧代-哌嗪-1-基甲基}-苯甲脒	565
118	3-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲脒	463，465 Cl花样

119	3-{4-[2-(3-氯-苯基)-乙烯磺酰基]-2-氧代-哌嗪-1-基甲基}-苯甲腈	433, 435 Cl花样
120	3-[2-氧代-4-(4-苯偶氮基-苯磺酰基)-哌嗪-1-基甲基]-苯甲腈	477
121	3-[4-(苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲腈	429

实施例122

4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌嗪-1-基甲基]苯甲腈

将氯化氢气体鼓泡通入冰冷却下的4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌嗪-1-基甲基]-苯甲腈(100 mg, 0.264 mmol)(通过使4-(4-氯基苄基)-3-氧代哌嗪-1-甲酸苄酯，实施例66，部分A，进行脱保护，再用6-氯-2-氯甲基苯并咪唑进行烷基化制得)的15 mL的甲醇溶液。溶解包含3Å分子筛。将反应混合物在-30℃下贮藏。旋转蒸发除去甲醇，加入新鲜的甲醇(20 ml)，再加入氨气。将所得混合物加热回流3小时。将反应混合物室温下过滤。将母液浓缩，将所得残余物进行反相HPLC纯化(0-50 %ACN/水)。分离出产物，为一种白色固体，其熔点为91-95℃。

MS $C_{20}H_{21}ClN_6O$ m/z：397, 399。分析计算值$C_{20}H_{21}ClN_6O\cdot 3C_2HF_3O_2$: C, 42.26 ; H, 3.27; N, 11.37; 实测值C, 42.20; H, 3.44; N, 11.36。

实施例123

4-4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-2-氧代哌嗪-1-基甲基}苯甲腈

向4-(2-氧代哌嗪-1-基甲基)苯甲腈二三氟乙酸盐(75 mg, 0.16 mmol) (实施例66)的1.5 mL的DMF溶液中加入N,N-二异丙基乙基胺(0.14 mL, 0.80 mmol)。在室温下搅拌10分钟后，加入3-(5-氯-噻吩-2-基)-(E)-丙烯酸(32 mg, 0.17 mmol)(实施例25)，再加入2-(1H-

苯并三唑-1-基)-1,1,3,3-四甲基四氟硼酸铵(TBTU) (55 mg, 0.17 mmol)。将所得混合物在室温下搅拌16小时,将溶液浓缩。粗品产物进行RP-HPLC纯化,进行梯度洗脱:10%乙腈/水(0.1%TFA)至70%乙腈/水(0.1%TFA),合并适宜的产物馏分,冷冻干燥,得到标题化合物(77 mg, 0.15 mmol),为一种白色固体。

^{1}H NMR (d6-DMSO, 300 MHz) δ 9.27 (bs, 2H), 9.10 (bs, 2H), 7.77 (d, 2H), 7.65 (d, 1H), 7.49 (dd, 2H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1 H), 4.65 (s, 2H), 4.45, 4.21 (m, 2H, 旋转异构体), 3.80 (m, 2H), 3.35 (m, 2H)。ESI MS, $[M+H]^+$=403,405 (Cl 花样)。

实施例124

3-{4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-2-氧代哌嗪-1-基甲基}苯甲腈

此标题化合物按照实施例123所述制备,采用3-(5-氯噻吩-2-基)-(E)-丙烯酸(实施例25), 3-(2-氧代哌嗪-1-基甲基)苯甲腈二三氟乙酸盐(如实施例66所述由3-溴甲基甲苯基腈制备)。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.32 (bs, 2H), 9.16 (bs, 2H), 7.65 (m, 5H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1H), 4.64 (s, 2H), 4.44, 4.21 (m, 2H, 旋转异构体), 3.93, 3.79 (m, 2H, 旋转异构体), 3.36 (m, 2H)。ESI MS, $[M+H]^+$=403,405 (Cl 花样)。

实施例125

3-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌嗪-1-基甲基]苯甲腈

白色固体(13.0 mg, 13%)。$C_{20}H_{21}ClN_6O$ MS m/z: 397, 399 分析计算值$C_{20}H_{21}ClN_6O\cdot 3C_2HF_3O_2$: C, 42.26; H, 3.27; N, 11.37; 实测值C, 43.70; H, 3.71; N, 11.95。

实施例126

1-(2-氨基喹啉-6-基甲基)-4-(5'-氯-[2,2']联噻吩-5磺酰基)哌嗪-2-酮

按照实施例101所述制备标题化合物，采用1-(2-氨基喹啉-6-基甲基)哌嗪-2-酮(实施例67)和5'-氯-[2,2']联噻吩-5-磺酰氯(实施例2)。将粗品产物与二氯甲烷研制，过滤,得到标题化合物，为一种白色固体。^{1}H NMR (d_6-DMSO, 300 MHz) δ 7.82 (d, 1 H), 7.68 (d, 1 H), 7.42 (m, 3H), 7.36 (d, 1H), 7.25 (d, 1H), 7.20 (d, 1H), 6.70 (d, 1H), 6.43 (bs, 2H), 4.53 (s, 2H), 3.78 (s, 2H), 3.31 (m, 4H)。MS (离子喷雾) m/z 519, 521, (M+H), Cl 花样。

实施例127

6-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基甲基]-1H喹啉-2-酮

此标题化合物按照实施例101所述制备，采用6-(2-氧代哌嗪-1-基甲基)-1H-喹啉-2-酮，来自实施例67，部分D的少量产物和6-氯苯并[b]噻吩-2-磺酰氯(实施例1)。将粗品产物与二氯甲烷研制，过滤，得到标题化合物，为一种白色固体。^{1}H NMR (d_6-DMSO, 300 MHz) δ 11.72 (bs, 1 H), 8.33 (s, 1H), 8.18 (s, 1H), 8.07 (d, 1H), 7.78 (d, 1H), 7.58 (dd, 1H), 7.45 (s, 1H), 7.30 (dd, 1H), 7.18 (d, 1H), 6.46 (d, 1H), 4.52 (s, 2H), 3.86 (s, 2H), 3.43 (m, 2H), 3.31 (m, 2H)。MS (离子喷雾) m/z 488, 490, (M+H), Cl 花样(pattern)。

按照实施例123的方法，采用在实施例67、68和73中所述制备的原料，以及适宜的羧酸，制备下述化合物。

实施例	名称	m/z(M+H)
128	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-噻吩并[2,3-c]吡啶-3-基甲基-哌嗪-2-酮	478,480 Cl花样

129	1-(2-氨基-喹喔啉-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	
130	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-噻吩并[2,3-c]吡啶-2-基甲基-哌嗪-2-酮	478,480 Cl花样
131	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-噻吩并(6-氯-苯并[b]噻吩-2-磺酰基)-1-噻吩并[3,2-c]吡啶-2-基甲基-哌嗪-2-酮	478,480 Cl花样
132	1-(2-氨基-喹啉-6-基甲基)-4-(6-氯-噻吩并[2,3-b]吡啶-2-磺酰基)-哌嗪-2-酮	488,490 Cl花样
133	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1-羟基-异喹啉-6-基甲基)-哌嗪-2-酮	488,490 Cl花样
134	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1-氯-异喹啉-6-基甲基)-哌嗪-2-酮	506,508 Cl花样
135	7-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-2H-异喹啉-1-酮	488,490 Cl花样
136	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1-氯-异喹啉-7-基甲基)-哌嗪-2-酮	506,508 Cl花样
137	1-(7-氨基-噻吩并[2,3-c]吡啶-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	493,495 Cl花样
138	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(2-氯-喹啉-6-基甲基)-哌嗪-2-酮	506,508 Cl花样
139	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-喹啉-6-基甲基-哌嗪-2-酮	472,474 Cl花样
140	7-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-1H-喹啉-2-酮	488,490 Cl花样
141	1-(2-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	487,489 Cl花样
142	1-(4-氨基-噻吩并[3,2-c]吡啶-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	493,495 Cl花样

143	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(1,2,3,4-四氢-异喹啉-6-基甲基)-哌嗪-2-酮	475,477 Cl花样
144	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-异喹啉-6-基甲基-哌嗪-2-酮	472,474 Cl花样
145	1-(2-氨基-喹啉-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	487,489 Cl花样
146	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(十氢-异喹啉-6-基甲基)-哌嗪-2-酮	482,484 Cl花样
147	1-(1-氨基-异喹啉-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	487,489 Cl花样
148	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(十氢-异喹啉-6-基甲基)-哌嗪-2-酮	482,484 Cl花样
149	1-(1-氨基-异喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	487,489 Cl花样
150	1-(4-氨基-噻吩并[3,2-c]吡啶-3-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	493,495 Cl花样
151	(+/-)-[1-(6-氯-苯并[b]噻吩-2-磺酰基)-3-氧代-4-噻吩并[3,2-c]吡啶-2-基甲基-哌嗪-2-基]-乙酸	536,538 Cl花样
152	(+/-)-[1-(6-氯-苯并[b]噻吩-2-磺酰基)-3-氧代-4-噻吩并[2,3-c]吡啶-2-基甲基-哌嗪-2-基]-乙酸	536,538 Cl花样
153	1-(1-氨基-异喹啉-6-基甲基)-4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	471,473 Cl花样
154	1-(1-氨基-异喹啉-6-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	475,477 Cl花样
155	(3S)-1-(7-氯-异喹啉-3-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-甲氧基甲基-哌嗪-2-酮	494,496,498, Cl_2花样

156	(3S)-1-(7-氯-异喹啉-3-基甲基)-4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-3-甲氧基甲基-哌嗪-2-酮	490, 492, 494, Cl_2花样
157	(S)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-乙基-1-(4-羟基-喹啉-7-基甲基)-哌嗪-2-酮	456, 458 Cl花样
158	1-(2-氨基-喹啉-6-基甲基)-4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-哌嗪-2-酮	427, 429 Cl花样

由实施例67所述制备的原料和适宜的芳基-甲基溴或烯丙基-甲基溴，采用碳酸钾介导的烷基化反应制备下述化合物。

实施例	名称	m/z(M+H)
159	1-(2-氨基喹啉-6-基甲基)-4-(4-甲氧基苄基)哌嗪-2-酮	377
160	1-(2-氨基喹啉-6-基甲基)-4-6-氯苯并[b]噻吩-2-基甲基)哌嗪-2-酮	436, 438 Cl花样
161	1-(2-氨基喹啉-6-基甲基)-4-(5-甲氧基-1H-苯并咪唑-2-基甲基)哌嗪-2-酮	417
162	1-(2-氨基喹啉-6-基甲基)-4-(5'-氯-[2,2']联噻吩-5-基甲基)哌嗪-2-酮	469, 471 Cl花样
163	1-(2-氨基喹啉-6-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2-酮	413, 415 Cl花样
164	1-(2-氨基喹啉-6-基甲基)-4-[3-(3,5-二溴-4-甲氧基-苯基)-[1,2,4]噁二唑-5-基甲基]哌嗪-2-酮	601, 603, 605 Br_2花样
165	3-[4-2-氨基喹啉-6-基甲基)-3-氧代-哌嗪-1-基甲基]-7-氟-1H-喹啉-2-酮	431
166	1-(2-氨基喹啉-6-基甲基)-4-(6-氯萘-2-基甲基)-哌嗪-2-酮	430

由实施例66、67、68和73所述制备的原料和适宜的芳基-甲基溴或烯丙基-甲基溴，采用碳酸钾介导的烷基化反应制备下述化合物。

实施例	名称	m/z (M+H)
167	3-(4-联苯基-3-基甲基-3-氧代-哌嗪-1-基甲基)-苯甲腈	399
168	4-(5-氯-1H-吲哚-2-基甲基)-1-(4-氯-喹啉-7-基甲基)-哌嗪-2-酮	439, 441 Cl花样
169	1, 4-二-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮	427
170	1-(4-氨基-噻吩并[3, 2-d]嘧啶-6-基甲基)-4-(7-氯-异喹啉-3-基甲基)-哌嗪-2-酮	439, 441 Cl花样
171	1-(4-氨基-噻吩并[3, 2-d]嘧啶-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	444, 446 Cl花样
172	1-(4-氨基-噻吩并[3, 2-d]嘧啶-6-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2-酮	420, 422 Cl花样
173	1-(3-氨基-1H-吲唑-6-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2-酮	401
174	1-(3-氨基-1H-吲唑-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	426
175	1-(4-氨基-噻吩并[2, 3-d]嘧啶-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	443
176	4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-2-氧代-哌嗪-1-基甲基]-苯甲腈	413, 415 Cl花样
177	4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-3-氧代-哌嗪-1-基甲基]-苯甲腈	415, 413 Cl花样
178	4-(4-环己基甲基-2-氧代-哌嗪-1-基甲基)-苯甲腈	329
179	1-(1-氨基-异喹啉-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	437, 439 Cl花样

180	1-(1-氨基-异喹啉-6-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲氧基甲基-哌嗪-2-酮	457,459 Cl花样
181	4-[3-(5-氯-噻吩-2-基)-烯丙基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-甲基-哌嗪-2-酮	468
182	4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	454
183	(S)-4-(5-氯-1H-吲哚-2-基甲基)-1-(4-氯-喹啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮	483
184	(S)-4-(5-氯-1H-吲哚-2-基甲基)-1-(4-氯-喹啉-7-基甲基)-3-甲基-哌嗪-2-酮	453

实施例185

1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2磺酰基)哌嗪-2-酮

此标题化合物按照实施例101所述制备，用1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮二盐酸盐(实施例72)代替4-(2-氧代哌嗪-1-基甲基)-苯甲腈。将产物用RP-HPLC进行纯化，进行梯度洗脱：10%乙腈/水(0.1%TFA)至70%乙腈/水(0.1%TFA)。将适当收集的馏分进行冷冻干燥，得到标题化合物，为一种白色固体。MS(离子喷雾) m/z 488, 490, (M+H)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.65 (s, 2H), 8.80 (s, 1H), 8.30 (m, 2H), 8.20 (s, 1 H), 8.05 (d, 1 H), 7.60 (m, 3H), 4.70 (s, 2H), 3.85 (s, 2H), 3.50-3.20 (m, 4H)。

实施例186

4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-磺酸3-氯苄基酰胺

向1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮二盐酸盐(实施例72)(0.10g, 0.30mmol)的9 mL的DMF溶液中加入3-氯苄基氨磺酰基儿茶酚(0.09g, 0.30mmol)(实施例4)，三乙胺(0.08g, 0.75 mmol)，DMAP

(0.001 g, 0.12 mmol)。将溶液加热至60℃。16小时后，将溶液浓缩。粗品产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1 %TFA)至100% 乙腈。将产物馏分冷冻干燥，得到标题化合物(0.077g, 0.17 mmol)，为TFA盐。^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.82 (bs, 2H), 8.98 (s, 1H), 8.52 (d, 1H), 8.32 (d, 1H), 7.60 (m, 2H), 7.35 (m, 4H), 4.69 (AB, 2H), 4.11 (m, 2H), 3.77 (s, 2H), 3.38 (m, 2H), 3.27 (m, 2H)。MS (离子喷雾) m/z 461,463, (M+H), Cl花样。

采用实施例101的方法，由实施例72的化合物，适当的磺酰氯，制备下述化合物。

实施例	名称	m/z(M+H)
187	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-噻吩并[2,3-b]吡啶-2-磺酰基)-哌嗪-2-酮	489,491 Cl花样
188	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩-5-磺酰基)-哌嗪-2-酮	520,522 Cl花样
189	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-磺酸4-氯-苄基酰胺	460
190	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-异噁唑-3-基-噻吩-2-磺酰基)-哌嗪-2-酮	471
191	1-(4-氨基-喹唑啉-7-基甲基)-4-(噻吩并[3,2-b]吡啶-2-磺酰基)-哌嗪-2-酮	455
192	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-磺酸[2-(3-氯-苯基)-乙基]-酰胺	474
193	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-磺酸[2-(4-氯-苯基)-乙基]-酰胺	474
194	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并味唑-2-磺酰基)-哌嗪-2-酮	472

195	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮	464, 466 Cl花样
196	4-(3-氨基-苯磺酰基)-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮	413

采用实施例101的方法，由实施例75-78所述获得的原料和适当的磺酰氯，制备下述化合物。

实施例	名称	m/z(M+H)
197	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-3-(S)-乙基-哌嗪-2-酮	492, 494 Cl花样
198	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-3-(S)-乙基-哌嗪-2-酮	516, 518 Cl花样
199	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2, 2']联噻吩-5-磺酰基)-3-(S)-乙基-哌嗪-2-酮	548, 550 Cl花样
200	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2, 2']联噻吩-5-磺酰基)-3-(S)-甲基-哌嗪-2-酮	534, 536 Cl花样
201	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-3-(S)-甲基-哌嗪-2-酮	502, 504 Cl花样
202	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基-哌嗪-2-酮	502, 504 Cl花样
203	(+/-)-[4-(4-氨基-喹唑啉-7-基甲基)-1-(6-氯-苯并[b]噻吩-2-磺酰基)-3-氧代-哌嗪-2-基]-乙酸	546, 548 Cl花样

采用实施例101的方法，由实施例72和73所述获得的原料和适当的磺酰氯，或者采用实施例123的方法，由由适当的羧酸，制备下述化合物。

实施例	名称	m/z(M+H)
204	1-(4-氨基-噻吩并[3,2-d]嘧啶-6-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮	470,472 Cl花样
205	1-(4-氨基-噻吩并[3,2-d]嘧啶-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	493,495 Cl花样
206	1-(4-氨基-噻吩并[2,3-d]嘧啶-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	494,496 Cl花样
207	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-羟基-喹唑啉-6-基甲基)-哌嗪-2-酮	489,491 Cl花样
208	1-(4-氨基-噻吩并[3,2-d]嘧啶-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	494,496 Cl花样
209	1-(4-氨基-喹唑啉-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	488,490 Cl花样
210	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-羟基-喹唑啉-7-基甲基)-哌嗪-2-酮	489,491 Cl花样
211	1-(4-氨基-噻吩并[3,2-d]嘧啶-6-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-哌嗪-2-酮	478,480 Br花样
212	1-(4-氨基-噻吩并[3,2-d]嘧啶-6-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-哌嗪-2-酮	434,436 Cl花样

实施例213

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮

A. 2-{4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-2-氧代哌嗪-1-基甲基)吡咯并[3,2c]吡啶-1-甲酸叔丁酯

向2-(2-氧代哌嗪-1-基甲基)吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(0.71 g, 2.1 mmol)(实施例69)的乙腈 (7 mL)溶液中加入三乙胺(0.60 mL, 4.3 mmol), 再加入2-(5-氯-噻吩-2-基)-乙烯磺酰氯(实施例3)(0.57 g, 2.1 mmol). 将混合物搅拌过夜, 然后, 浓缩至干. 将残余物用二氯甲烷稀释, 用饱和碳酸氢钠和盐水洗涤. 有机层用硫酸镁干燥, 过滤并真空浓缩, 得到标题化合物(1.2 g, 2.1 mmol), 为一种浅黄色固体. 粗品产物可不经进一步纯化用于下一步骤. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (s, 1 H), 8.42 (d, 1 H), 7.88 (d, 1H), 7.55 (d, 1H), 7.14 (d, 1H), 6.98 (d, 1H), 6.41 (s, 1H), 6.36 (d, 1H), 5.00 (s, 2H), 3.98 (s, 2H), 3.61 (m, 4H), 1.71 (s, 9H). 离子喷雾 MS, $[M+H]^+$=537, 539, Cl花样.

B. 4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-(1H-吡咯并[3,2-c]吡啶-2基甲基)哌嗪-2-酮

在0℃下, 将三氟乙酸(2.2 mL, 28.6 mmol)滴加至2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基甲基]吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(1.32 g, 2.4 mmol)在二氯甲烷(25 mL)中的浆液中. 1.5小时后, 除去冰浴, 将溶液在室温下搅拌4小时. 将反应混合物用二氯甲烷稀释, 用饱和碳酸氢钠和盐水洗涤. 有机层用硫酸镁干燥, 过滤并真空浓缩, 得到标题化合物, 为一种游离碱. 将粗品产物用RP-HPLC进行纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至100%乙腈, 适当的产物馏分进行冷冻干燥, 得到标题化合物(1.29 g, 2.2 mmol), 为一种白色固体. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 14.90 (bs, 1H), 12.81 (s, 2H), 9.12 (s, 1H), 8.41 (d, 1H), 7.89 (d, 1H), 7.60 (d, 1H),

7.50 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1 H), 6.95 (s, 1H), 4.80 (s, 2H), 3.98 (s, 2H), 3.48 (s, 4H)。离子喷雾 MS, $[M+H]^+$=437, 439, Cl花样。

实施例214

4-(6-氯苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮

A. 2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基甲基]吡咯并[3,2c]吡啶-1-甲酸叔丁酯

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.7 (s, 1H), 8.41 (d, 1H), 7.9-7.8 (m, 3H), 7.45 (d, 1H), 7.25 (d, 1H), 6.31 (s, 1 H), 4.95 (s, 2H), 3.98 (s, 2H), 3.65 (m, 2H), 3.55 (m, 2H), 1.68 (s, 9H)。离子喷雾 MS, $[M+H]^+$ =561, 563, Cl花样。

B. 4-(6-氯苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮三氟乙酸盐

^{1}H NMR (d_6-DMSO, 300 MHz) δ 14.68 (bs, 1H), 12.6 (s, 1H), 9.1 (s, 1H), 8.36 (d, 1 H), 8.29 (d, 1H), 8.17 (s, 1H), 8.05 (d, 1H), 7.82 (d, 1 H), 7.56 (m, 2H), 6.83 (s, 1H), 4.1 (s, 2H), 3.84 (s, 2H), 3.38 (m, 4H)。离子喷雾 MS, $[M+H]^+$=461,463, Cl花样。

实施例215

4-(6-氯苯并[b]噻吩-2-磺酰基)-1-(5-氧代-1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮

将4-(6-氯苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮(0.06 g, 0.13 mmol)溶解于无水二氯甲烷(20 ml)中，用间氯过苯甲酸(0.03 g, mmol)处理，在室温下搅拌4小时。将溶液用二氯甲烷稀释，用碳酸氢钠洗涤，干燥(硫酸钠)，浓缩。将

残余物用快速色谱纯化(5-10 %甲醇/二氯甲烷)，转变为TFA盐，得到标题化合物(0.015 g，0.032 mmol)。^{1}H NMR ($CDCl_3$，300 MHz) δ 9.14 (bs，1H)，8.95 (d，1H)，7.8-7.87 (m，3H)，7.57 (d，1H)，7.48 (dd，1H)，6.87 (s，1 H)，4.90 (s，2H)，3.95 (s，2H)，3.86 (s，3H)，3.49 (s，3H)。EI MS，[M$^+$]=474，476，Cl花样。

实施例216

4-(6-氯苯并[b]噻吩-2-磺酰基)-1-(1-甲基-1H-吡咯并[3,2-c]吡啶2-基甲基)哌嗪-2-酮

将4-(6-氯苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2基甲基)哌嗪-2-酮(0.59 g，1.28 mmol)(实施例214)溶解于无水DMF (30 ml)中，在冰浴中冷却，用60 %氢化钠(0.061 g，1.53 mmol)处理，在室温下搅拌30分钟。将溶液用甲基碘(83 mL，1.33 mmol)处理，在4小时内升温至室温。此反应用氯化铵溶液中止，用乙酸乙酯稀释和分离。有机层用盐水(3x)洗涤，干燥(硫酸钠)，浓缩。将残余物用快速色谱纯化(5-10 %甲醇/二氯甲烷)，得到标题化合物(0.31 g，0.65 mmol)。^{1}H NMR (CD_3OD，300 MHz) δ 8.55 (d，1 H)，7.99 (dd，1 H)，7.82 (m，3H)，7.49 (dd，1 H)，7.43 (d，1 H)，6.55 (s，1H)，4.75 (s，2H)，3.96 (s，2H)，3.52 (m，4H)，3.86 (s，3H)，3.49 (s，3H)。Ion Spray MS，[M+H]$^+$=477。

采用实施例101的方法，由实施例69所述获得的原料和适当的磺酰氯，制备下述化合物。

实施例	名称	m/z (M+H)
217	4-(3-氯苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	460

218	4-(6-氯噻吩并[2,3-b]吡啶-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	462,464 Cl花样
219	4-(6-溴苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	505
220	2-[3-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-1-磺酰基]-苯并[b]噻吩-6-甲腈	452
221	4-(5'-氯-[2,2']联噻吩-5-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	493
222	4-[2-(4-氯苯基)乙烯磺酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	431
223	{2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基甲基]吡咯并[3,2-c]吡啶-1-基}乙酸	519,521 Cl花样
224	4-(5-吡啶-4-基噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	454
225	{2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基甲基]吡咯并[3,2-c]吡啶-1-基}乙酸乙酯	547,549 Cl花样
226	4-(6-氯苯并[b]噻吩-2-磺酰基)-1-[1-(2-甲氧基乙基)-1H-吡咯并[3,2-c]吡啶-2-基甲基]哌嗪-2-酮	519,520 Cl花样
227	4-(6-氯噻吩并[3,2-b]吡啶-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	462,464 Cl花样
228	(2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基甲基]吡咯并[2,3-c]吡啶-1-基}乙酸甲酯	533,535 Cl花样

229	2-[3-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-1-磺酰基]苯并[b]噻吩-5-甲腈	452
230	4-(5-氨基甲基苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮	456
231	2-{2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基甲基]吡咯并[3,2-c]吡啶-1-基}乙酰胺	518,520 Cl花样
232	4-(6-氯苯并[b]噻吩-2-磺酰基)-1-[1-(2-羟基乙基)-1H-吡咯并[3,2-c]吡啶-2-基甲基]哌嗪-2-酮	505
233	4-(6-氯-1H-苯并咪唑-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	445,447 Cl花样
234	4-(1H-苯并咪唑-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	411
235	4-(6-氨基甲基-苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	456
236	1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-4-(噻吩并[2,3-b]吡啶-2-磺酰基)-哌嗪-2-酮	428
237	1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-4-(噻吩并[3,2-b]吡啶-2-磺酰基)-哌嗪-2-酮	428
238	4-[2-(5-氯-噻吩-2-基)-乙磺酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	439,441 Cl花样
239	4-(2-苯并[b]噻吩-2-基-乙烯磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	453

240	4-[2-(5-氯-4-甲氧基-噻吩-2-基)-乙烯磺酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	467,469
241	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-呋喃并[3,2-c]吡啶-2-基甲基-哌嗪-2-酮	462,464
242	4-(6-氟-苯并[b]噻吩-2-磺酰基)-1-呋喃并[3,2-c]吡啶-2-基甲基-哌嗪-2-酮	446
243	4-(6-氯苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[2,3-c]吡啶-2-基甲基)哌嗪-2-酮	460,462 Cl花样
244	4-(6-氯噻吩并[2,3-b]吡啶-2-磺酰基)-1-(1H-吡咯并[2,3-c]吡啶-2-基甲基)哌嗪-2-酮	462,464 Cl花样
245	{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-吡咯并[2,3-c]吡啶-1-基}-乙酸甲酯	533,535 Cl花样
246	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-H-吡咯并[3,2-b]吡啶-2-基甲基)-哌嗪-2-酮	461,463 Cl花样

实施例247

1-(4-氨基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)哌嗪-2-酮

A. (2-氯-吡啶-4-基)-氨基甲酸叔丁酯

在室温下，将NaHMDS (61.7 mL, 1.0M THF溶液)迅速加至2-氯吡啶-基胺(4.0 g, 30.9 mmol)和BOC酸酐(6.74 g, 30.9 mmol)的THF (28 mL)溶液中。将反应混合物在冰水浴(0℃)中冷却1小时，然后，在室温下搅拌3小时。将凝胶状的混合物进行真空浓缩，用乙酸乙酯和饱和氯化铵溶液稀释。有机层用0.1N盐酸，饱和碳酸氢钠和盐水洗涤。然后，有机层用硫酸镁干燥，过滤并浓缩至干。粗品产物进行色谱处理，用1

%甲醇/二氯甲烷洗脱，得到标题化合物(5.57 g，24.4 mmol)，为一种黄色固体。^{1}H NMR ($CDCl_3$，300 MHz) δ 8.18 (d，1H)，7.48 (d，1H)，7.12 (dd，1H)，1.60 (s，9H)。EI MS $[M]^+$=228。

B. (2-氯-3-碘-吡啶-4-基)-氨基甲酸叔丁酯

在-78℃下，在氩气氛下，将叔丁基锂(36.3 mL，1.7M戊烷溶液)滴加至(2-氯-吡啶-4-基)-氨基甲酸叔丁酯(6.00 g，26.2 mmol)的THF (46 mL)溶液中。将黄色/橙色混合物在-78℃下搅拌2小时，然后，升温至-40℃，再搅拌1小时，然后，冷却至-78℃，再滴加THF (49 mL)中的I_2(15.65 g，61.7 mmol)。将反应混合物在-78℃下搅拌1.5小时，然后，在-10℃下搅拌30分钟。用饱和氯化铵溶液中止反应，然后，用二氯甲烷稀释，用饱和氯化铵，饱和硫代硫酸钠，水及盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩至干。粗品产物进行色谱处理，用1-2%甲醇/二氯甲烷洗脱，得到标题化合物(7.96 g，22.5 mmol)，为一种亮黄色固体。^{1}H NMR ($CDCl_3$，300 MHz) δ 8.14 (d，1 H)，8.02 (d，1 H)，7.32 (bs，1 H)，1.60 (s，9H)。EI MS $[M]^+$=354，356，Cl花样。

C. 4-(4-氯-1H-吡咯并[3,2-c]吡啶-2-基甲基)-3-氧代-哌嗪-1-甲酸苄酯

将三氟乙酸(10 mL)加至2-(4-苄氧基羰基-2-氧代-哌嗪-1-基甲基)-4-氯-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(5.66 g，11.3 mmol，以与前述相同的方式制备)的二氯甲烷(10 mL)溶液中。将溶液搅拌过夜，然后，用二氯甲烷稀释，用饱和碳酸氢钠和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩至干。粗品产物进行色谱处理，用1-5%甲醇/二氯甲烷洗脱，得到标题化合物(3.81 g，9.56 mmol)，为一种泡沫状黄色固体。^{1}H NMR ($CDCl_3$，300 MHz) δ 9.43 (bs，1H)，8.08 (d，1H)，7.38 (s，5H)，7.18 (d，1H)，6.51 (s，1H)，5.15 (s，2H)，4.58 (s，2H)，4.20 (s，2H)，3.71 (m，2H)，3.50 (m，2H)。离子喷雾 [M+H]+=399，

401，Cl花样。

D. 4-(1-苯磺酰基-4-氯-1H-吡咯并[3,2-c]吡啶-2-基甲基)-3-氧代-哌嗪-1-甲酸苄酯

在室温下，将粉末氢氧化钠(0.96 g，23.9 mmol)，再加入nBu_4NHSO_4(0.32 g，0.96 mmol)和苯磺酰基氯(1.8 mL，14.1 mmol)加至4-(4-氯-1H-吡咯并[3,2-c]吡啶-2-基甲基)-3-氧代-哌嗪-1-甲酸苄酯(3.81 g，9.56 mmol)的二氯甲烷(32 mL)溶液中。将所得浆液搅拌3.5小时后，用二氯甲烷稀释，用饱和碳酸氢钠和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩至干。粗品产物进行色谱处理，用1-5%甲醇/二氯甲烷，得到标题化合物(5.06 g，9.38 mmol)。^1H NMR ($CDCl_3$，300 MHz)，δ 8.23 (d，1H)，7.97 (d，1H)，7.84 (d，2H)，7.61 (d，1H)，7.51 (m，2H)，7.38 (s，5H)，6.50 (s，1H)，5.18 (s，2H)，5.03 (s，2H)，4.29 (s，2H)，3.80 (m，2H)，3.51 (m，2H)。离子喷雾$[M+H]^+$=539，541，Cl花样。

E. 1-(1-苯磺酰基-4-氯-1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

在0℃下，将TMSI(2.7 mL，19.0 mmol)加至4-(1-苯磺酰基-4-氯-1H-吡咯并[3,2-c]吡啶-2-基甲基)-3-氧代-哌嗪-1-甲酸苄酯(5.06 g，9.38 mmol)的乙腈(134 mL)溶液中。将反应混合物升温至室温，再搅拌5小时。将反应混合物浓缩至干，用甲醇稀释红色的残余物，浓缩至干(重复两次)。将混合物用二氯甲烷稀释，用饱和碳酸氢钠和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩至干。粗品产物进行色谱处理，用1-5%甲醇/二氯甲烷洗脱，得到标题化合物(0.70 g，1.74 mmol)，未反应的原料(3.58 g，6.64 mmol)。^1H NMR ($CDCl_3$，300 MHz) δ 8.20 (d，1 H)，7.93 (d，1H)，7.85 (d，2H)，7.60 (d，1H)，7.51 (m，2H)，6.50 (s，1H)，5.01 (s，2H)，3.45 (m，2H)，3.18 (m，2H)。离子喷雾 $[M+H]^+$=405，407，Cl花样。

F. 1-(4-氨基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)哌嗪-2-酮

将无水乙酸铵(0.56 g, 7.2 mmol), 苯酚(0.45 g, 4.8 mmol), 1-(1-苯磺酰基-4-氯-1H-吡咯并[3,2-c]吡啶-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮(0.31 g, 0.48 mmol, 如前制备)加热至100℃搅拌3.5天. 将混合物冷却至室温, 然后, 将粗品产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至100%乙腈 , 然后, 将适当的产物馏分冷冻干燥, 得到标题化合物(1.29 g, 2.2 mmol), 为一种白色固体(22.4 mg, 0.038 mmol). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.40 (bs, 1H), 12.00 (bs, 1H), 8.31 (d, 1H), 8.20 (s, 1H), 8.06 (d, 1H), 8.02 (bs, 2H), 7.57 (dd, 1H), 7.48 (m, 1H), 6.89 (d, 1H), 6.81 (s, 1H), 4.60 (s, 2H), 3.81 (s, 2H), 3.40 (m, 4H). LR-FAB MS, $[M+H]^+$=476, 478.

实施例248

4-(2-(5-氯-噻吩-2-基)-乙磺酰基]-5-(±)-羟基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 2-{4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-2-(±)-羟基甲基-6-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

在室温下, 将硼氢化钠(0.005 g, 0.13 mmol)加至2-{4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-2-(±)-甲氧基羰基-6-氧代-哌嗪-1-基甲基}-吡咯并[3,2c]吡啶-1-甲酸叔丁酯(0.04 g, 0.07 mmol) (由2-(2-(±)-甲氧基羰基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯制备, 实施例71, 和2-(5-氯-噻吩-2-基)-乙烯磺酰氯, 实施例3制备, 采用实施例214, 部分A的方法)的甲醇 (3 mL)溶液中. 将反应混合物搅拌6小时后, 用水中止反应, 真空浓缩. 粗品产物(0.04 g)不经纯化即可用于下一步骤.

B. 4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-5-(±)-羟基甲基-1-1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

在室温下，将三氟乙酸(1.8 mL)加至2-{4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-2-(±)-羟基甲基-6-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(0.04 g)的二氯甲烷(4.2 mL)溶液中。将反应混合物搅拌4小时后，真空浓缩。将标题化合物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1 %TFA)至100%乙腈，对适当的产物馏分进行冷冻干燥。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.10 (s, 1 H), 8.46 (d, 1 H), 7.82 (d, 1 H), 7.50 (d, 1H) 7.43 (d, 1 H), 7.14 (d, 1H), 7.01 (d, 1H), 6.94 (s, 1H), 5.12 (bs, 1H), 4.80 (AB, 2H), 3.98 (d, 2H0, 3.90 (m, 1H), 3.40-3.50 (m, 4H)。APCl MS, $[M+H]^+$ = 467, 469。

采用实施例101的方法，由实施例69、70和71所述获得的原料和适当的磺酰氯，制备下述化合物。

实施例	名称	m/z
249	1-(6-氯-苯并[b]噻吩-2-磺酰基)-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸甲酯	519,521 Cl花样
250	1-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸甲酯	495,497 Cl花样
251	1-(6-氯-苯并[b]噻吩-2-磺酰基)-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸	505,507 Cl花样
252	4-(6-氯-苯并[b]噻吩-2-磺酰基)-5-(±)-羟基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	491,493 Cl花样

下述对映体纯的化合物通过在CHIRACEL OD prep柱上进行手性拆

分获得。

实施例	名称	%ee	m/z
253	1-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(-)-甲酸甲酯	99%(-)	495,497 Cl花样
254	1-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(+)-甲酸甲酯	95%(+)	495,497 Cl花样

实施例255

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-(R)-羟基甲基-1-(1H吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 6-(R)-(叔丁基-二甲基-硅烷氧基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

在室温下，将三氟乙酸(0.25 mL)加至2-{2-(R)-(叔丁基-二甲基-硅烷氧基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(0.025 g, 0.037 mmol)的二氯甲烷(0.5 mL)溶液中。将反应混合物搅拌2小时后，浓缩至干。将残余物用二氯甲烷稀释，用饱和碳酸氢钠和盐水洗涤。有机层用硫酸镁干燥，过滤并真空浓缩。粗品产物(0.019 g, 0.033 mmol)不经进一步纯化即可用于下一步骤。

B. 4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-(R)-羟基甲基-1-(1H-吡咯并[3,2c]吡啶-2-基甲基)-哌嗪-2-酮

将冰醋酸(3 mL, 0.046 mmol)，四丁基氟化铵(92 mL, 0.092 mmol)加至6-(R)-(叔丁基-二甲基-硅烷氧基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-(1H-吡咯并(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮(0.019 g, 0.033 mmol)的THF (0.5 mL)溶液中。将所

得溶液搅拌4小时后，真空浓缩。粗品产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1%TFA)至100%乙腈，将适当的产物馏分冷冻干燥，得到标题化合物(0.009 g, 0.016 mmol)，为一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.50 (bs, 1H), 12.60 (bs, 1 H), 9.18 (s, 1 H), 8.38 (d, 1H), 7.89 (d, 1H), 7.61 (d, 1H), 7.50 (d, 1H), 7.21 (d, 1H), 7.08 (d, 1H), 6.90 (s, 1 H), 5.03 (s, 2H), 4.63 (d, 2H), 3.70-3.90 (AB, 2H), 3.75 (m, 1 H), 3.21 (m, 2H)。[on spray MS, $[M+H]^+$=467, 469, Cl花样。

采用实施例101的方法，由实施例69、70和71所述获得的原料和适当的磺酰氯，制备下述化合物。

实施例	名称	m/z
256	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(R)-羟基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	491,493
257	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸甲酯	495,497 Cl花样
258	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸甲酯	519,521 Cl花样
259	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸	481,483 Cl花样
260	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸	505,507 Cl花样

261	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(±)-羟基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	491,493 Cl花样
262	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-(±)-羟基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	467,469 Cl花样
263	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸酰胺	504,506 Cl花样
264	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	481,483
265	4-(6-氯-苯并[b]噻吩-2-磺酰基)-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	505,507
266	4-(5'-氯-[1,2']联噻吩-5-磺酰基)-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	537,539
267	4-[2-(4-氯-苯基)-乙烯磺酰基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	475,477

实施例268

1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2基甲基)哌嗪-2-酮

向1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮二盐酸盐(1.84 g, 5.73 mmol) (实施例72)的DMF (20 mL)溶液中加入2-溴甲基-6-氯-苯并[b]噻吩(实施例5) (1.5 g, 5.73 mmol), 碳酸钾(4.0 g, 28.7 mmol)。将溶液搅拌16小时。此后, 将溶液用水稀释。将溶液用三氟乙酸酸化。

将产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1%TFA)至50%乙腈/水(0.1%TFA)。冷冻干燥适当的收集的馏分，得到标题化合物，为一种白色固体。^{1}H NMR (d^4-DMSO, 300MHz) δ 9.78 (bs, 3H), 8.82 (s, 1 H), 8.34 (d, 1 H), 8.07 (s, 1 H), 7.81 (d, 1 H), 7.63 (d, 1 H), 7.51 (s, 1H), 7.32 (m, 2H), 4.71 (s, 2H), 3.95 (s, 2H), 3.28 (m, 4H), 2.80 (m, 2H)。

实施例269

1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2基甲基)哌嗪-2-酮

将1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮(50 mg, 0.15 mmol)(实施例72)，6-氯-2-氯甲基苯并咪唑(30.5 mg, 0.15 mmol)，碳酸钾(83 mg, 0.6 mmol)在2 mL的DMF中的混合物在室温下搅拌过夜。将混合物通过反相HPLC纯化(乙腈/水/TFA)，得到1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-基甲基)哌嗪-2-酮(25 mg)的三氟乙酸盐，为一种固体。^{1}H NMR (CD_3OD, 300 MHz) δ 8.69 (s, 1 H), 8.33 (d, 1 H), 7.79 (s, 1 H), 7.75-7.69 (m, 3H), 7.57-7.54 (m, 1 H), 4.86 (s, 2H), 4.22 (s, 2H), 3.31 (m, 4H), 2.99 (m, 2H)。MS m/z 422 (M+H)。

实施例270

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并噻唑-2-基甲基)哌嗪-2-酮

向1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮(76 mg, 0.23 mmol)(实施例72)在2 mL DMF中的溶液中加入碳酸钾(127 mg, 0.92 mmol)，再加入6-氯-2-氯甲基-苯并噻唑(按照以下方面制备：B. L. Mylari, Synsis Comm. 1989, 16, 2921) (50 mg, 0.23 mmol)。将所得混合物室温下搅拌过夜。滤除未溶解的碳酸钾，将母液经反相HPLC纯化(10-100%乙腈/水)。获得所需产物，为一种白色固体，其熔

点为123-126℃。$C_{21}H_{19}ClN_6OS$ MS m/z: 439, 441. 分析计算值$C_{21}H_{19}ClN_6OS \cdot 2C_2HF_3O_2$: C, 45.02; H, 3.17 N, 12.60; 实测值C, 44.15; H, 3.19; N, 11.79。

实施例271

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并噁唑-2-基甲基)哌嗪-2-酮

所需产物(10.0 mg, 7%)以一种白色固体分离出来。$C_{21}H_{19}ClN_6O_2$ MS m/z: 423, 425。

实施例272

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并噻唑-2-基甲基)哌嗪-2-酮

所需产物(19.0 mg, 22%), 为一种白色固体。$C_{21}H_{19}ClN_6OS$ MS m/z: 438, 440。分析计算值$C_{21}H_{19}ClN_6OS \cdot 2C_2HF_3O_2$: C, 45.02; H, 3.17 N, 12.60; 实测值C, 43.35; H, 3.26; N, 12.65。

实施例273

3-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代哌嗪-1-基甲基]-7-氯-1H喹啉-2-酮

此标题化合物按照实施例268所述制备, 用3-溴甲基-7-氯-1H-喹啉-2-酮(实施例8)代替2-溴甲基-6-氯苯并[b]噻吩。将产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至50%乙腈/水(0.1%TFA)。冷冻干燥适当的收集的馏分, 得到标题化合物, 为一种白色固体。

^{1}H NMR(d_6-DMSO, 300MHz) δ 12.18 (bs, 1H), 9.75 (m, 1H), 8.86 (s, 1H), 8.40 (m, 1H), 8.11 (d, 1H), 8.10 (s, 1H), 7.78 (m, 1H), 7.69 (m, 2H), 7.37 (m, 1H), 4.80 (s, 2H), 4.10 (m, 2H), 3.47 (m, 4H), 3.30 (m, 2H)。MS (离子喷雾) m/z 449, (M+H)。

实施例274

1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1H-吲哚-6-基甲基)-哌嗪基2-酮

A. 1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1-(甲苯-4-磺酰基)-1H-吲哚-6-基甲基)-哌嗪-2-酮

此标题化合物按照实施例268所述制备，采用6-溴甲基-3-氯-1-(甲苯-4-磺酰基)-1H-吲哚，(甲苯-4-磺酰基)-1H-吲哚(实施例16)代替2-溴甲基-6-氯-苯并[b]噻吩。粗品产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1%TFA)至80%乙腈/水(0.1%TFA)，将适当的产物馏分进行冷冻干燥，得到一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.75 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.64 (m, 2H), 7.60 (m, 2H), 7.40 (d, 1H), 7.23 (m, 1 H), 7.19 (m, 2H), 6.99 (d, 2H), 5.09 (s, 2H), 4.78 (s, 2H), 4.10 (m, 2H), 3.40 (m, 4H), 2.49 (s, 3H)。

B. 1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1H-吲哚-6-基甲基)-哌嗪-2-酮

向1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1-(甲苯-4-磺酰基)-1H-吲哚-6-基甲基)-哌嗪-2-酮二三氟乙酸盐(31 mg, 0.04 mmol)的2 mL的甲醇溶液中加入0.3 mL的1N氢氧化钠溶液。将溶液在100℃下加热搅拌3小时。此后，将溶液用水/乙腈稀释，用三氟乙酸中和。粗品产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1%TFA)至60%乙腈/水(0.1 %TFA)，合并适当的产物馏分，冷冻干燥，得到标题化合物(21 mg, 0.03 mmol)，为一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.71 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.63 (m, 3H), 7.53 (d, 1 H), 7.50 (s, 1H), 7.20 (d, 1H), 4.78 (s, 2H), 4.30-3.10 (m, 8H)。ESI MS, $[M+H]^+$=421,423 (Cl花样)。

实施例275

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-(E)-烯丙基]-哌嗪-2-酮

向1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮二盐酸盐(100 mg, 0.31 mmol)(实施例72)的3 mL的DMF溶液中加入2-(3-溴-(E)-丙烯基)-5-氯-噻吩(73 mg, 0.31 mmol)(如实施例17所述制备)和碳酸钾(0.21 g, 1.54 mmol)。将溶液在室温下搅拌16小时。此后,将溶液用水/乙腈稀释,三氟乙酸中和。粗品产物用RP-HPLC纯化,进行梯度洗脱:10%乙腈/水(0.1%TFA)至60%乙腈/水(0.1%TFA),合并适当的产物馏分,冷冻干燥,得到标题化合物(80 mg, 0.12 mmol),为一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.76 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.70 (s, 1H), 7.62 (dd, 1H), 7.10 (m, 2H), 6.90 (d, 1H), 6.05 (dt, 1H), 4.80 (s, 2H), 3.77 (m, 4H), 3.50 (m, 2H), 3.37 (m, 2H)。ESI MS, $[M+H]^+$=414, 416 (Cl花样)。分析值 $C_{20}H_{20}ClN_5OS\cdot 2.0TFA\cdot 1.1H_2O$ C, H, N.

实施例276

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丁-2-(E)-烯基]-哌嗪-2-酮二三氟乙酸盐

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.70 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.68 (s, 1H), 7.61 (d, 1H), 7.10 (m, 2H), 5.88 (t, 1H), 4.79 (s, 2H), 3.75 (m, 4H), 3.49 (m, 2H), 3.29 (m, 2H), 2.09 (s, 3H)。EI MS, $[M+H]^+$=427, 429 (Cl花样)。

实施例277

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-2-甲基-(E)-烯丙基]-哌嗪-2-酮二三氟乙酸盐

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.80 (bs, 2H), 8.85 (s, 1H), 8.41 (d, 1H), 7.70 (s, 1H), 7.68 (d, 1 H), 7.06 (d, 1H), 7.05 (d,

1 H), 6.70 (bs, 1H), 4.80 (s, 2H), 4.30 (bs, 2H), 3.45 (m, 4H), 3.10 (m, 2H), 1.99 (s, 3H)。ESI MS, $[M+H]^+$=428, 430 (Cl花样)。

实施例278

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-呋喃-2-基)-(E)-烯丙基]-哌嗪-2-酮

向1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮(50 mg, 0.20 mmol)(实施例72)的3 mL的乙腈溶液中加入3-(4-溴-呋喃-2-基)-(E)-丙烯醛(43 mg, 0.22 mmol)(如实施例18所述制备), 2滴HOAc, 三乙酰氧基硼氢化钠(62 mg, 0.29 mmol)。将溶液在室温下搅拌16小时。此后, 将溶液用水/乙腈稀释。粗品产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至80%乙腈/水(0.1 %TFA), 合并适当的产物馏分, 冷冻干燥, 得到标题化合物(48 mg, 0.07 mmol), 为一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.75 (bs, 2H), 8.85 (s, 1H), 8.60 (d, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1 H), 6.80 (s, 1H), 6.65 (d, 1 H), 6.19 (dt, 1H), 4.80 (s, 2H), 3.70 (m, 4H), 3.50 (m, 2H), 3.28 (m, 2H)。ESI MS, $[M+H]^+$=441,443 (Br花样)。

实施例279

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(6-甲氧基-吡啶-3-基)-(E)-烯丙基]-哌嗪-2-酮

将氮气(g)鼓泡通过1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮(100 mg, 0.39 mmol)(实施例72)的2 mL的乙腈溶液。5分钟后, 向溶液中加入乙酸3-(6-甲氧基-吡啶-3-基)-(E)-烯丙基酯(75 mg, 0.36 mmol, 如实施例19所述制备)的2 mL的乙腈溶液, 乙酸钯(II)(催化量), 三苯膦(催化量), 2mL的水, 0.5 mL的三乙胺。将混合物在80℃下加热搅拌1小时。此时, 将混合物冷却, 过滤并真空浓缩。粗品产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1 %TFA)至60%乙腈/

水(0.1 %TFA)，合并适当的产物馏分，冷冻干燥，得到标题化合物(44 mg，0.07 mmol)，为一种白色固体。

^{1}H NMR (DMSO-d_6，300 MHz) δ 9.86 (s，1 H)，9.79 (s，1 H)，8.83 (s，1 H)，8.40 (d，1 H)，8.25 (s，1 H)，7.95 (d，1H)，7.75 (s，1H)，7.63 (d，1H)，6.86 (d，1H)，6.82 (d，1H)，6.32 (dt，1H)，4.78 (s，2H)，3.98 (s，2H)，3.93 (m，2H)，3.85 (s，3H)，3.53 (m，4H)。ESI MS，$[M+H]^+$=405。

实施例280

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-(E)-烯丙基-4-氧基-哌嗪-2-酮

向1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-(E)-烯丙基]-哌嗪-2-酮二三氟乙酸盐(0.60 g，0.94 mmol)(实施例275所述制备)的25 mL的二氯甲烷溶液中加入间氯过氧苯甲酸(0.30 g，0.96 mmol，55%纯度)。将混合物在室温下搅拌3小时，然后，真空浓缩。粗品产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1 %TFA)至60%乙腈/水(0.1 %TFA)，合并适当的产物馏分，冷冻干燥，得到标题化合物(0.5 mg，0.76 mmol)，为一种白色固体。^{1}H NMR (DMSO-d_6，300 MHz) δ 9.68 (bs，2H)，8.79 (s，1 H)，8.39 (d，1 H)，7.68 (s，1 H)，7.60 (d，1 H)，7.17 (d，1H)，7.12 (d，1 H)，7.06 (d，1 H)，6.17 (dt，1H)，4.84 (s，2H)，4.53 (m，2H)，4.50 (AB，2H)，4.04 (m，2H)，3.78 (m，1H)，3.60 (m，1H)。ESI MS，$[M+H]^+$=430，432 (Cl花样)。分析值($C_{20}H_{20}ClN_5O_2S\cdot 2.0TFA\cdot 1.4H_2O$) C，H，N。

实施例281

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙-2-炔基]哌嗪-2-酮

此标题化合物按照实施例275所述制备，采用2-(3-溴-丙-1-炔基)-5-氯-噻吩(如实施例20所述制备)代替2-(3-溴-(E)丙烯基)-5-氯

-噻吩。粗品产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1%TFA)至70%乙腈/水(0.1%TFA)，合并适当的产物馏分，冷冻干燥，得到标题化合物，为一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1 H), 8.38 (d, 1 H), 7.63 (d, 1 H), 7.58 (s, 1 H), 7.25 (d, 1H), 7.13 (d, 1H), 4.74 (s, 2H), 3.74 (s, 2H), 3.32 (m, 4H), 2.85 (m, 2H)。ESI MS, $[M+H]^+$=412, 414 (Cl花样)。

实施例282

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙基]哌嗪-2-酮

此标题化合物按照实施例278所述制备，采用3-(5-氯-噻吩-2-基)-丙醛(实施例28，部分A)代替3-(4-溴-呋喃-2-基)-(E)-丙烯醛。粗品产物用RP-HPLC纯化，进行梯度洗脱：10%乙腈/水(0.1%TFA)至60%乙腈/水(0.1%TFA)，合并适当的产物馏分，冷冻干燥，得到标题化合物，为一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1 H), 8.39 (d, 1 H), 7.71 (s, 1 H), 7.60 (d, 1 H), 6.95 (d, 1H), 6.77 (d, 1H), 4.78 (s, 2H), 3.88 (m, 2H), 3.50 (m, 2H), 3.42 (m, 2H), 3.05 (m, 2H), 2.80 (t, 2H), 1.96 (m, 2H)。ESI MS, $[M+H]^+$=416, 418 (Cl花样)。

实施例283

1-(4-氨基-喹唑啉-7-基甲基)-4-丙-2-炔基-哌嗪-2-酮

A. 1-(4-氨基-喹唑啉-7-基甲基)-4-丙-2-炔基-哌嗪-2-酮

在室温下，将炔丙基溴(0.29 g, 1.95 mmol)加至包含1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮(0.5 g, 1.95 mmol)(实施例72)和碳酸钾(0.40 g, 2.93 mmol)的DMSO(10 mL)溶液中。15分钟后，将反应混合物在碳酸氢钠水溶液(100 mL)与二氯甲烷(100 mL)间分配。分层。水相用氯化钠饱和，并用氯仿(50 mL)萃取三次。合并的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。将残余物进行快速硅胶色谱

纯化(二氯甲烷-10%甲醇/二氯甲烷)，得到390 mg (68%)的标题化合物，为一种白色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (m, 1H), 3.13-3.37 (m, 6H), 4.07 (app q, J =5.2 Hz, 1 H), 4.63 (s, 2H), 7.28 (dd, J =8.4, 1.4 Hz, 1H), 7.42 (s, 1H), 7.72 (br s, 2H), 8.14 (d, J =8.4 Hz, 1 H), 8.34 (s, 1H) ppm; MS (ISP周线): m/z 296 (M+H)。

实施例284

1-(4-氨基-喹唑啉-7-基甲基)-4-(3-联苯基-2-基-丙-2-炔基)-哌嗪-2-酮

将包含1-(4-氨基-喹唑啉-7-基甲基)-4-丙-2-炔基-哌嗪-2-酮(50 mg, 0.17 mmol)(实施例283)，2-溴联苯(44 mg, 0.19 mmol)，三乙胺(69 mg, 0.68 mmol)，$(Ph_3P)_4PdCl_2$ (6 mg, 0.008 mmol)，碘化铜(1 mg, 0.005 mmol)的无水DMF (2 mL)溶液在80℃下加热搅拌1小时。将反应混合物冷却至50℃，在氮气氛下于16小时内除去溶剂。将粗品残余物进行快速硅胶色谱纯化(二氯甲烷-10%甲醇 二氯甲烷)，得到一种无色的胶状物，将其与乙醇研制，得到4 mg (5%)的标题化合物，为一种白色固体。^{1}H NMR (300 MHz, d_6-DMSO) δ 3.03 (s, 2H), 3.14 (m, 2H), 3.31 (m, 2H), 3.50 (s, 2H), 7.21-7.55 (m, 11 H), 7.76 (br s, 2H), 8.18 (d, J =8.6 Hz, 1H), 8.36 (s, 1H) ppm; MS (离子喷雾): m/z 448 (M+H)。

实施例285

1-(4-氨基-喹唑啉-7-基甲基)-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. (3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-丙-1-炔基}-吡啶-4-基)-氨基甲酸叔丁酯

在室温下，将包含1-(4-氨基-喹唑啉-7-基甲基)-4-丙-2-炔基-哌嗪-2-酮(100 mg, 0.34 mmol)(实施例283)，(3-碘-吡啶-4-基)-氨

基甲酸叔丁酯(实施例69, 部分B)(108 mg, 0.34 mmol), 三乙胺(140 mg, 1.36 mmol), $(Ph_3P)_4PdCl_2$ (12 mg, 0.017 mmol), 碘化铜(2 mg, 0.01 mmol)的无水DMF (5 mL)溶液进行搅拌。5小时后, 将反应混合物用乙酸乙酯(50 mL)和水(50 mL)稀释, 分层。水层用用乙酸乙酯(25 mL)萃取两次, 合并后的有机相用盐水洗涤, 用无水硫酸钠干燥, 过滤并浓缩。粗品残余物进行快速硅胶色谱纯化(二氯甲烷-10%甲醇 二氯甲烷), 得到59 mg (36%)的标题化合物, 为一种无色油。^{1}H NMR (300 MHz, $CDCl_3$) δ1.49 (s, 9H), 2.84 (m, 2H), 3.35 (m, 2H), 3.44 (s, 2H), 3.71 (s, 2H), 4.75 (s, 2H), 6.19 (br s, 2H), 7.24 (d, J =5.5 Hz, 1 H), 7.41 (d, J =8.4 Hz, 1H), 7.66 (s, 1H), 7.79 (d, J =8.4 Hz, 1H), 8.05 (d, J =5.5 Hz, 1 H), 8.37 (s, 1H), 8.49 (s, 1 H), 8.58 (s, 1H) ppm; MS (ISP周线): m/z 488 (M+H)。

B. 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1甲酸叔丁酯

将1,8-二氮杂二环[5.4.0]十一碳-7-烯(37 mg, 0.24 mmol)加至包含(3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-丙-1-炔基}-吡啶-4-基)-氨基甲酸叔丁酯(59 mg, 0.12 mmol)的无水乙腈(5 mL)悬浮液中, 将混合物升温至50℃。加入二甲基甲酰胺(1 mL)以增溶, 将均匀的溶液在50℃下保持5小时, 将反应混合物用乙酸乙酯(50 mL)和水(50 mL)稀释, 分层。水层用乙酸乙酯(25 mL)萃取两次, 合并后的有机相用盐水洗涤, 用无水硫酸钠干燥, 过滤并浓缩, 得到50 mg的产物, 为一种粗品固体, 其不经进一步纯化即可直接使用。^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 9H), 2.78 (m, 2H), 3.30 (m, 2H), 3.37 (s, 2H), 3.95 (s, 2H), 4.74 (s, 2H), 6.24 (br s, 2H), 6.63 (s, 1 H), 7.40 (dd, J =8.5, 1.6 Hz, 1 H), 7.64 (s, 1 H), 7.81 (d, J =5.8 Hz, 1 H), 7.83 (d, J =8.5 Hz, 1 H), 7.99 (s, 1H), 8.39 (d, J =5.8 Hz, 1H), 8.58 (s, 1H), 8.77 (s, 1H) ppm。

C. 1-(4-氨基-喹唑啉-7-基甲基)-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

在室温下，向包含2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(50 mg, 0.12 mmol)的二氯甲烷(5 mL)溶液中加入TFA (1 mL)。16小时后，将反应混合物浓缩至干，用水稀释，通过反相HPLC纯化[缓冲液A: 水w/0.1 %TFA; 缓冲液B: 乙腈 w/0.1 %TFA; 梯度: 0%B至45%B, 30分钟内]，得到34 mg (73%, 两步)的标题化合物，为一种白色冻干的固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (s, 3H), 3.23 (s, 2H), 3.31 (m, 2H), 3.89 (s, 2H), 4.00 (br s, 3H), 4.71 (s, 2H), 6.94 (s, 1H), 7.60 (m, 2H), 7.84 (d, J =6.5 Hz, 1H), 8.36 (m, 2H), 8.81 (s, 1H), 9.18 (s, 1 H), 9.73 (br s, 2H), 12.87 (s, 1 H) ppm; MS (离子喷雾): m/z 388 (M+H)。

采用如上所述方法，由实施例72的化合物制备下述化合物。

实施例	名称	m/z (M+H)
286	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基氧基)-乙基]-哌嗪-2-酮	418, 420 Cl花样
287	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1-甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮	435, 437 Cl花样
288	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-烯丙基]-哌嗪-2-酮	414, 416 Cl花样
289	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(6-氯-苯并[b]噻吩-2-基)-烯丙基]-哌嗪-2-酮	464, 466 Cl花样
290	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-4-甲基-噻吩-2-基)-烯丙基]-哌嗪-2-酮	428, 430 Cl花样
291	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并呋喃-2-基甲基)-哌嗪-2-酮	422, 424 Cl花样

292	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1H-吲哚-5-基甲基)-哌嗪-2-酮	421, 423 Cl花样
293	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-5-基甲基)-哌嗪-2-酮	421, 423 Cl花样
294	1-(4-氨基-喹唑啉-7-基甲基)-4-(5, 7-二氯-1H-吲哚-2-基甲基)-哌嗪-2-酮	455, 457 Cl花样
295	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮	421, 423 Cl花样
296	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-对甲苯基-丙-2-炔基)-哌嗪-2-酮	386
297	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-间甲苯基-丙-2-炔基)-哌嗪-2-酮	386
298	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-丙-2-炔基]-哌嗪-2-酮	406, 408 Cl花样
299	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-丙-2-炔基]-哌嗪-2-酮	406, 408 Cl花样
300	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(2-氯-苯基)-丙-2-炔基]-哌嗪-2-酮	406
301	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-联苯基-4-基-丙-2-炔基)-哌嗪-2-酮	448
302	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4, 5-二溴-噻吩-2-基)-烯丙基]-哌嗪-2-酮	536, 538, 540 OBr_2花样
303	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-联苯基-3-基-丙-2-炔基)-哌嗪-2-酮	448
304	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(2, 5-二氯-噻吩-3-基)-丙-2-炔基]-哌嗪-2-酮	446, 448 Cl花样
305	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-丙基]-哌嗪-2-酮	410, 412 Cl花样
306	1, 4-二-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮	415

307	1-(4-氨基-喹唑啉-7-基甲基)-4-(1H-吡咯并[2,3-c]吡啶-2-基甲基)-哌嗪-2-酮	388
308	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-硝基-噻吩-2-基)-烯丙基]-哌嗪-2-酮	425
309	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(6-氯-吡啶-3-基)-烯丙基]-哌嗪-2-酮	409,411 Cl花样
310	1-(4-氨基-喹唑啉-7-基甲基)-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	388
311	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-3-基)-烯丙基]-哌嗪-2-酮	414,416 Cl花样
312	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-溴-呋喃-2-基)-烯丙基]-哌嗪-2-酮	442,444 Br花样
313	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-甲基-噻吩-2-基)-戊-2,4-二烯]-哌嗪-2-酮	420
314	1-(4-氨基-喹唑啉-7-基甲基)-4-(2-氯-苯并[b]噻吩-5-基甲基)-哌嗪-2-酮	438,440 Cl花样
315	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-甲基-噻吩-2-基)-烯丙基]-哌嗪-2-酮	394
316	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-甲氧基-噻吩-2-基)-烯丙基]-哌嗪-2-酮	410
317	4-(1-氨基-7-氯-异喹啉-3-基甲基)-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮	448,450 Cl花样
318	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-N-(5-氯-噻吩-2-基)-乙酰胺	431
319	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-哌嗪-2-酮	433,435 Cl花样
320	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(3-氯-苯基)-2-(S)-羟基-乙基]-哌嗪-2-酮	412,414 Cl花样

321	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(3-氯-苯基硫烷基)-乙基]-哌嗪-2-酮	428, 430 Cl花样
322	1-(4-氨基-喹唑啉-7-基甲基)-4-(2-亚甲基-1, 1-二氧代-2, 3-二氢-1H-1, 6-苯并[b]噻吩-3-基)-哌嗪-2-酮	470
323	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-硝基-苯基)-烯丙基]哌嗪-2-酮	419
324	1-(4-氨基-喹唑啉-7-基甲基)-4-(2-氯-苯并[b]噻吩-6-基甲基)-哌嗪-2-酮	438, 440 Cl花样
325	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-N-(4-氯-苯基)-乙酰胺	425, 427 Cl花样
326	1-(4-氨基-喹唑啉-7-基甲基)-4-[1-(4-氯苯基)-吡咯烷-3-基]-哌嗪-2-酮	437, 439 Cl花样
327	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙基]-哌嗪-2-酮	402, 404 Cl花样
328	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-丙基]-哌嗪-2-酮	410, 412 Cl花样
329	2-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-3-(4-氯苯基)-丙烯酸	452, 454 Cl花样
330	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-1-羟基-异喹啉-3-基甲基)-哌嗪-2-酮	449, 451 Cl花样
331	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-萘-2-花样基甲基)-哌嗪-2-酮	432, 434 Cl花样
332	1-(4-氨基-喹唑啉-7-基甲基)-4-异喹啉-3-基甲基-哌嗪-2-酮	399
333	1-(4-氨基-喹唑啉-7-基甲基)-4-[1-(3-氯-苯基)-吡咯烷基-3-基]-哌嗪-2-酮	437, 439 Cl花样
334	1-(4-氨基-喹唑啉-7-基甲基)-4-(1, 7-二氯-异喹啉-3-基甲基)-哌嗪-2-酮	467, 469 Cl花样

335	4-(2-氨基-7-氯-喹啉-3-基甲基)-4-(1,7-二氯-异喹啉-3-基甲基)-哌嗪-2-酮	448,450 Cl花样
336	1-(4-氨基喹唑啉-7-基甲基)-4-(5-氯-苯并[b]噻吩-2-基甲基)哌嗪-2-酮	438,440 Cl花样
337	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(4-氯-苯基硫烷基)-乙基]-哌嗪-2-酮	428,430 Cl花样
338	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(6-氯-苯并[b]噻吩-2-基)-乙基]-哌嗪-2-酮	452,454 Cl花样
339	1-(4-氨基喹唑啉-7-基甲基)-4-[2-(4-氯-苯氧基)-乙基]-哌嗪-2-酮	412,414 Cl花样
340	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-6-氯-4H-苯并[1,4]噻嗪-3-酮	469,471 Cl花样
341	1-(4-氨基-喹唑啉-7-基甲基)-4-(2,7-二氯-喹啉-3-基甲基)-哌嗪-2-酮	467,469 Cl_2花样
342	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-(4-氯-苯基)-甲基]-丙烯酸乙酯	480,482 Cl花样
343	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-3-(4-氯-苯基)-丙烯酸乙酯	480,482 Cl花样
344	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-烯丙基]哌嗪-2-酮	408,410 Cl花样
345	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-烯丙基]-哌嗪-2-酮	408,410 Cl花样
346	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-溴-噻吩-2-基)-烯丙基]-哌嗪-2-酮	458,460 Br花样
347	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-烯丙基]-哌嗪-2-酮	458,460 Br花样
348	3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-7-氟-1H-喹啉-2-酮	433

349	3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-6-氯-1H-喹喔啉-2-酮	450, 452 Cl花样
350	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1-甲基-1H-苯并咪唑-2-基甲基)-哌嗪-2-酮	436, 438 Cl花样
351	1-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-6-氯-3H-喹唑啉-4-酮	492, 494 Cl花样
352	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-噻吩-2-基-丙基)-哌嗪-2-酮	382
353	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-喹啉-3-基甲基)-哌嗪-2-酮	432, 434 Cl花样
354	3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5, 7-二氯-1H-喹啉-2-酮	483, 485 Cl花样
355	1-(4-氨基-喹唑啉-7-基甲基)-4-(6, 7-二氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	472, 474 Cl_2花样
356	3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-1H-喹啉-2-酮	449, 451 Cl花样
357	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-[2, 3']联噻吩-5'-基甲基)-哌嗪-2-酮	470, 472 Cl花样
358	4-(6-氨基-苯并[b]噻吩-2-基甲基)-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮	419
359	1-(4-氨基-喹唑啉-7-基甲基)-4-(2-氯-喹啉-6-基甲基)-哌嗪-2-酮	433, 435 Cl花样
360	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-溴-1H-苯并咪唑-2-基甲基)-哌嗪-2-酮	466, 468 Br花样
361	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-硝基-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	449
362	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(3-氯-苯基)-噻吩-2-基甲基]-哌嗪-2-酮	464, 466 Cl花样

363	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-3-甲氧基-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	468, 470 Cl花样
364	3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-6-氯-1H-喹啉-2-酮	449, 451 Cl花样
365	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-三氟甲基-1H-苯并咪唑-2-基甲基)-哌嗪-2-酮	456
366	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-甲基-[2, 2']联噻吩-5-基甲基)-哌嗪-2-酮	450
367	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-甲基-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	418
368	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-3, 3'-二甲基-[2, 2']联噻吩-5-基甲基)-哌嗪-2-酮	498, 500 Cl花样
369	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3, 5-二溴-4-甲氧基-苯基)-[1, 2, 4]噁二唑-5-基甲基]-哌嗪-2-酮	602, 604, 606 Br_2花样
370	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-甲基-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	418
371	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-甲基-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	418
372	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	438, 440 Cl花样
373	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-3'-甲基-[2, 2']联噻吩-5-基甲基)-哌嗪-2-酮	484, 486 Cl花样
374	1-(4-氨基-喹唑啉-7-基甲基)-4-(1H-苯并咪唑-2-基甲基)-哌嗪-2-酮	388
375	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-溴-[2, 2']联噻吩-5-基甲基)-哌嗪-2-酮	514, 516 Br花样

376	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(2,3-二氢-苯并[1,4]二噁英-6-基)-噁唑-2-基甲基]-哌嗪-2-酮	473
377	1-(4-氨基-喹唑啉-7-基甲基)-4-(5,6-二氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	472,474 Cl花样
378	1-(4-氨基-喹唑啉-7-基甲基)-4-(4,5-二氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	472,474 Cl花样
379	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并噁唑-2-基甲基)-哌嗪-2-酮	423,425 Cl花样
380	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-5-氟-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	456,458 Cl花样
381	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-氯-5-氟-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	456,458 Cl花样
382	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-3-甲基-[2,2']联噻吩-5-基甲基)-哌嗪-2-酮	484,486 Cl花样
383	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-噻吩并[3,2-b]吡啶-2-基甲基)-哌嗪-2-酮	439,441 Cl花样
384	1-(4-氨基-喹唑啉-7-基甲基)-4-(5,6-二氯-1H-苯并咪唑-2-基甲基)-哌嗪-2-酮	456
385	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-苯并噁唑-2-基-苄基)-哌嗪-2-酮	464
386	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(4-氯-苯基)-噻吩-2-基甲基]-哌嗪-2-酮	464,466 Cl花样
387	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-甲基-1H-苯并咪唑-2-基甲基)-哌嗪-2-酮	402
388	1-(4-氨基-喹唑啉-7-基甲基)-4-[2,2']联噻吩-5-基甲基-哌嗪-2-酮	435
389	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-氟-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	422

390	1-(4-氨基喹唑啉-7-基甲基)-4-(6-氟-苯并[b]噻吩-2-基甲基)哌嗪-2-酮	422
391	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(1-甲基-5-三氟-甲基-1H-吡唑-3-基)-噻吩-2-基甲基]-哌嗪-2-酮	501
392	1-(4-氨基-喹唑啉-7-基甲基)-4-(3,4-二甲基-噻吩并[2,3-b]噻吩-2-基甲基)-哌嗪-2-酮	438
393	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-氯-3-甲基-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	452,454 Cl花样
394	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-3-甲基-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	452,454 Cl花样
395	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(2-甲基-5-三氟甲基-2H-吡唑-3-基)噻吩-2-基甲基]哌嗪-2-酮	502
396	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(3-硝基-苯基)-呋喃-2-基甲基]-哌嗪-2-酮	459
397	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-噻吩并[3,2-b]吡啶-6-基甲基)-哌嗪-2-酮	439,441 Cl花样
398	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(4-甲氧基-苯基)-噻吩-2-基甲基]-哌嗪-2-酮	460
399	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-羟基-2-吡啶-2-基-嘧啶-5-基甲基)-哌嗪-2-酮	443
400	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯氧基)-苄基]-哌嗪-2-酮	458
401	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(4-氯-苯基)-噻唑-4-基甲基]-哌嗪-2-酮	465,467 Cl花样
402	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-溴-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	482,484 Br花样

403	1-(4-氨基-喹唑啉-7-基甲基)-4-苯并[b]噻吩-2-基甲基-哌嗪-2-酮	404
404	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩-5-基甲基)-哌嗪-2-酮	470,472 Cl花样
405	1-(4-氨基-喹唑啉-7-基甲基)-4-(3,5-二-三氟甲基-苄基)-哌嗪-2-酮	488
406	1-(4-氨基-喹唑啉-7-基甲基)-4-联苯基-4-基甲基-哌嗪-2-酮	423(M+)
407	1-(4-氨基-喹唑啉-7-基甲基)-4-萘-2-基甲基-哌嗪-2-酮	397(M+)
408	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并[b]噻吩-3-基甲基)-哌嗪-2-酮	438,440 Cl花样
409	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-噻吩并[2,3-b]吡啶-2-基甲基)-哌嗪-2-酮	438,440 Cl花样

实施例410

1-(4-氨基喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]哌嗪-2-酮

此标题化合物按照实施例123所述制备，采用1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮二盐酸盐(实施例72)代替4-(2氧代哌嗪-1-基甲基)苯甲脒二三氟乙酸盐。^{1}H NMR (d6-DMSO, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1H), 8.40 (dd, 1 H), 7.68 (d, 1H), 7.65 (s, 1H), 7.58 (d, 2H), 7.15 (d, 2H), 4.80 (s, 2H), 4.33,4.15 (m, 2H, 旋转异构体), 3.70 (m, 2H), 3.49 (m, 2H)。ESI MS, $[M+H]^+$=456, 458 (Br花样)。

采用上述方法，由实施例72的化合物制备下述化合物。

实施例	名称	m/z [M+H]

411	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-氯-噻吩-2-羰基)-哌嗪-2-酮	402, 404 Cl花样
412	4-[3-(3-氨基-4-氯-苯基)-(E)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮	437, 439 Cl花样
413	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1H-吲哚-6-羰基)-哌嗪-2-酮	435, 437 Cl花样
414	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]哌嗪-2-酮	432, 434 Cl花样
415	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-溴-噻吩-2-基)-(E)-丙烯酰基]哌嗪-2-酮	472, 474Br 花样
416	5-氯-噻吩-2-甲酸{2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-2-氧代-乙基}-酰胺	459, 461 Cl花样
417	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-(E)-丙烯酰基]-哌嗪-2-酮	428, 430 Cl花样
418	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-氯-1H-吲哚-2-羰基)-哌嗪-2-酮	435, 437 Cl花样
419	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(6-氯-苯并[b]噻吩-2-基)-(E)-丙烯酰基]-哌嗪-2-酮	478, 480 Cl花样
420	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-(E)-丙烯酰基]-哌嗪-2-酮	472, 474 Br花样
421	5-氯-噻吩-2-甲酸{2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-1-甲基-2-氧代-乙基}-酰胺	473, 475 Cl花样
422	5-氯-噻吩-2-甲酸{3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-3-氧代-丙基}-酰胺	473, 475 Cl花样
423	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯氧基)-乙酰基]-哌嗪-2-酮	426, 428 Cl花样
424	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-2-甲基-苯氧基)-乙酰基]-哌嗪-2-酮	440, 442 Cl花样

425	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩-5-羰基)-哌嗪-2-酮	484,486 Cl花样
426	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙酰基]-哌嗪-2-酮	430,432 Cl花样
427	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-(E)-丙烯酰基]-哌嗪-2-酮	422,424 Cl花样
428	N-[2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-1-(5-氯-噻吩-2-基甲基)-2-氧代-乙基]-苯甲酰胺	428,430 Cl花样
429	N-[1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-花样羰基]-2-(5-氯-噻吩-2-基)-乙烯基]-苯甲酰胺	549,550 Cl花样
430	N-[1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-花样羰基]-2-(5-氯-噻吩-2-基)-乙烯基]-乙酰胺	485,487 Cl花样
431	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-(E)-丙烯酰基]-哌嗪-2-酮	422,424 Cl花样
432	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基)-乙酰基]-哌嗪-2-酮	415,417 Cl花样
433	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-哌嗪-2-酮	451,453 Cl花样
434	2[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-羰基]-6-氯-4H-苯并[1,4]噻嗪-3-酮	483,485 Cl花样
435	1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-苯并[b]噻吩-2-基)-乙酰基]-哌嗪-2-酮	466,468 Cl花样

实施例436

4-(4-氨基喹唑啉-7-基甲基)-3-氧代哌嗪-1-甲酸4-氯苄基酰胺

向1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮(25 mg, 0.097

mmol)(实施例72)的1 mL的DMF溶液中加入4-氯-苄基异氰酸酯(22 mg, 0.13 mmol, 如实施例37所述制备)。在室温下搅拌1小时后, 将溶液浓缩。粗品产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至80%乙腈/水(0.1%TFA), 合并适当的产物馏分, 冷冻干燥, 得到标题化合物(36 mg, 0.067 mmol), 为一种白色固体。^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.76 (bs, 2H), 8.83 (s, 1H), 8.38 (d, 1H), 7.64 (d, 1H), 7.60 (s, 1 H), 7.34 (d, 2H), 7.31 (m, 1 H), 7.26 (d, 2H), 4.75 (s, 2H), 4.22 (d, 2H), 4.08 (s, 2H), 3.60 (m, 2H), 3.35 (m, 2H)。ESI MS, $[M+H]^+$=425, 427 (Cl花样)。

实施例437

4-(4-氨基喹唑啉-7-基甲基)-3-氧代哌嗪-1-甲酸(5-氯-噻吩-2-基甲基)酰胺

向(5-氯-噻吩-2-基)-乙酸(0.18 g, 1.04 mmol)(如实施例27所述制备)的6 mL的无水二氯甲烷溶液中加入三乙胺(0.15 mL g, 1.04 mmol), 二苯基磷酰基叠氮化物(0.24 mL, 1.04 mmol)。将混合物在室温下搅拌2.5小时后, 在50℃下加热搅拌2小时。向溶液中加入1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮(0.10 g, 0.41 mmol)(实施例72), 三乙胺(0.15 mL g, 1.04 mmol), 将混合物在50℃下加热搅拌2小时后, 在室温下搅拌16小时。将所得混合物浓缩。粗品产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至60%乙腈/水(0.1%TFA), 合并适当的产物馏分, 冷冻干燥, 得到标题化合物(10 mg, 0.02 mmol), 为一种白色固体。^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.69 (bs, 2H), 8.80 (s, 1 H), 8.48 (d, 1 H), 7.61 (d, 1 H), 7.60 (s, 1 H), 7.41 (t, 1 H), 6.90 (d, 1 H), 6.80 (d, 1 H), 4.77 (d, 2H), 4.30 (d, 2H), 4.10 (s, 2H), 3.61 (m, 2H), 3.38 (m, 2H)。ESI MS, $[M+H]^+$=431, 433 (Cl花样)。

实施例438

4-(4-氨基喹唑啉-7-基甲基)-3-氧代哌嗪-1-甲酸(5-氯-噻吩-2-基)酰胺

将5-氯-噻吩-2-羰基叠氮化物(55 mg, 0.29 mmol, 如实施例38所述制备), 1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮(50 mg, 0.20 mmol)(实施例72)的3 mL的无水甲苯溶液在105℃下加热1小时。将所得混合物真空浓缩。粗品产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至60%乙腈/水(0.1%TFA), 合并适当的产物馏分, 冷冻干燥, 得到标题化合物(35 mg, 0.02 mmol), 为一种白色固体。^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.04 (s, 1 H), 9.71 (bs, 2H), 8.81 (s, 1 H), 8.38 (dd, 1 H), 7.64 (d, 1 H), 7.61 (s, 1 H), 6.77 (d, 1 H), 6.42 (d, 1 H), 4.76 (s, 2H), 4.21 (s, 2H), 3.73 (m, 2H), 3.40 (m, 2H)。ESI MS, $[M+H]^+$=417, 419 (Cl花样)。

采用上述方法, 由实施例72的化合物制备下述化合物。

实施例	名称	m/z [M+H]
439	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸(4-氯-噻吩-2-基)-酰胺	417, 419 Cl花样
440	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸(5-溴-噻吩-2-基)-酰胺	461, 463 Br花样
441	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸(3-氨基-4-氯-苯基)-酰胺	426, 428 Cl花样
442	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸(4-溴-苯基)-酰胺	455, 457 Br花样
443	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	411, 413 Cl花样
444	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸(4-甲氧基-苯基)-酰胺	407
445	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸(3, 4-二氯-苯基)-酰胺	445, 447 Cl_2花样

实施例446

4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸5-氯-噻吩-2-基甲酯

向5-氯-2-噻吩-甲醇(0.10 g, 0.67 mmol, 通过$NaBH_4$ 还原5-氯-2-噻吩-甲醛制得)的6 mL的二氯甲烷溶液中加入1,1'-羰基二咪唑(0.11 g, 0.67 mmol)。将混合物在室温下搅拌3小时。然后, 向溶液中加入1-(4-氨基喹唑啉-7-基甲基)哌嗪-2-酮(0.17 g, 0.67 mmol, 实施例72), 催化剂量的DMAP , 并将所得混合物在35℃下加热18小时。将混合物溶解于水/甲醇中, 粗品产物用RP-HPLC纯化, 进行梯度洗脱: 10%乙腈/水(0.1%TFA)至100%乙腈.合并适当的馏分, 冷冻干燥, 得到标题化合物, 为一种白色固体。ESI MS, $[M+H]^+$=432,434 (Cl花样)。

采用上述方法, 由实施例72的化合物制备下述化合物。

实施例	名称	m/z [M+H]
447	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸6-氯-苯并噁唑-2-基甲基酯	467,469 Cl花样
448	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-甲酸1-(3-氯-苯基)-吡咯烷-3-基酯	481,483 Cl花样

实施例449

1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲基-哌嗪-2-酮

向1-(4-氨基-喹唑啉-7-基甲基)-3-甲基-哌嗪-2-酮(实施例80)(0.06g, 0.2mmol)的2 mL的DMF溶液中加入3-溴甲基-7-氯异喹啉基(实施例11, 0.052g, 0.20mmol)和碳酸钾(0.08 g, 0.06 mmol)。16小时后, 将反应混合物浓缩至干。粗品产物用RP-HPLC纯化, 进行梯度洗脱: 5%乙腈/水(0.1%TFA)至50%乙腈/水(0.1%TFA)。将产物馏分

冷冻干燥，得到标题化合物，为一种三三氟乙酸盐(0.06g，0.08 mmol)，为一种白色固体。^{1}H NMR (d_6-DMSO，300 MHz) δ 9.79 (bs，2H)，9.40 (s，1 H)，8.73 (s，1 H)，8.33 (d，1H)，8.25 (s，1 H)，8.06 (s，1H)，8.00 (d，1H)，7.79 (d，1H)，7.60 (m，2H)，4.80 (AB，2H)，4.72 (AB，2H)，4.28 (m，1 H)，3.54 (m，4H)，1.96 (d，3H)。MS (离子喷雾) 447，449，(Cl花样)。元素分析$C_{28}H_{25}ClF_6N_6O_6\cdot 3CF_3CO_2H\cdot 0.28H_2O$，计算值 C=45.38%，H=3.35%，N=10.58%；实测值C=45.38%，H=3.35%，N=10.63%。

实施例450

4-(3-氯-1H-吲哚-6-基甲基)-3-(S)-甲基-哌嗪-2-酮

此标题化合物按照实施例274所述制备，采用1-(4-氨基-喹唑啉-7-基甲基)-3-甲基-哌嗪-2-酮(实施例80)。^{1}H NMR (DMSO-d_6，300 MHz) δ 9.79 (bs，2H)，8.82 (s，1 H)，8.39 (d，1 H)，7.61 (m，3H)，7.57 (d，1H)，7.52 (d，1 H)，7.49 (d，1H)，7.20 (d，1 H)，7.10 (d，1H)，4.75 (AB，2H)，4.57 (m，1H)，4.23 (m，1H)，3.97 (m，1H)，3.50 (m，3H)，1.65 (d，3H)。ESI MS，$[M+H]^+$=435，437 (Cl花样)。分析($C_{23}H_{23}ClN_6O\cdot 2.15TFA\cdot 0.25H_2O$) C，H，N。

采用上述方法，由实施例80的化合物制备下述化合物。

实施例	名称	m/z [M+H]
451	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-烯丙基]-3-(S)-甲基-哌嗪-2-酮	428，430 Cl花样
452	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(6-氯-苯并[b]噻吩-2-基)-烯丙基]-3-(S)-甲基-哌嗪-2-酮	478，480 Cl花样
453	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙基]-3-(S)-甲基-哌嗪-2-酮Cl(S)-甲基-哌嗪-2-酮	429，431 Cl花样

454	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3-(S)-甲基-哌嗪-2-酮	435, 437 Cl花样
455	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丁-2-烯基]-3-(S)-甲基-哌嗪-2-酮	442, 444 Cl花样
456	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2, 2']联噻吩-5-基甲基)-3-(S)-甲基-哌嗪-2-酮	483(M+) (EI)
457	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-苯并咪唑-2-基甲基)-3-(S)-甲基-哌嗪-2-酮	536, 538 Cl花样
458	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲基-哌嗪-2-酮	428, 430 Cl花样
459	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-萘-2-基甲基)-3-(S)-甲基-哌嗪-2-酮	446, 448 Cl花样
460	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-噻吩并[2, 3-b]吡啶-2-基甲基)-3-(S)-甲基-哌嗪-2-酮	453, 455 Cl花样
461	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3-(S)-甲基-哌嗪-2-酮	452, 454 Cl花样
462	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并[b]噻吩-2-基甲基)-3-(S)-甲基-哌嗪-2-酮	452, 454 Cl花样
463	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并[b]噻吩-2-基甲基)-3-(R)-甲基-哌嗪-2-酮	452, 454 Cl花样
464	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3-(R)-甲基-哌嗪-2-酮	452, 454 Cl花样

实施例465

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-(S)-甲基-哌嗪-2-酮

此标题化合物按照实施例123所述制备，采用1-(4-氨基-喹唑啉-7-基甲基)-3-甲基-哌嗪-2-酮(实施例80)，3-(4-氯-噻吩-2-基)-(E)-丙烯酸(实施例26)。^{1}H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H),

8.82 (s, 1 H), 8.40 (d, 1 H), 7.62 (m, 5H), 7.05 (d, 1 H), 4.92 (m, 1 H), 4.80 (m, 2H), 4.73 (m, 1 H), 4.50 (m, 1 H), 3.40 (m, 2H), 1.42 (m, 3H)。ESI MS, $[M+H]^+$=442,444 (Cl花样)。

采用上述方法，由实施例80的化合物制备下述化合物。

实施例	名称	m/z [M+H]
466	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-3-(S)-甲基-哌嗪-2-酮	446,448 Cl花样
467	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲基-哌嗪-2-酮	446,448 Cl花样
468	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-溴-噻吩-2-基)-丙烯酰基]-3-(S)-甲基-哌嗪-2-酮	486,488 Br花样
469	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1H-吲哚-6-羰基)-3-(S)-甲基-哌嗪-2-酮	449,451 Cl花样
470	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉基-3-羰基)-3-(S)-甲基-哌嗪-2-酮	461,463 Cl花样
471	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲基-哌嗪-2-酮	446,448 Cl花样
472	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-(S)-甲基-哌嗪-2-酮	486,488 Br花样
473	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯氧基)-乙酰基]-3-(S)-甲基-哌嗪-2-酮	440,442 Cl花样
474	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩-5-羰基)-3-(S)-甲基-哌嗪-2-酮	498,500 Cl花样
475	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丁-2-烯酰基]-3-(S)-甲基-哌嗪-2-酮	456,458 Cl花样
476	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-3-(S)-甲基-哌嗪-2-酮	466,468 Cl花样

477	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-甲基-哌嗪-2-酮	442,444 Cl花样

实施例478

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙基]-3-(S)乙基-哌嗪-2-酮

此标题化合物按照实施例278所述制备，采用1-(4-氨基喹唑啉-7-基甲基)-3-乙基-哌嗪-2-酮(实施例77)，3-(5-氯噻吩-2-基)-丙醛(实施例28)。^{1}H NMR (d_6-DMSO + 1滴TFA, 300 MHz) δ 9.80 (bs, 2H), 8.79 (s, 1 H), 8.32 (d, 1 H), 7.58 (m, 2H), 6.88 (d, 1 H), 6.70 (d, 1 H), 4.72 (AB, 2H), 4.00 (m, 1H), 3.72 (m, 1H), 3.48 (m, 2H), 3.23 (m, 3H), 2.72 (m, 2H), 1.96 (m, 4H), 0.98 (m, 3H)。MS (离子喷雾), m/z, (M+H) =444, 446 (Cl花样)。

采用上述方法，由实施例77的化合物制备下述化合物。

实施例	名称	m/z [M+H]
479	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-烯丙基]-3-(S)-乙基-哌嗪-2-酮	442,444 Cl花样
480	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丁-2-烯基]-3-(S)-乙基-哌嗪-2-酮	456,458 Cl花样
481	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3-(S)-乙基-哌嗪-2-酮	461,463 Cl花样
482	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-乙基-哌嗪-2-酮	442,444 Cl花样
483	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-萘-2-花样基甲基)-3-(S)-乙基-哌嗪-2-酮	460,462 Cl花样

484	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3-(S)-乙基-哌嗪-2-酮	466,468 Cl花样
485	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-噻吩并[2,3-b]吡啶-2-基甲基)-3-(S)-乙基-哌嗪-2-酮	467,469 Cl花样

实施例486

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-乙基-哌嗪-2-酮

此标题化合物按照实施例123所述制备，采用1-(4-氨基喹唑啉-7-基甲基)-3-乙基-哌嗪-2-酮(实施例77)，3-(5-氯-噻吩-2-基)-(E)-丙烯酸(实施例25)。^{1}H NMR (d6-DMSO + 1滴TFA, 300 MHz) δ 9.78 (bs, 2H), 8.79 (s, 1H), 8.37 (d, 1H), 7.65 (m, 2H), 7.50 (s, 1H), 7.41 (m, 1H), 7.11 (d, 1H), 6.98 (d, 1 H), 4.88 (m, 2H), 4.60 (m, 1 H), 4.31 (m, 1 H), 3.52 (m, 1 H), 3.30 (m, 2H), 1.96 (m, 2H), 0.88 (m, 3H)。MS (离子喷雾), m/z, (M+H) =456, 458 (Cl花样)。元素分析，计算值$C_{22}H_{22}ClN_5O_2S \cdot 1.5C_2HF_3O_2$ %C=47.89, %H=3.78, %N=11.17; 实测值 %C=47.34, %H=4.00, %N=11.12。

采用上述方法，由实施例77的化合物制备下述化合物。

实施例	名称	m/z [M+H]
487	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-3-基氧基)-乙酰基]-(S)-3-乙基-哌嗪-2-酮460,	462 Cl花样
488	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-(S)-3-乙基-哌嗪-2-酮	460,462 Cl花样
489	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-3-基)-丙烯酰基]-(S)-3-乙基-哌嗪-2-酮	456,458 Cl花样

490	2-(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-乙基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-乙酰胺	517, 519 Cl花样
491	(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-乙基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-乙酸	518, 520 Cl花样
492	1-(4-氨基-喹唑啉-7-基甲基)-4-(2, 3-二氯-苯并[b]噻吩-6-羰基)-(S)-3-乙基-哌嗪-2-酮	514, 516, 518 Cl_2花样
493	1-(4-氨基-喹唑啉-7-基甲基)-4-(2-氯-苯并[b]噻吩-6-羰基)-(S)-3-乙基-哌嗪-2-酮	480, 482 Cl花样
494	(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-乙基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-乙酸乙酯	546, 548 Cl花样
495	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3, 5-二氯-噻吩-2-基氧基)-乙酰基]-(S)-3-乙基-哌嗪-2-酮	494, 496 Cl花样
496	(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-乙基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-乙酸甲酯	532, 534 Cl花样
497	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1H-吲哚-6-羰基)-(3S)-乙基-哌嗪-2-酮	463, 465
498	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉基-3-羰基)-3-(S)-乙基-哌嗪-2-酮	475, 477 Cl花样
499	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-乙基-哌嗪-2-酮	460, 462 Cl花样
500	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-溴-噻吩-2-基)-丙烯酰基]-3-(S)-乙基-哌嗪-2-酮	500, 502 Br花样
501	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-(S)-乙基-哌嗪-2-酮	456, 458 Cl花样

502	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-(S)-乙基-哌嗪-2-酮	500, 502 Br花样
503	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙酰基]-3-(S)-乙基-哌嗪-2-酮	458, 460 Cl花样
504	1-(4-氨基-喹唑啉-7-基甲基)-4-[1-(4-氯-苯基)-1H-吡咯-2-羰基]-3-(S)-乙基-哌嗪-2-酮	489, 491 Cl花样
505	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯基硫烷基)-乙酰基]-3-(S)-乙基-哌嗪-2-酮	470, 472 Cl花样
506	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丁-2-烯酰基]-3-(S)-乙基-哌嗪-2-酮	470, 472 Cl花样
507	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯氧基)-乙酰基]-3-(S)-乙基-哌嗪-2-酮	454, 456 Cl花样
508	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-丙烯酰基]-3-(S)-乙基-哌嗪-2-酮	450, 452 Cl花样
509	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-羰基)-3-(S)-乙基-哌嗪-2-酮	463, 465 Cl花样
510	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-丙酰基]-3-(S)-乙基-哌嗪-2-酮	452, 454 Cl花样
511	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-乙基-4-[3-(4-甲氧基-苯基)-丙酰基]-哌嗪-2-酮	448
512	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-3-(S)-乙基-哌嗪-2-酮	480, 482 Cl花样

实施例513

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)丙基-哌嗪-2-酮

此标题化合物按照实施例123所述制备，采用1-(4-氨基喹唑啉-7-基甲基)-3-丙基-哌嗪-2-酮(实施例78)和5-氯-2-噻吩基氧基乙酸(实施例24)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.78 (bs, 2H), 8.81 (s,

1 H), 8.35 (d, 1 H), 7.60 (m, 2H), 7.51 (s, 1 H), 6.69 (m, 1 H), 6.21 (d, 1 H), 4.91 (AB, 2H), 4.72 (m, 2H), 3.84 (m, 1 H), 3.52 (m, 2H), 3.23 (m, 1H), 1.80 (m, 2H), 1.24 (m, 2H), 0.82 (m, 3H). MS (离子喷雾), m/z, 474, 476, (M+H) (Cl 花样). 元素分析 计算值 $C_{22}H_{22}ClN_5O_2S \cdot C_2HF_3O_2 \cdot 1.15H_2O$ %C=47.31, %H=4.52, %N=11.50实测值%C=47.39, %H=4.140, %N=11.19.

实施例514

4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-丙基-哌嗪-2-酮

此标题化合物按照实施例123所述制备，采用1-(4-氨基喹唑啉-7-基甲基)-3-丙基-哌嗪-2-酮(实施例78)和3-(6-氨基吡啶-3-基)-丙烯酸(实施例36)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1 H), 8.36 (m, 2H), 8.22 (m, 3H), 7.62 (d, 1H), 7.52 (m, 1H), 7.39 (m, 1H), 7.21 (m, 1 H), 6.91 (d, 1H), 5.00 (m, 1H), 4.78 (m, 1 H), 4.60 (m, 2H), 4.34 (m, 1 H), 3.30 (m, 2H), 1.87 (m, 2H), 1.24 (m, 2H), 0.90 (m, 3H). MS (离子喷雾), m/z, 446, 448 (M+H), (Cl花样)。

采用上述方法，由实施例77的化合物制备下述化合物。

实施例	名称	m/z [M+H]
515	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2,5-二氯-噻吩-3-基氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮	508, 509, 511, Cl_2花样
516	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮	474, 476 Cl花样
517	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-(S)-丙基-哌嗪-2-酮	514, 516 Br花样
518	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-(S)-丙基-哌嗪-2-酮	470, 472 Cl花样
519	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮	468, 470 Cl花样

520	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮	474,476 Cl花样
521	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-5-甲氧基-苯氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮	498,500 Cl花样
522	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-3-基)-丙烯酰基]-3-(S)-丙基-哌嗪-2-酮	470,472 Cl花样
523	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-丙基-哌嗪-2-酮	470,472 Cl花样

实施例524

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲氧基甲基-哌嗪-2-酮

此标题化合物按照实施例278所述制备，采用1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮(实施例75)和2-(3-溴-(E)-丙烯基)-5-氯-噻吩(实施例17)。^{1}H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.80 (s, 1H), 8.38 (d, 1H), 7.69 (m, 2H), 7.02 (dd, 1H), 6.84 (d, 1H), 6.02 (m, 1H), 4.76 (AB, 2H), 3.86 (m, 4H), 3.30 (s, 3H), 3.23 (m, 2H), 3.02 (m, 2H)。MS (离子喷雾), m/z, 458, 460, (M+H) (Cl花样)。元素分析，计算值 $C_{22}H_{24}ClN_5O_2S \cdot 2C_2HF_3O_2 \cdot 1.45H_2O$; %C=43.85, %H=4.09, %N=9.83; 实测值%C=43.92, %H=3.61, %N=9.63。

采用上述方法，由实施例77的化合物制备下述化合物。

实施例	名称	m/z [M+H]
525	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-氯-1H-吲哚-6-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	465,467
526	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基氧基)-乙基]-3-(S)-甲氧基甲基-哌嗪-2-酮	446,448 Cl花样

527	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	446,448 Cl花样
528	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3-(R)-甲氧基甲基-哌嗪-2-酮	477,479 Cl花样
529	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	477,479 Cl花样
530	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-萘-2-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	476,478 Cl花样
531	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	482,484 Cl花样

实施例532

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮

向4-(4-氨基-喹唑啉-7-基甲基)-2-甲氧基甲基-3-氧代-哌嗪基-1-甲酸苄酯(实施例75)(0.69g, 2.29mmol)的9mL的DMF溶液中加入N,N-二异丙基乙基胺(0.89g, 6.87mmol), TBTU (0.76g, 2.36mmol), 5-氯-2-噻吩基氧基乙酸(实施例24)(0.40g, 2.08mol)。将溶液搅拌16小时。此后,将溶液浓缩。粗品产物用RP-HPLC纯化,进行梯度洗脱:10%乙腈/水(0.1%TFA)至80%乙腈/水(0.1%TFA)。将产物馏分冷冻干燥,得到产物,为一种白色固体(1.0g, 1.57mmol)。^{1}H NMR (d6 DMSO, 300MHz) δ 9.70 (bs, 2H), 8.78 (s, 1 H), 8.29 (m, 1H), 7.55 (m, 2H), 6.72 (m, 1H), 6.22 (m, 1H), 4.80 (m, 4H), 3.78 (m, 4H), 3.59 (m, 3H), 3.31, 3.2 (s, 3H转动异构体)。MS (离子喷雾) M+H=476。元素分析: $C_{21}H_{22}ClN_5O_4S \cdot 1.4CF_3CO_2H$; 计算值: C=45.03%, H=3.68%, N=11.04%; 实测值C=44.98%, H=3.71%, N=11.02%。

实施例533

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-羰基)-3-

(S)-甲氧基甲基-哌嗪-2-酮

向4-(4-氨基-喹唑啉-7-基甲基)-2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯(实施例75)(20 mg, 0.066 mmol)的1.5 mL的DMF溶液中加入TBTU (923.4 mg, 0.073 mmol), 二异丙基乙基胺(0.013 ml, 0.073 mmol), 6-氯-1H苯并咪唑-2-甲酸(按照下述文献制备: Eur. J. med. Chem. 1993, 28, 71) (14.3 mg, 0.073 mmol)。将所得混合物在室温下下搅拌过夜。粗品混合物直接用反相HPLC纯化(10-70%ACN/水)。分离出产物(30.1 mg, 55%), 为一种白色粉末。$C_{23}H_{22}ClN_7O_3$ MS m/z: 480, 481。分析计算值$C_{23}H_{22}ClN_7O_3 \cdot 2C_2HF_3O_2$: C, 45.81; H, 3.42; N, 13.85; 实测值C, 45.19; H, 3.59; N, 13.76。

采用上述方法, 由实施例75的化合物制备下述化合物。

实施例	名称	m/z [M+H]
534	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	476, 478 Cl花样
535	4-[3-(4-氨基-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	447
536	1-(4-氨基-喹唑啉-7-基甲基)-4-(3-3H-咪唑-4-基-丙烯酰基)-3-(S)-甲氧基甲基-哌嗪-2-酮	
537	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2,5-二氯-噻吩-3-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	510, 512, Cl_2花样
538	(1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-羰基)-3-(S)-甲氧基甲基-哌嗪-2-酮	480, 482 Cl花样
539	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-噻吩-2-羰基)-3-(S)-甲氧基甲基-哌嗪-2-酮	446, 448 Cl花样
540	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-溴-呋喃-2-基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	500, 502 Br花样

541	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-苯基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	510, 512 Br花样
542	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	466, 468 Cl花样
543	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-溴-苯基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	576, 578 Br花样
544	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	466, 468 Cl花样
545	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-溴-噻吩-2-基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	576, 578 Br花样
546	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	476, 478 Cl花样
547	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-吡啶-3-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	471, 473 Cl花样
548	1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡啶-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	471, 473 Cl花样
549	4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	448
550	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-5-甲氧基-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	500, 502 Cl花样
551	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-3-基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	472, 474 Cl花样
552	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2, 5-二氯-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	504, 506, 508 Cl_2花样
553	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氟-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	460

554	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氟-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	453
555	1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(3-氯-苯氧基)-丙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	484, 486 Cl花样
556	1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡啶-3-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	471, 473 Cl花样
557	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-4-[(4-三氟甲基硫烷基-苯氧基)-乙酰基]-哌嗪-2-酮	536
558	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯基氨基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	469, 471 Cl花样
559	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯基氨基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	469, 471 Cl花样
560	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	471, 473 Cl花样
561	(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-乙酸	534, 536 Cl花样
562	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基硫烷基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	492, 494 Cl花样
563	1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡啶-3-基氨基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	470, 472 Cl花样
564	2-(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-乙酸乙酯	533, 535 Cl花样
565	1-(4-氨基-喹唑啉-7-基甲基)-4-(2-氯-苯并[b]噻吩-6-羰基)-3-(S)-甲氧基甲基-哌嗪-2-酮	496, 498 Cl花样

566	1-(4-氨基-喹唑啉-7-基甲基)-4-(2,3-二氯-苯并[b]噻吩-6-羰基)-3-(S)-甲氧基甲基-哌嗪-2-酮	530,532,534 Cl花样
567	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3,5-二氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	510,512,514Cl$_2$花样
568	(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-乙酸甲酯	548,550 Cl花样
569	(2-{2-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-氧代-哌嗪-1-基]-2-氧代-乙氧基}-5-氯-噻吩-3-基)-3-乙酸乙酯	562,564 Cl花样
570	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2-氯-吡啶-3-基氨基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	470,472 Cl花样
571	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2,3-二氯-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	504,506,508Cl$_2$花样
572	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氟-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	454
573	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-2-甲基-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	484,486 Cl花样
574	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2,4-二氯-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	504,506,508Cl$_2$花样
575	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉基-3-羰基)-3-(S)-甲氧基甲基-哌嗪-2-酮	491,493 Cl花样
576	(1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	516,518 Br花样
577	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	472,474 Cl花样

578	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(R)-甲氧基甲基-哌嗪-2-酮	472,474 Cl花样
579	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	472,474 Cl花样
580	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-3-(S)-甲氧基甲基-哌嗪-2-酮	496,498 Cl花样
581	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	470,472 Cl花样

实施例582

1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡啶-3-基氧基)-乙酰基]-3-(S)-乙氧基甲基-哌嗪-2-酮

此标题化合物按照实施例123所述制备，采用1-(4-氨基喹唑啉-7-基甲基)-3-乙氧基甲基-哌嗪-2-酮(实施例79)和(6-氯-吡啶-3-基氧基)-乙酸(与实施例29所述类似的方法制备)。^{1}H NMR (d6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1H), 8.37 (m, 1H), 8.10 (m, 1 H), 7.61 (m, 2H), 7.40 (m, 2H), 4.98 (m, 2H), 4.65 (m, 2H), 4.50 (m, 1 H), 3.91 (m, 1 H), 3.75 (m, 1 H), 3.59 (m, 2H), 3.31 (m, 2H), 1.07 (m, 3H)。MS (离子喷雾), m/z, 485, 487 (M+H), (Cl花样)。

采用上述方法，由实施例77的化合物制备下述化合物。

实施例	名称	m/z [M+H]
583	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-乙氧基甲基-4-[(3-氟-苯氧基)-乙酰基]-哌嗪-2-酮	454
584	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-乙氧基甲基-哌嗪-2-酮	486,488 Cl花样

585	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2-氯-吡啶-3-基氨基)-乙酰基]-3-(S)-乙氧基甲基-哌嗪-2-酮	484, 486 Cl花样
586	1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡啶-3-基氨基)-乙酰基]-3-(S)-乙氧基甲基-哌嗪-2-酮	484, 486 Cl花样
587	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-乙氧基甲基-哌嗪-2-酮	490, 492 Cl花样

采用上述方法，由实施例81-85的化合物制备下述化合物。

实施例	名称	m/z [M+H]
588	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-苄基-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-哌嗪-2-酮	518, 520 Cl花样
589	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-苄基-4-(6-氯-苯并[b]噻吩-2-羰基)-哌嗪-2-酮	542, 544 Cl花样
590	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-苄基-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2-酮	504, 506 Cl花样
591	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-苄基-4-(6-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮	528, 530 Cl花样
592	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-苄基-4-[(4-氯-苯氧基)-乙酰基]-哌嗪-2-酮	516, 518 Cl花样
593	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-苄基-4-[(6-氯-萘-2-基甲基)-哌嗪-2-酮	522, 524 Cl花样
594	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-苄基-4-[3-(5-氯-噻吩-2-基)-丙基]-哌嗪-2-酮	506, 508 Cl花样
595	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-((R)-1-甲氧基-乙基)-哌嗪-2-酮	490, 492 Cl花样

596	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-((R)-1-甲氧基-乙基)-哌嗪-2-酮	472,474 Cl花样
597	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-((R)-1-甲氧基-乙基)-哌嗪-2-酮	486,488 Cl花样
598	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-(S)-((R)-1-甲氧基-乙基)-哌嗪-2-酮	530,532 Br花样
599	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3-(S)-((R)-1-甲氧基-乙基)-哌嗪-2-酮	491,493 Cl花样
600	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3-(S)-异丙基-哌嗪-2-酮	480,482 Cl花样
601	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3,3-二甲基-哌嗪-2-酮	466,468 Cl花样
602	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,3-二甲基-哌嗪-2-酮	442,444 Cl花样
603	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3,3-二甲基-哌嗪-2-酮	456,458 Cl花样
604	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-3,3-二甲基-哌嗪-2-酮	480,482 Cl花样
605	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-(2-甲氧基-乙基)-哌嗪-2-酮	490,492 Cl花样
606	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-(2-甲氧基-乙基)-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	469,471 Cl花样

607	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-3-(S)-(2-甲氧基-乙基)-哌嗪-2-酮	490,492 Cl花样
608	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-3-(S)-(2-甲氧基-乙基)-哌嗪-2-酮	510,512 Cl花样

实施例609

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-萘-2-基甲基)-3-(S)-甲氧基甲基-6-(S)-甲基-哌嗪-2-酮

此标题化合物按照实施例268所述制备，采用1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-6-甲基-哌嗪-2-酮(实施例87)和2-溴甲基-6-氯萘(实施例12)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 7.79 (d, 1H), 7.70-7.12 (m, 3H), 7.68-7.67 (m, 2H), 7.55 (d, 1H), 7.39 (d, 1H), 4.78 (d, 2H), 3.98 (d, 2H), 3.44 (s, 3H), 3.38 (t, 1H), 2.64 (m, 2H), 1.26 (d, 3H)。MS (ISP) 490, 492, (M+H), Cl花样。

采用上述方法，由实施例87获得的原料制备下述化合物。

实施例	名称	m/z [M+H]
610	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙基]-3-(S)-乙基-6-甲基-哌嗪-2-酮	458,460 Cl花样
611	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-萘-2-基甲基)-3-(S)-甲氧基甲基-6-(R)-甲基-哌嗪-2-酮	490,492 Cl花样
612	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	472,474 Cl花样

613	(1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	490,492 Cl花样
614	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-6-二甲基-哌嗪-2-酮	491,493 Cl花样
615	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-萘-2-基甲基)-6-甲基-哌嗪-2-酮	442,446 Cl花样
616	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-甲基-哌嗪-2-酮	428,430 Cl花样

实施例617

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-6-甲基-哌嗪-2-酮

此标题化合物按照实施例123所述制备，采用1-(4-氨基喹唑啉-7-基甲基)-3-甲氧基甲基-6-甲基-哌嗪-2-酮(实施例87)和5-氯-2-噻吩基氧基乙酸(实施例24)。^{1}H NMR (CD_3OD300 MHz) δ 8.68 (s, 1H), 8.27 (d, 1 H), 7.62 (m, 2H), 6.54 (d, 1H), 6.18 (m, 1 H), 7.39 (d, 1H), 4.94 (m, 4H), 4.15 (m, 2H), 3.76 (m, 2H), 3.44 (s, 3H), 3.10 (m, 2H), 1.28 (d, 3H)。

采用上述方法，由实施例75-87获得的化合物制备下述化合物。

实施例	名称	m/z [M+H]
618	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-(S)-3-甲氧基甲基-6-甲基-哌嗪-2-酮	490,492 Cl花样
619	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-(S)-3-甲氧基甲基-6-甲基-哌嗪-2-酮	490,492Cl_2 花样

620	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-4-氟-苯氧基)-乙酰基]-3(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	502, 504 Cl花样
621	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3, 5-二氯-苯氧基)-乙酰基]-3(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	502, 504 Cl花样
622	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(2, 5-二氯-苯基)-丙烯酰基]-3(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	514
623	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-2-甲基-基氧基)-乙酰基]-3(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	498, 500 Cl_2花样
624	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2, 5-二氯-苯氧基)-乙酰基]-3(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	518
625	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯氧基)-乙酰基]-3-(S)-甲氧基甲基-6-甲基-哌嗪-2-酮	484
626	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙酰基]-3(S)-乙基-6-甲基-哌嗪-2-酮	472, 474 Cl花样
627	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-乙基-6-甲基-哌嗪-2-酮	474
628	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3(S)-乙基-6-甲基-哌嗪-2-酮	514, 516 Br花样
629	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-乙基-6-甲基-哌嗪-2-酮	470, 472 Cl花样
630	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-甲氧基甲基-6-甲基-哌嗪-2-酮	486, 488 Cl花样

631	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-甲氧基甲基-6-甲基-哌嗪-2-酮	530,532 Br花样
632	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-3(S)-6-二甲基-哌嗪-2-酮	480 Cl花样
633	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3(S)-6-二甲基-哌嗪-2-酮	500,502 Br花样
634	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-6-二甲基-哌嗪-2-酮	456,458 Cl花样
635	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-6-甲基-哌嗪-2-酮	442,444 Cl花样

实施例636

4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺

此标题化合物按照实施例436所述制备，采用1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮(实施例75)和4-氯苯基异氰酸酯。^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1H), 8.70 (s, 1H), 8.40 (d, 1 H), 7.64 (d, 1H), 7.61 (s, 1 H), 7.49 (d, 2H), 7.28 (d, 2H), 4.88 (m, 1H), 4.80 (AB, 2H), 4.19 (m, 1H), 3.96 (m, 1H), 3.74-3.42 (m, 4H), 3.28 (s, 3H). ESI MS, $[M+H]^+$=455, 457 (Cl花样)。分析值 ($C_{22}H_{23}ClN_6O_3$·TFA·1.5H_2O) C, H, N.

实施例637

4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲基-3-氧代-哌嗪-1-甲酸(5-氯-噻吩-2-基)-酰胺

此标题化合物按照实施例438所述制备，采用1-(4-氨基-喹唑啉-7-基甲基)-3-甲基-哌嗪-2-酮(实施例80)和5-氯-噻吩-2羰基叠氮化

物(实施例38)。^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.01 (s, 1H), 9.73 (bs, 2H), 8.83 (s, 1 H), 8.39 (d, 1 H), 7.65 (d, 1 H), 7.58 (s, 1 H), 6.79 (d, 1 H), 6.44 (d, 1 H), 4.85 (d, 1 H), 4.71 (m, 1H), 4.69 (d, 1 H), 4.17 (d, 1H), 3.50 (m, 3H), 1.45 (d, 3H)。ESI MS, $[M+H]^+$=431,433 (Cl花样)。分析($C_{19}H_{19}ClN_6O_2S\cdot$ TFA·1.9H_2O) C, H, N。

实施例638

4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-氯-噻吩-2-基)-酰胺

此标题化合物按照实施例439所述制备，采用1-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮(实施例75)和5-氯-噻吩-2-羰基叠氮化物(实施例38)。^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.00 (s, 1 H), 9.73 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.65 (d, 1 H), 7.60 (s, 1 H), 6.80 (d, 1 H), 6.42 (d, 1 H), 4.86 (d, 1H), 4.80 (m, 1H), 4.70 (d, 1H), 4.18 (d, 1H), 3.96 (dd, 1H), 3.60 (m, 4H), 3.30 (s, 3H)。ESI MS, $[M+H]^+$=461,463 (Cl花样)。分析值($C_{20}H_{21}ClN_6O_3S\cdot$TFA·1.1$H_2O$) C, H, N。

下列化合物用如上所述方法制备。

实施例	名称	m/z [M+H]
639	4-(4-氨基-喹唑啉-7-基甲基)-2(S)-(2-甲氧基-乙基)-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	469
640	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-丁基-3-氧代-哌嗪-1-羧酸(4-氯-苯基)-酰胺	467,469 Cl花样
641	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-溴-噻吩-2-基)-酰胺	505,507

642	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-氯-噻吩-3-基)-酰胺	461, 463
643	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4-氯-噻吩-2-基)-酰胺	461
644	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(S)-2-丙基-哌嗪-1-羧酸(4-氯-苯基)-酰胺	453, 455 Cl花样
645	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(3-溴-苯基)-酰胺	499
646	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(2S)-丙基-哌嗪-1-羧酸(4-氯-噻吩-2-基)-酰胺	459, 461
647	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(S)-2-丙基-哌嗪-1-羧酸(5-氯-2-甲氧基-苯基)-酰胺	483, 485 Cl花样
648	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4-溴-2-氯-苯基)-酰胺	533, 535
649	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4-三氟甲氧基-苯基)-酰胺	505
650	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4-氟-苯基)-酰胺	439
651	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(2, 4-二氯-苯基)-酰胺	489, 491
652	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(2, 4-二氟-苯基)-酰胺	457
653	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(3-氯-苯基)-酰胺	455
654	4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(2S)-丙基-哌嗪-1-羧酸(5-氯-噻吩-2-基)-酰胺	459, 460 Cl花样
655	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲基-3-氧代-哌嗪-1-甲酸(6-氯-噻吩-3-基)-酰胺426, 428	426, 428

656	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4-溴-苯基)-酰胺	499, 501
657	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲基-3-氧代-哌嗪-1-羧酸(4-溴-苯基)-酰胺	486, 488
658	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-5-(R, S)-甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	469, 471
659	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-乙基-3-氧代-哌嗪-1-羧酸(4-溴-苯基)-酰胺	483, 485
660	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲基-3-氧代-哌嗪-1-羧酸(4-氯-苯基)-酰胺	425, 427
661	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-乙基-3-氧代-哌嗪-1-羧酸(4-氯-苯基)-酰胺	439, 441
662	4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-氯-4-甲氧基-噻吩-2-基)-酰胺	491, 493 Cl花样

实施例663

(3S, 5RS)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2基甲基)-3, 5-二甲基-哌嗪-2-酮

将(3S, 5RS)-1-(4-氨基-喹唑啉-7-基甲基)-3, 5-二甲基-哌嗪-2-酮(260 mg, 0.56 mmol)(实施例88)溶解于5 mL的DMF中。加入碳酸钾(193.4 mg, 1.4 mmol), 再加入2-溴甲基-6-氯-苯并[b]噻吩(218 mg, 0.84 mmol)(实施例5)。将反应混合物搅拌过夜。 粗品混合物用反相HPLC纯化 (10-70%ACN/水), 得到产物(27 mg, 6%), 为一种澄清蜡状物, 其熔点为130-131℃。$C_{24}H_{24}ClN_5OS$ MS m/z: 466, 468。

实施例664

(3S, 5S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯

丙基]-3,5-二甲基-哌嗪-2-酮和

实施例665

(3S,5R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮

将(3S,5RS)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮(60 mg, 0.13 mmol)溶解于1 mL的DMF中。加入碳酸钾(53 mg, 0.39 mmol), 再加入3-溴烯丙基-5-氯-噻吩(75 mg, 0.32 mmol)。将反应混合物搅拌过夜。 通过反相HPLC (10-70%ACN)分离两种差向异构体, 收率43%。主要的差向异构体为(3S,5S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮三氟乙酸盐(30.8 mg), 分离后为一种黄色固体, 其熔点为69-72℃。$C_{22}H_{24}ClN_5OS$ MS m/z: 442,444。次要的差向异构体为(3S,5R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮三氟乙酸盐(13.1 mg), 其熔点为67-70℃。$C_{22}H_{24}ClN_5OS$ MS m/z: 442,444。^1H NMR (CD_3OD) δ 8.67 (s, 1 H); 8.31 (d, 1 H, J =8.56 Hz); 7.83 (s, 1H); 7.74 (d, 2H, J =8.56 Hz); 7.14 (d, 1H, J =15.6 Hz); 6.92 (d, 1H, J =3.74 Hz); 6.10-6.03 (m, 1 H); 5.0-4.74 (m, 2H); 4.25-3.63 (m, 6 H); 1.78 (d, 3H, J =7.03 Hz); 1.50 (d, 3H, J =6.47 Hz)。

实施例666

(3S,5R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-3,5-二甲基-哌嗪-2-酮

将(3S,5R)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮(43 mg, 0.123 mmol)(来自实施例88, 部分D的次要差向异构体)吸收于二氯甲烷中, 向其中加入三乙胺(0.034 ml, 0.25 mmol), 再加入2-(5-氯-噻吩-2-基)-乙烯磺酰基氯(40 mg, 0.16 mmol)(实施例3)。将反应混合物搅拌过夜, 粗品产物用制备薄层色谱纯化(15 %甲醇/二氯甲烷)。分离出产物(1.4 mg, 2.3%), 为一种黄色蜡状物。

$C_{21}H_{22}ClN_5O_3S_2$ MS m/z: 492, 494. 1 ^{1}H NMR (CD_3OD) δ 8.36 (s, 1H); 8.03 (d, 1 H, J =7.5 Hz); 7.61 (s, 1H); 7.49-7.44 (m, 2H); 7.19 (d, 1H, J =3.83 Hz); 6.98 (d, 1H, J =3.75 Hz); 6.76 (d, 1H, J =15.1 Hz); 4.86-4.71 (m, 2H); 4.45-4.39 (m, 1H); 4.13-4.09 (m, 1H); 3.64-3.7 (m, 2H); 1.63 (d, 3H, J =7.09 Hz); 1.33 (d, 3H, J =6.80 Hz)。

实施例667

(3S,5S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-3,5-二甲基-哌嗪-2-酮

分离出产物(7 mg, 9.4 %), 为一种黄色固体, 其熔点为218-221℃。$C_{21}H_{22}ClN_5O_3S_2$ MS m/z: 492, 494。^{1}H NMR (CD_3OD) δ 8.37 (s, 1H); 8.10 (d, 1H, J =8.57 Hz); 7.61-7.45 (m, 3H); 7.24 (d, 1 H, J =3.94 Hz); 6.98 (d, 1 H, J =3.85 Hz); 6.71 (d, 1 H, J =15.1 Hz); 4.76 (s, 2H); 4.32 (m, 1H); 3.71 (m, 1H); 3.36 (m, 2H); 1.62 (d, 3H, J =7.06 Hz); 1.20 (d, 3H, J =6.63 Hz)。

实施例668

(3S,5S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-3,5-二甲基-哌嗪-2-酮

分离出目的产物(5.4 mg, 8.5 %), 为一种黄色固体, 其熔点为224-226℃。$C_{23}H_{22}ClN_5O_3S_2$ MS m/z: 516, 518。

实施例669

(3S,5S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3,5-二甲基-哌嗪-2-酮

向(3S,5S)-1-(4-氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮(42 mg, 0.147 mmol)(实施例88, 部分D的主要差向异构体)的2 mL的DMF溶液中加入TBTU (52 mg, 0.162 mmol), 三乙胺(0.02 mL, 0.162

mmol)，3-(5-氯-噻吩-2-基)-丙烯酸(28 mg，0.15 mmol)(实施例25)。搅拌2小时，将反应混合物直接经反相HPLC纯化(10-70 %ACN/水)。分离出产物(35.5 mg，36%)，为一种黄色固体，其熔点为116-120℃。$C_{22}H_{22}ClN_5O_2S$：MS m/z：456，458。元素分析理论值$C_{22}H_{22}ClN_5O_2S \cdot C_2HF_3O_2$：C，50.57；H，4.07；N，12.29；实测值：C，46.48；H，3.64；N，11.04。

实施例670

(3S,5R)-4-(4-氨基-喹唑啉-7-基甲基)-2,6-二甲基-氧代-哌嗪-1-甲酸(4-溴-苯基)-酰胺

将4-溴-苯基异氰酸酯(20.8 mg，0.105 mmol)加至(3S,5R)-1-(4氨基-喹唑啉-7-基甲基)-3,5-二甲基-哌嗪-2-酮(30 mg，0.105 mmol)(实施例88，部分D次要差向异构体)的1 mL的DMF溶液中。将反应混合物在室温下搅拌2小时。反相HPLC纯化(10-70%ACN/水)分离出产物(21.4 mg，33%)，为一种白色固体。化合物的熔点为142-144℃。$C_{22}H_{23}BrN_6O_2$ MS m/z：483,485。分析计算值$C_{22}H_{23}BrN_6O_2 \cdot 2C_2HF_3O_2$：C，43.90；H，3.54；N，11.81；实测值：C，44.52；H，3.86；N，12.44。

实施例671

(3S,5S)-4-(4-氨基-喹唑啉-7-基甲基)-2,6-二甲基-氧代-哌嗪-1-甲酸(4-溴-苯基)-酰胺

分离出目的产物(35 mg，47%)，为一种白色固体，其熔点为142-144℃。$C_{22}H_{23}BrN_6O_2$ MSm/z：483,485。分析计算值$C_{22}H_{23}BrN_6O_2 \cdot 2C_2HF_3O_2$：C，43.90；H，3.54；N，11.81；实测值：C，44.73；H，3.59；N，12.38。

实施例672

(3S,5S)-4-(4-氨基-喹唑啉-7-基甲基)-2,6-二甲基-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺

获得产物(24.7 mg, 50%)，为一种白色固体，其熔点为123-125℃。$C_{22}H_{23}ClN_6O_2$ MS m/z: 439, 441。分析计算值$C_{22}H_{23}ClN_6O_2 \cdot 2C_2HF_3O_2$: C, 46.82; H, 3.78; N, 12.60; 实测值: C, 47.69; H, 4.33; N, 13.32。

实施例673

1-(4-氨基喹啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

A. 1-(4-氯喹啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

在0℃下，将1-(4-氯喹啉-7-基甲基)-3-(S)-甲基哌嗪-2-酮盐酸盐(0.49 g, 1.4 mmol)(实施例89)用乙腈(20 mL)，三乙胺(1.2 ml, 8.4 mmol)，6-氯苯并[b]噻吩-2-磺酰基氯(0.41 g, 1.54 mmol)(实施例1)的乙腈(10 mL)溶液进行处理。2小时后，将溶液倒入水中，用乙酸乙酯萃取。有机层用水洗涤，用硫酸钠干燥并浓缩，得到标题化合物(0.45 g, 0.95 mmol)。MS m/z: 506, $[M+1]^+$; ^1H NMR (CD_3OD, 300 MHz) δ 8.8 (d, 1H), 8.15 (d, 1H), 7.9 (d, 2H), 7.85 (s, 1H), 7.4-7.5 (m, 2H), 6.8 (s, 1H), 4.8 (s, 2H), 4.0 (s, 2H), 3.4-3.45 (m, 4H)。

B. 1-(4-叠氮基喹啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

将1-(4-氯喹啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮(0.52 g, 1.03 mmol)溶解于DMF (15 mL)中，用叠氮化钠(0.52 g, 8.0 mmol)和四丁基氯化铵(0.1 g, 0.36 mmol)处理，加热至65℃过夜。将反应混合物冷却，倒入水中，用乙酸乙酯萃取。有机层用水洗涤，干燥(硫酸钠)，浓缩，得到标题化合物(0.5 g, 1.04 mmol)。^1H NMR (CD_3OD, 300 MHz) δ 9.0 (d, 1 H), 8.2 (d, 1H), 8.0 (s, 1H), 7.9 (d, 2H), 7.8 (d, 1 H), 7.6 (d, 1 H), 7.5 (d, 1H), 6.9 (s,

1 H), 4.85 (s, 2H), 4.0 (s, 2H), 3.5-3.7 (m, 4H)。

C. 1-(4-氨基喹啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

将1-(4-叠氮基喹啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮(0.50 g, 1.04 mmol)在100 mL的乙酸/甲醇(约1:10)中的悬浮液用10%Pd/C (0.15 g)处理，在氢气氛下搅拌1.5小时。所得溶液用硅藻土过滤，将滤液真空蒸发。将有机层浓缩，残余物用反相HPLC纯化(梯度洗脱：30 %的0.1 %TFA水溶液/乙腈至100 %乙腈)，冷冻干燥，得到标题化合物(0.39 g, 0.86 mmol)。MS (ISP) m/z 487, 489, (M+H), Cl花样。

采用如上所述的方法，由实施例89或91的化合物制备下述化合物。

实施例	名称	m/z [M+H]
674	1-(4-氨基-喹啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯-磺酰基]-哌嗪-2-酮	463, 465
675	(S)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-3-甲基-哌嗪-2-酮	501, 503
676	(3S, 5S)-1-(4-氨基-喹啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-3, 5-二甲基-哌嗪-2-酮	491, 493
677	(3S, 5R)-1-(4-氨基-喹啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-3, 5-二甲基-哌嗪-2-酮	491, 493
678	(S, R)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸	531, 533

679	1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酰胺	544
680	1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸乙基酰胺	558
681	1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸二甲基酰胺	558
682	1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(吗啉-4-羰基)-哌嗪-2-酮	600

实施例683

(S)-1-(4-氨基喹啉-7-基甲基)-4-[3-(5-氯噻吩-2-基)-烯丙基]-3-甲基哌嗪-2-酮

A. (S)-1-(4-氯喹啉-7-基甲基)-4-[3-(5-氯噻吩-2-基)-烯丙基]-3-甲基哌嗪-2-酮

将(S)-1-(4-氯喹啉-7-基甲基)-3-甲基哌嗪-2-酮盐酸盐(0.25 g, 1.0 mmol)(实施例91)用2-(3-溴-(E)-丙烯基)-5-氯-噻吩(0.35 g 1.2 mmol)(实施例17)和碳酸钾(0.5 g, 3 mmol)处理。所得悬浮液超声处理10分钟，然后，在室温下剧烈搅拌16小时。将反应混合物倒入水中，用乙酸乙酯萃取(2 x 150 mL)。有机层用水(4 x 200 mL)洗涤，用硫酸钠干燥，浓缩。将残余物进行色谱处理(3%甲醇/二氯甲烷)，得到标题化合物(0.31 g, 0.73 mmol)。

B. (S)-1-(4-氨基喹啉-7-基甲基)-4-[3-(5-氯噻吩-2-基)-烯丙基]-3-甲基哌嗪-2-酮

将(S)-1-(4-氯喹啉-7-基甲基)-4-[3-(5-氯噻吩-2-基)-烯丙基]-3-甲基哌嗪-2-酮(0.35 g, 0.82 mmol)用苯酚(2 g)和乙酸铵(0.7 g, 9.1 mmol)处理，在密封容器中加热至120℃加热1小时。冷却后，将溶液在2N氢氧化钠与乙酸乙酯间分配。分离出有机层，用新配制的2N氢氧化钠(3 x 100 mL)和水洗涤。将有机层浓缩，残余物用反相HPLC

纯化，得到标题化合物，为一种白色固体(0.15 g，0.35 mmol)。MS (ISP) m/z 427，429，(M+H)，Cl花样。

采用如上所述的方法，由实施例61-64，89或91所述制备的原料制备下述化合物。

实施例	名称	m/z [M+H]
684	1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2-酮	413,415
685	(3S,5R)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3,5-二甲基-哌嗪-2-酮	465,467
686	(3S,5S)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-3,5-二甲基-哌嗪-2-酮	464
687	(S)-1-(4-氨基-喹啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3-甲基-哌嗪-2-酮	446,448
688	(S)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-萘-2-基甲基)-3-甲基-哌嗪-2-酮	444
689	(3S,5S)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮	441,443
690	(3S,5R)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3,5-二甲基-哌嗪-2-酮	441,443
691	1-(4-氨基-喹啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮	420,422
692	(S)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-萘-2-基甲基)-3-乙基-哌嗪-2-酮	458
693	1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-(S)-3-((R)-1-甲氧基-乙基)-哌嗪-2-酮	470
694	1-(4-氨基-喹啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-(S)-3-((R)-1-甲氧基-乙基)-哌嗪-2-酮	489

695	(S)-1-(4-氨基-喹啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3-甲氧基甲基-哌嗪-2-酮	464, 466
696	(S)-1-(4-氨基-喹啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3-甲基-哌嗪-2-酮	434, 436
697	4-(5-氯-1H-吲哚-2-基甲基)-1-[4-(2-羟基-乙基氨基)-喹啉-7-基甲基]-哌嗪-2-酮	464
698	(S)-4-(5-氯-1H-吲哚-2-基甲基)-1-(4-乙基氨基-喹啉-7-基甲基)-3-甲基-哌嗪-2-酮	462
699	(S)-4-(5-氯-1H-吲哚-2-基甲基)-1-(4-乙基氨基-喹啉-7-基甲基)-3-甲氧基甲基-哌嗪-2-酮	492
700	(S)-4-(5-氯-1H-吲哚-2-基甲基)-3-甲基-1-(4-甲基氨基-喹啉-7-基甲基)-哌嗪-2-酮	448
701	(S)-4-(5-氯-1H-吲哚-2-基甲基)-3-甲氧基甲基-1-(4-甲基氨基-喹啉-7-基甲基)-哌嗪-2-酮	478
702	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-甲基-4-氧基-哌嗪-2-酮	443

实施例703

(S)-1-(4-氨基喹啉-7-基甲基)-4-[3-(4-溴噻吩-2-基)丙烯酰基]-3-甲基-哌嗪-2-酮

A. (S)-1-(4-氯喹啉-7-基甲基)-4-[3-(4-溴噻吩-2-基)丙烯酰基]-3-甲基哌嗪-2-酮

将(S)-1-(4-氯喹啉-7-基甲基)-3-甲基哌嗪-2-酮盐酸盐(0.35 g, 1.4 mmol)(实施例91)用DMF (20 mL), 3-(4-溴噻吩-2-基)-(E)-丙烯酸(0.32 g, 1.4 mmol)(按照实施例26制备, 采用4-溴噻吩-2甲醛, 三乙胺(0.21 ml, 1.4 mmol), 2-(1H-苯并三唑-1-基)1,1,3,3-四甲基四氟硼酸铵(0.45 g, 1.4 mmol))处理, 加热至50℃搅拌5分钟。将反应混合物在室温下搅拌16小时后, 在乙酸乙酯和水间分配。将有

机层浓缩，残余物进行色谱处理(5%甲醇/二氯甲烷)，得到粗品标题化合物(0.5 g, 0.9 mmol)。MS m/z: $[M+H]^+$ =504. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.9 (d, 1 H), 8.2-8.3 (m, 2H), 8.0 (s, 1 H), 7.7-7.8 (m, 1H), 7.4 (s, 1H), 7.3-7.4 (m, 1H), 6.7-6.8 (m, 1 H), 6.6 (d, 1H), 5.1-5.2 (m, 1 H), 4.6-4.7 (m, 2H), 3.4-3.6 (m, 2H), 3.0-3.3 (m, 2H), 1.5 (d, 3H)。

B. (S)-1-(4-氨基喹啉-7-基甲基)-4-[3-(4-溴噻吩-2-基)丙烯酰基]-3-甲基-哌嗪-2-酮

将(S)-1-(4-氯喹啉-7-基甲基)-4-[3-(4-溴噻吩-2-基)丙烯酰基]-3-甲基哌嗪-2-酮(0.50 g, 0.9 mmol)用苯酚(约2 g)和乙酸铵(0.5 g, 6.4 mmol)处理，在密封的容器中加热至120℃加热1小时。冷却后，将溶液在2N氢氧化钠和乙酸乙酯间分配。分离出有机层，用新配制的2N氢氧化钠(3 x 100 mL)和水洗涤。将有机层浓缩，残余物用反相HPLC纯化(梯度洗脱：10 %的0.1%TFA水溶液/乙腈至100%乙腈)，得到标题化合物(0.22 g, 0.56 mmol)。MS m/z: $[M+H]^+$ =485, 487, Cl花样。^1H NMR (CD_3OD, 300 MHz) δ 8.2-8.4 (m, 2H), 7.7-7.8 (m, 2H), 7.6 (d, 1H), 7.5 (s, 1 H), 7.3 (s, 1H), 6.9-7.0 (m, 1 H), 6.7 (d, 1H), 5.0-5.1 (m, 1H), 4.9 (q, 2H), 4.3-4.4 (m, 1 H), 3.5-3.7 (m, 2H), 3.3-3.4 (m, 2H), 1.5 (d, 3H)。

采用上述方法，由实施例75-87所述制备的原料制备下述化合物。

实施例	名称	m/z [M+H]
704	1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-乙基-6-甲基-哌嗪-2-酮	469 Cl花样
705	4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-(S)-3-乙基-1-(4-羟基氨基-喹啉-7-基甲基)-哌嗪-2-酮	471,473

706	1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-哌嗪-2-酮	427, 429
707	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-乙基-哌嗪-2-酮	454
708	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-甲基-哌嗪-2-酮	441, 443
709	1-(4-氨基-喹啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-哌嗪-2-酮	471, 473
710	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-甲氧基甲基-哌嗪-2-酮	470
711	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(4-溴-噻吩-2-基)-丙烯酰基]-3-乙基-哌嗪-2-酮	498
712	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-乙基-哌嗪-2-酮	458
713	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-甲氧基甲基-6-甲基-哌嗪-2-酮	488
714	1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-(S)-3-(1-(R)-甲氧基-乙基)-哌嗪-2-酮	484
715	1-(4-氨基喹啉-7-基甲基)-4-[3-(4-溴噻吩-2-基)-丙烯酰基]-3-(S)-(1-(R)-甲氧基乙基)-哌嗪-2-酮三氟乙酸盐	528
716	1-(4-氨基喹啉-7-基甲基)-4-[(5-氯噻吩-2-基氧基-乙酰基]-3-(S)-(1-(R)-甲氧基乙基)-哌嗪-2-酮三氟乙酸盐	488
717	(S)-1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-乙基-哌嗪-2-酮	454

实施例718

1-(4-氨基噌啉-7-基甲基)-4-[2-(5-氯噻吩-2-基)-乙烯磺酰基]哌嗪-2-酮

A. 1-(4-氯噌啉-7-基甲基)-4-[2-(5-氯噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮

在0℃下，将1-(4-氯噌啉-7-基甲基)-哌嗪-2-酮盐酸盐(0.14 g, 0.4 mmol)(实施例90)用乙腈 (20 mL)，三乙胺(2 mL, 14 mmol)，2-(5-氯噻吩-2-基)乙烯-磺酰基氯(0.097 g, 0.4 mmol)(实施例3)处理。在1.5小时内，将溶液升温至室温，用乙酸乙酯稀释。将溶液用10 %碳酸氢钠溶液和水洗涤，干燥(硫酸钠)，浓缩，得到标题化合物(0.17 g, 0.35 mmol)。MS m/z: $[M+H]^+$ =483; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.4 (s, 1H), 8.4 (s, 1H), 8.3 (d, 1H) 7.85 (d, 1 H), 7.7 (d, 1H), 7.1 (d, 1H), 6.95 (d, 1 H), 6.35 (d, 1H), 4.9 (s, 2H), 4.0 (s, 2H), 3.4-3.5 (m, 4H)。

B. 1-(4-氨基噌啉-7-基甲基)-4-[2-(5-氯噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮

将1-(4-氯噌啉-7-基甲基)-4-[2-(5-氯噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮(0.06 g, 0.12 mmol)用苯酚(0.20 g)和乙酸铵(0.2 g, 2.6 mmol)处理，加热至120℃并搅拌45分钟。将反应混合物冷却，用乙酸乙酯稀释，用1N氢氧化钠(3 x 100 mL)和水洗涤。将有机层浓缩，残余物用反相HPLC纯化(20 % TFA水溶液(0.1 %)/乙腈至100 %乙腈)。将包含目的产物的馏分冷冻干燥，获得标题化合物(0.02 g, 0.043 mmol)。MS m/z: $[M+H]^+$ =464; ^1H NMR (CD_3OD, 300 MHz) δ 8.6 (s, 1H), 8.4 (d, 1H), 7.75 (d, 1 H), 7.65 (d, 1 H), 7.35 (d, 1H), 7.1 (d, 1H), 6.8 (d, 1H), 4.9 (s, 2H), 4.05 (s, 2H), 3.6 (m, 4H)。

实施例719

4-(6-氯-噻吩并[2,3-b]吡啶-2-磺酰基)-1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮

将1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮(0.20 mmol)(实施例90)溶解于乙腈(5 mL)中，用4-甲基吗啉(0.055 ml, 0.50 mmol)处理。滴加入6-氯噻吩并[2,3-b]吡啶-2-磺酰基氯(54 mg, 0.20 mmol)的乙腈(2 mL)溶液。将反应混合物在室温下搅拌1.5小时后，进行HPLC纯化，得到标题化合物，为一种白色固体(0.021 g, 0.037 mmol)。MS m/z 452,454 (M+1)；^{1}H NMR (CD_3OD, 300 MHz) δ 8.37 (d, 1H), 8.30 (b, 1H), 8.12 (d, 1H), 8.02 (s, 1H), 7.97 (d, 1H), 7.57 (d. 1H), 6.98 (d, 1 H), 6.88 (d, 2H), 3.73 (s, 2H), 3.60-3.48 (m, 8H)。

实施例720

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[2-(甲基-吡啶-4-基-氨基)乙基]-哌嗪-2-酮

将实施例93的一部分(约50%)粗品1-[2-{(甲基)-(吡啶-4-基)-氨基}-乙基]-哌嗪-2-酮与6-氯-苯并[b]噻吩-2-磺酰基氯(54 mg, 0.20 mmol)(实施例1)反应，采用与实施例719所述相同的方法。将进行HPLC纯化获得的残余物进行硅胶色谱处理，采用氢氧化铵/甲醇/二氯甲烷(1:4:95)作为洗脱剂，得到标题化合物(30 mg, 0.064 mmol)，为一种白色固体。MS m/z 465, 457 (M+1)；^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, 2H), 7.88 (s, 1 H), 7.85 (d, 1H), 7.79 (s, 1 H), 7.47 (d, 1 H), 6.47 (d. 2H), 3.80 (s, 2H), 3.50 (m, 4H), 3.43 (d, 2H), 3.30 (d, 2H), 2.98 (s, 3H)。

实施例721

4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-[2-(3-甲基-吡啶-4-基氨基)-乙基]-哌嗪-2-酮

将1-[2-(3-甲基吡啶-4-基-氨基)-乙基]-哌嗪-2-酮(38 mg, 0.16 mmoi)(实施例94)与2-(5-氯-噻吩-2-基)-乙烯磺酰基氯(40 mg, 0.16

mmol)(实施例3)进行反应，采用与实施例719相同的方法。经反相HPLC纯化后，得到标题化合物(29 mg, 0.052 mmol)，为一种白色固体。MS m/z 441, 443 (M+H)；^{1}H NMR (CD_3OD, 300 MHz) δ 8.08 (d, 1 H), 7.98 (s, 1H), 7.56 (d, 1 H), 7.30 (d, 1H), 7.02 (s, 1H), 7.00 (d. 1H), 6.78 (d, 1H), 3.87 (s, 2H), 3.70-3.50 (m, 8H), 2.15 (s, 3H)。

采用上述方法，由实施例92-97所述获得的原料制备下述化合物。

实施例	名称	m/z [M+H]
722	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮	520(M+)
723	1-[2-(吡啶-4-基氨基)-乙基]-4-(噻吩并[2,3-b]吡啶-2-磺酰基)-哌嗪-2-酮	417
724	4-(5'-氯-[2,2']联噻吩-5-磺酰基)-1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮	483, 485
725	1-[2-(吡啶-4-基氨基)-乙基]-4-(噻吩并[3,2-b]吡啶-2-磺酰基)-哌嗪-2-酮	418
726	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮	427, 429
727	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-[2-(甲基吡啶-4-基氨基)-乙基]-哌嗪-2-酮	441
728	4-(2-苯并[b]噻吩-2-基-乙烯磺酰基)-1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮	443
729	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[2-(3-甲基-吡啶-4-基氨基)-乙基]-哌嗪-2-酮	465, 467
730	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-(2-吡咯并[3,2-c]吡啶-1-基-乙基)-哌嗪-2-酮	450, 452

731	1-[2-(2-氨基-3-氯-吡啶-4-基氨基)-乙基]-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮	476, 478
732	1-[2-(2-氨基-5-氯-吡啶-4-基氨基)-乙基]-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮	476, 478
733	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-[2-(2, 3, 5, 6-四氯-吡啶-4-基氨基)-乙基]-哌嗪-2-酮	563, 565, 567, 569
734	1-[2-(2-氨基-3, 5, 6-三氯-吡啶-4-基氨基)-乙基]-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮	544, 546, 548
735	4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-1-[2-(吡啶-4-基氨基)-乙基]-哌嗪-2-酮	391, 393

实施例736

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[2-(哒嗪-4-基-氨基)-乙基]-哌嗪-2-酮

将1-[2-(哒嗪-4-基氨基)-乙基]-哌嗪-2-酮盐酸盐(0.5 g, 1.7 mmol)(实施例95)与6-氯-苯并[b]噻吩-2-磺酰基氯(0.40 g, 1.5 mmol)(实施例1)反应，采用与实施例719所述基本相同的方法。进行反相HPLC纯化，得到标题化合物(0.34 g, 0.75 mmol)，为一种白色固体。MS m/z (M+H=452)；^{1}H NMR (CD_3OD, 300 MHz) δ 8.6 (d, 1 H), 8.4 (d, 1 H), 8.05 (s, 1 H), 8.05 (s, 1 H), 7.9 (d, 1 H), 7.5 (d, 1 H), 7.2 (d, 1 H), 3.8 (s, 2H), 3.4-3.7 (m, 8H)。

实施例737

1-[3-(4-氨基-吡啶-3-基)-丙烯基]-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮

将4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙烯基]-3-氧代-哌嗪-

1-甲酸叔基酯(实施例96, 部分B)(45 mg, 0.10 mmol)溶解于20%TFA/二氯甲烷中,在室温下搅拌2小时。将溶液浓缩成残余物。将残余物溶解于乙腈(2.5 ml)中, 用4-甲基吗啉(0.027 ml, 0.25 mmol)处理。然后, 滴加入2-(5-氯-噻吩-2-基)-乙烯磺酰基氯(24 mg, 0.10 mmol)(实施例3)的乙腈(1 mL)溶液。将反应混合物在室温下搅拌1小时后, 进行反相HPLC纯化, 得到标题化合物, 为一种白色固体(0.040 g, 0.037 mmol)。MS m/z 439, 441 (M+H); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.20 (br, 1H), 8.10 (s, 1H), 8.08 (d, 1H), 7.60 (d, 1H), 7.53 (d. 1 H), 7.35 (d, 1 H), 7.21 (d, 1H), 7.07 (d, 1H), 6.82 (d, 1H), 5.27 (m, 1 H), 3.88 (s, 2H), 3.60-3.50 (m, 4H), 3.30 (d, 2H)。

采用上述方法, 由实施例92-97所述获得的原料制备下述化合物。

实施例	名称	m/z [M+H]
738	1-[3-(4-氨基-吡啶-3-基)-丙烯基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	463, 465
739	1-[3-(4-氨基-吡啶-3-基)-烯丙基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	463, 465
740	1-[3-(4-氨基-吡啶-3-基)-烯丙基]-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮	439, 441
741	1-[3-(4-氨基-吡啶-3-基)-丙基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	465, 467
742	1-[3-(4-氨基-吡啶-3-基)-丙基]-4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-哌嗪-2-酮	441, 443

实施例743

4-[2-(5-氯噻吩-2-基)-乙烯磺酰基]-1-(2-吡咯并[3,2-c]吡啶-1-

基乙基)-哌嗪-2-酮

将4-(苄氧基羰基)-1-(2-吡咯并[3,2-c]吡啶-1-基乙基)-哌嗪-2-酮(0.028 g, 0.074 mmol)(实施例98)用4 %甲酸/甲醇(5 mL)和催化量的Pd黑处理5分钟。将反应混合物过滤，用甲醇洗涤，将滤液浓缩成残余物。将残余物用乙腈(3 mL)，过量的N-甲基吗啉(0.04 mL)，2-(5-氯噻吩-2-基)乙烯-磺酰基氯(0.018 g, 0.074 mmol)(实施例3)按照常规(实施例719)处理。进一步进行色谱纯化(氢氧化铵/甲醇/二氯甲烷: 1/4/95)，得到标题化合物: MS m/z 451,453 (M+H); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.93 (bs, 1H), 8.24 (bs, 1H), 7.41 (d, 1 H), 7.23 (d, 1H), 7.14 (m, 2H), 6.94 (d, 1 H), 6.68 (d. 1 H), 6.18 (d, 1H), 4.43 (t, 2H), 3.67 (t, 2H), 2.88 (t, 2H), 2.66 (t, 2H)。

实施例744

4-丙-2-炔基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 2-(2-氧代-4-丙-2-炔基-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

将包含2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(4.3 g, 13.0 mmol)(实施例69)的乙腈(250 mL)溶液冷却至0 C。向反应混合物中加入碳酸钾(1.98 g, 14.3 mmol)，再加入炔丙基溴(1.55g, 13.0 mmol)。将混合物缓慢升温至室温，保持该温度直至通过TLC观察到原料完全消耗(大约8小时)。将混合物浓缩至干然后，在碳酸氢钠水溶液(200 mL)与二氯甲烷(200 mL)间分配，分层。水相用二氯甲烷(100 mL)萃取两次，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行快速硅胶色谱纯化(二氯甲烷-5%甲醇/二氯甲烷)，得到3.38 g (70%)的标题化合物，为一种浅黄色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 9H), 2.34 (t, J =2.4 Hz, 1 H), 2.89 (m, 2H), 3.42 (s, 2H), 3.45 (d, J =2.4 Hz, 2H), 3.52 (m, 2H), 4.95 (d, J =1.4 Hz, 2H), 6.42 (br s, 1 H), 7.88 (dd, J =5.8, 0.8 Hz, 1 H), 8.41 (d, J =5.8 Hz, 1 H), 8.78 (d,

J =0.8 Hz, 1 H) ppm; MS (EI): m/z 368 (M^+)。

B. 4-丙-2-炔基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

在0℃下，向包含2-(2-氧代-4-丙-2-炔基-哌嗪-1-基甲基)-吡咯并[3,2c]吡啶-1-甲酸叔丁酯(1.3 g, 3.53 mmol)的二氯甲烷(100 mL)溶液中加入TFA(20 mL)。6小时后，将反应混合物浓缩至干，在碳酸氢钠水溶液(500 mL)和二氯甲烷(200 mL)间分配，分层。水相用二氯甲烷(100 mL)萃取4次，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行快速硅胶色谱纯化(二氯甲烷-10%甲醇/二氯甲烷)，得到616 mg (65%)的标题化合物，为一种浅黄色固体。^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (app t, J =2.4 Hz, 1 H), 2.76 (m, 2H), 3.33 (s, 2H), 3.83 (d, J =2.4 Hz, 2H), 3.45 (m, 2H), 4.57 (s, 2H), 6.47 (s, 1H), 7.23 (d, J =5.7 Hz, 1H), 8.28 (d, J =5.7 Hz, 1 H), 8.85 (d, J =0.9 Hz, 1 H), 9.34 (br s, 1 H) ppm; MS (EI): m/z 268 (M^+)。

实施例745

1,4-二-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 2-{4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙-2-炔基]-2-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

将包含2-(2-氧代-4-丙-2-炔基-哌嗪-1-基甲基)-吡咯并[3,2c]吡啶-1-甲酸叔丁酯(100 mg, 0.27 mmol)(实施例743)，(3-碘吡啶-4-基)-氨基甲酸叔丁酯(87 mg, 0.27 mmol)(实施例69, 部分B)，三乙胺(110 mg, 1.08 mmol)，$(Ph_3P)_4PdCl_2$ (10 mg, 0.013 mmol)，碘化铜 (1 mg, 0.008 mmol)的无水DMF(5 mL)溶液在室温下进行搅拌。5小时后，将反应混合物用乙酸乙酯(50 mL)和水(50 mL)稀释，分层。水层用乙酸乙酯(25 mL)萃取两次，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行快速硅胶色谱纯化(二氯甲烷-10%甲醇 二氯甲烷)，得到77 mg (51 %)的标题化合物，为一种

无色油。^{1}H NMR (300 MHz, $CDCl_3$, 约2:1的旋转异构体混合物), 主要旋转异构体: δ 1.53 (s, 9H), 1.69 (s, 9H), 2.98 (m, 2H), 3.49 (s, 2H), 3.56 (m, 2H), 3.78 (s, 2H), 4.98 (s, 2H), 6.43 (s, 1H), 7.89 (m, 1 H), 8.09 (m, 2H), 8.34 (m, 1 H), 8.41 (m, 1H), 8.75 (m, 1H) ppm; MS (ISP周线): m/z 561 (M+H)。

B. 2-[4-(1-叔丁氧羰基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-2-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

将1,8-二氮杂二环[5.4.0]十一碳-7-烯(42 mg, 0.27 mmol)加至包含2-{4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙-2-炔基]-2-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(77 mg, 0.14 mmol)的无水乙腈(10 mL)悬浮液中, 将混合物升温至50℃。4小时后, 将反应混合物浓缩至干, 将残余物在二氯甲烷(50 mL)和水(50 mL)间分配, 分层。水层用二氯甲烷(25 mL)萃取两次, 合并后的有机相用盐水洗涤, 用无水硫酸钠干燥, 过滤并浓缩, 得到85 mg的标题化合物, 为一种粗品固体, 其无需进一步纯化即可直接使用。^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 9H), 1.70 (s, 9H), 2.91 (m, 2H), 3.41 (s, 2H), 3.49 (m, 2H), 4.26 (s, 2H), 4.95 (d, J =1.1 Hz, 2H), 6.39 (d, J =0.7 Hz, 1 H), 6.68 (d, J =0.7 Hz, 1 H), 7.86 (m, 1 H), 8.41 (m, 1 H), 8.76 (br s, 1 H), 8.82 (br s, 1 H) ppm; MS (EI): m/z 561 (M+H)。

C. 1,4-二-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

在0℃下, 向包含2-[4-(1-叔丁氧羰基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-2-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(85 mg, 0.14mmol)的二氯甲烷(5 mL)溶液中加入TFA (1 mL), 将溶液缓慢升温至室温。16小时后, 将反应混合物浓缩至干, 用水稀释, 进行反相HPLC纯化[缓冲液A: 水w/0.1 %TFA; 缓冲液B: 乙腈w/0.1%TFA; 梯度: 0%B至45%B, 30分钟内], 得到35 mg (36%, 两步)

的标题化合物，为一种浅黄色冷冻干燥的固体。^{1}H NMR (300 MHz, d_6-DMSO) δ 2.80 (m, 2H), 3.25 (s, 2H), 3.37 (m, 2H), 3.93 (s, 2H), 4.76 (s, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.85 (d, J =6.6 Hz, 1 H), 7.89 (d, J =6. 6 Hz, 1H), 8.37 (d, J =6.7 Hz, 1H), 8.38 (d, J =6.7 Hz, 1 H), 9.17 (s, 1H), 9.19 (s, 1H), 12.80 (s, 1H), 12.96 (s, 1 H), 14.91 (br s, 2H) ppm; MS (离子喷雾): m/z 361 (M+H)。$C_{23}H_{25}ClN_4OS$ MS m/z: 441, 443。

采用上述方法，由实施例69-71所述获得的原料制备下述化合物。

实施例	名称	m/z [M+H]
746	4-(6-氯-1H-苯并咪唑-2-基甲基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	395, 397
747	4-(5'-氯-[2,2']联噻吩-5-基甲基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	443, 445
748	4-[3-(5-氯-噻吩-2-基)-烯丙基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	386, 388
749	4-(5-氯-1H-吲哚-2-基甲基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	394, 396
750	4-(6-氯-萘-2-基甲基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	405, 407
751	4-(7-氯-异喹啉-3-基甲基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	406, 408
752	4-(5'-氯-[2,2']联噻吩-5-基甲基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸甲酯	501, 503
753	1-(5-氯-1H-吲哚-2-基甲基)-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(±)-甲酸甲酯	452, 454

754	1-[(5-氯-噻吩-2-基氧基)-乙酰基]-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-甲酸甲酯	463,465
755	1-(6-氯-苯并[b]噻吩-2-基羰基)-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-甲酸甲酯	483,485
756	1-[1-(3,5-二氯-苯基)-2,5-二甲基-1H-吡咯-3-羰基]-5-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-甲酸甲酯	554,556
757	1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	361
758	4-(3-苯基-丙-2-炔基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	345
759	4-[(3-(5-氯-噻吩-2-基)-丙-2-炔基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	384

用上述方法由3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2c]吡啶-2-基甲基)-哌嗪-2-酮制备下列化合物。

实施例	名称	m/z [M+H]
760	4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	431,433
761	4-(5-氯-1H-吲哚-2-基甲基)-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	438,440
762	4-(5'-氯-[2,2']联噻吩基-5-基甲基)-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	487,489

763	4-(6-氯-苯并[b]噻吩-2-羰基)-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	469,471
764	4-[1-(3,5-二氯-苯基)-2,5-二甲基-1H-吡咯-3-羰基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮,	540,542
765	4-[3-(4-氯-苯基)-(E)-丙烯酰基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	439,441
766	(S)-2-甲氧基甲基-3-氧代-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-1-甲酸(4-氯-苯基)-酰胺,	428,430
767	(S)-4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-3-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	445,447

实施例768

4-(6-氯-苯并[b]噻吩-2-羰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮

A. 2-[4-(6-氯-苯并[b]噻吩-2-羰基)-2-氧代哌嗪-1-基甲基]-(吡咯并[3,2c]吡啶-1-甲酸叔丁酯

此标题化合物按照实施例123所述制备，使用6-氯苯并[b]噻吩-2-甲酸实施例1，2-(2-氧代哌嗪-1-基甲基)吡咯并[3,2-c]吡啶-1-甲酸叔丁酯实施例69。将混合物搅拌过夜，然后浓缩至干。残余物用二氯甲烷、饱和碳酸氢钠、盐水洗涤。有机层用硫酸镁干燥，过滤并真空浓缩，得到标题化合物，为一种固体。粗品产物可以不经进一步纯化直接用于下步反应。

B. 4-(6-氯-苯并[b]噻吩-2-羰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮

在0℃下，将三氟乙酸(0.5 mL)滴加到2-[4-(6-氯-苯并[b]噻吩-2-羰基)-2-氧代哌嗪-1-基甲基]-(吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(0.14 g，0.27 mmol)的6 mL 二氯甲烷溶液中。1小时后，除去冰浴，溶液在室温下搅拌2小时。将此反应混合物真空浓缩。 粗品残余物通过RP-HPLC纯化，以10% 乙腈/H_2O(0.1% TFA)至100% 乙腈的梯度洗脱，合并适当的产物馏份，冻干得到标题化合物(0.07 g，0.13 mmol)，为一种白色固体。ESI MS，$[M+H]^+$=425，427(CI 花样)。

用上述方法，用如实施例69中所述获得的起始物制备下列化合物。

实施例	名称	m/z [M+H]
769	4-[3-(6-氯-苯并[b]噻吩-2-基)-(E)-丙烯酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	451,453
770	4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	405,407
771	4-[1-(3,5-二氯-苯基)-2,5-二甲基-1H-吡咯-3-羰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	497,499
772	4-(5'-氯-[2,2']联噻吩基-5-羰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	457,459
773	4-(5-氯-1H-吲哚-2-羰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	364,366
774	4-[4-(6-甲氧基-吡啶-3-基)-苯甲酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	442
775	4-(4-吡啶-3-基-苯甲酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	412
776	4-[3-(4-溴-噻吩-2-基)-(E)-丙烯酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	446

777	4-[3-(5-氯-噻吩-2-基)-丙酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	403,405
778	4-[(5-氯-3-甲基-苯并[b]噻吩-2-基)-乙酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	453,455
779	4-[2-(4-氯-苯基)-2-甲基-丙酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	411,413
780	4-[3-(3,4-二氯-苯基)-(E)-丙烯酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	431,433
781	4-[(4-氯-苯基)-乙酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	383,385
782	4-[3-(4-氯-苯基)-(E)-丙烯酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	395,397
783	4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	400,402

实施例784

(+)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸甲酯

A. (±)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-5-氧代-哌嗪-1,3-二甲酸1-烯丙基酯3-甲基酯

向含(S)-5-氧代-哌嗪-1,3-二甲酸1-烯丙基酯3-甲基酯(0.43 g, 1.77 mmol), 实施例56, 和2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(0.66 g, 1.77 mmol), 实施例13, 的无水DMF(5 mL)溶液中在0℃下加入60%氢化钠(78 mg, 1.95 mmol)。30分钟后, 此反应混合物升温至室温, 维持6小时。此反应混合物小心地用水停止反应, 然后用水和乙醚稀释。分层, 有机相用水、盐水洗涤两次, 用无水硫酸钠干燥, 过滤并浓缩。粗品残余物进行硅胶色谱处理(2:1己烷/乙酸乙酯至1:1己烷/乙酸乙酯)得到0.37 g(39%)的标题化合物, 为一种玻璃状固体。

^{1}H NMR(300 MHz, $CDCl_3$)δ 3.01-3.22(m, 2H), 3.58(m, 2H),

3.73(s, 3H), 3.86-3.92(m, 1H), 4.42-4.58(m, 4H), 5.25(m, 2H), 5.93(m, 1H), 6.57(br s, 1H), 6.85(d, J =8.2 Hz, 1H), 7.17-7.51(m, 9H), 7.76(m, 2H)ppm; MS(离子喷雾): m/z 537(M+H)。

B. (±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-2-甲酸甲基酯

将四(三苯基膦)钯(0)(237 mg, 0.2 mmol)加入到含(±)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-5-氧代-哌嗪-1,3-二甲酸1-烯丙基酯3-甲基酯(1.10 g, 2.05 mmol)、吗啉(894 mg, 10.2 mmol)的二氯甲烷(30 mL)溶液中。约5分钟后, 将此反应混合物吸附到硅胶上, 进行色谱处理(二氯甲烷至10% 甲醇/二氯甲烷)得到900 mg(97%)的标题化合物, 为粘稠黄色油状物。^{1}H NMR(300 MHz, $CDCl_3$) δ 1.83(br s, 1H), 2.95(dd, J =13.5, 4.3 Hz, 1H), 3.27(br d, J =13.5 Hz, 1H), 3.46-3.72(m, 4H), 3.73(s, 3H), 5.40(d, J =15.3 Hz, 1H), 6.57(br s, 1H), 6.83(dd, J =8.0, 1.2 Hz, 1H), 7.17-7.50(m, 9H), 7.75-7.77(m, 2H)ppm; MS(离子喷雾): m/z 453(M+H)。

C. (±)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲氧基羰基-5-氧代-哌嗪-1-基甲基}-5-氯-吲哚-1-甲酸叔丁酯

向(±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-2-羧酸甲基酯(630 mg, 1.39 mmol)、碳酸钾(380 mg, 2.78 mmol)的无水乙腈(5 mL)混合物中, 在0℃下加入存在于乙腈(4 mL)的2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯(720 mg, 2.09 mmol), 实施例21。此反应混合物升温至室温, 然后维持16小时。此反应混合物用乙醚/水稀释, 分层。有机相用水、盐水洗涤两次, 用无水硫酸钠干燥, 过滤并浓缩。粗品残余物在二氧化硅上进行色谱处理(二氯甲烷至2% 甲醇/二氯甲烷)得到550 mg(55%)的标题化合物, 其不经进一步鉴定直接用于下步反应。

D. (±)-2-{4-(3-氨基-4-氰基-苄基)-3-甲氧基羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯

将部分纯化的(±)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-

3-甲氧基羰基-5-氧代-哌嗪-1-基甲基}-5-氯-吲哚-1-甲酸叔丁酯(550 mg, 0.76 mmol)悬浮于试剂级甲醇(20 mL)中。向此多相混合物中加入12M HCl(5滴)并将此反应混合物维持在室温下直至均匀(约30分钟)。此反应混合物在乙醚、含过量的碳酸氢钠(500 mL)之间分配。分层，有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行硅胶色谱处理(二氯甲烷至2% 甲醇/二氯甲烷)得到400 mg(94%)的标题化合物，其直接用于下步反应。MS(ISP周线): 532(M+H)。

E. (±)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯

含(±)-2-[4-(3-氨基-4-氯基-苄基)-3-甲氧基羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(100 mg, 0.18 mmol)、1,3,5-三嗪(146 mg, 1.81 mmol)、冰醋酸(99 mg, 1.81 mmol)的纯乙醇(10 mL)溶液保持回流16小时。 加入第二批1,3,5-三嗪(146 mg, 1.81 mmol)、冰醋酸(99 mg, 1.81 mmol)并将此反应混合物再保持回流16小时。将此反应混合物真空浓缩，粗品产物用水/乙腈稀释，通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1% TFA; 梯度: 0% B至60% B在30分钟内]得到26 mg(20%)的标题化合物，为一种白色固体，其不经进一步鉴定直接用于下步反应。

F. (±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸甲酯

向(±)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-甲氧基羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(26 mg, 0.03 mmol)的二氯甲烷(4 mL)溶液中，室温下加入三氟乙酸(1 mL)。4小时后，将此反应混合物真空浓缩，然后溶解于水/乙腈，通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1% TFA; 梯度: 0% B至60% B在30分钟内]得到10 mg(47%)的标题化合物，为一种白色固体。^{1}H NMR(300 MHz, d_6-DMSO) δ 2.62(m, 1H), 3.05-3.51(m, 4H), 3.59(s, 3H), 3.81(d, J =14.0 Hz, 1H), 4.26(m, 1H), 4.69(ABq, Δ_{AB} =310

Hz, J_{AB} =16.4 Hz, 2H), 6.26(s, 1H), 7.02(dd, J =8.6, 2.0 Hz, 1H), 7.31(d, J =8.6 Hz, 1H), 7.49(d, J =2.0 Hz, 1H), 7.52(s, 1H), 7.61(d, J =8.7 Hz, 1H), 8.30(d, J =8.6 Hz, 1H), 8.47(s, 1H), 8.77(s, 1H), 9.69(br s, 2H), 11.17(s, 1H)ppm; MS(离子喷雾): m/z 479(M+H)。

实施例785

(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸

A. (±)-1-(3-氨基-4-氰基-苄基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸

室温下将氢氧化锂一水合物(380 mg, 9.06 mmol)加入到(±)-2-[4-(3-氨基-4-氰基-苄基)-3-甲氧基羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(1.0 g, 1.81 mmol), 实施例784, 部分E, 的1:1:1 THF/甲醇/水(30 mL)的溶液中。16小时后, 加入HOAc(0.5 mL)并将此反应混合物真空浓缩。 残余物溶解于乙腈/水, 通过反相HPLC纯化[缓冲液A: 水w/0.1% TFA; 缓冲液B: 乙腈 w/0.1% TFA; 梯度: 0% B至60% B在30分钟内]得到378 mg(48%)的标题化合物, 为一种白色固体。^{1}H NMR(300 MHz, d_6-DMSO) δ 3.03(m, 1H), 3.48(m, 1H), 3.51(ABq, Δ_{AB} =69.2 Hz, J_{AB} =16.4 Hz, 2H), 3.78(d, J =15.9 Hz, 1H), 4.05-4.09(m, 2H), 5.04(d, J =15.9 Hz, 1H), 6.41(m, 2H), 6.58(s, 1H), 7.04(dd, J =8.6, 2.0 Hz, 1H), 7.25(d, J =8.0 Hz, 1H), 7.35(d, J =8.6 Hz, 1H), 7.51, d, J =2.0 Hz, 1H)ppm; MS(ISP周线): m/z 438(M+H)。

B. (±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸

将(±)-1-(3-氨基-4-氰基-苄基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸(200 mg, 0.30 mmol)、1,3,5-三嗪(244 mg, 3.00 mmol)、冰醋酸(180 mg, 3.00 mmol)的纯乙醇(20 mL)溶液保持回流

16小时。此反应混合物冷却至室温,固体在瓷漏斗上收集,用乙醇洗涤,接着用乙醚洗涤。真空下烘箱干燥得到13 mg(76%)的标题化合物,为一种米黄色固体。^{1}H NMR(300 MHz, d_6-DMSO) δ 2.63(m, 1H), 3.06(d, J =16.4 Hz, 1H), 3.24-3.42(m, 4H), 3.68(ABq, Δ_{AB} =34.5 Hz, J_{AB} =14.1 Hz, 2H), 3.96(m, 1H), 4.63(ABq, Δ_{AB} =400 Hz, J_{AB} =15.8 Hz, 2H), 6.27(s, 1H), 6.99(dd, J =8.6, 2.0 Hz, 1H), 7.29(d, J =8.5 Hz, 2H), 7.40(s, 1H), 7.46(s, 1H), 7.69(br s, 2H), 8.10(d, J =8.5 Hz, 1H), 8.32(s, 1H), 11.20(s, 1H)ppm; MS(离子喷雾): m/z 465(M+H)。

实施例786. (±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸甲基酰胺

向(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸(25 mg, 0.03 mmol), 实施例785, 及N-甲基吗啉(36 mg, 0.36 mmol)的无水DMF(1 mL)溶液中, 室温下加入甲基胺盐酸盐(10 mg, 0.14 mmol), 接着加入HATU(40 mg, 0.10 mmol)。3小时后, 高真空下除去溶剂, 残余物溶解于乙腈/水, 通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1 % TFA; 梯度: 0% B至60% B在30分钟内]得到22 mg(88%)的标题化合物, 为一种白色固体。^{1}H NMR(300 MHz, d_6-DMSO) δ 2.57(d, J =4.4 Hz, 3H), 2.70(m, 1H), 3.0(m, 1H), 3.66(d, J =14.2 Hz, 1H), 3.77(d, J =14.2Hz, 1H), 3.85(m, 1H), 4.03(d, J =16.3 Hz, 1H), 5.18(d, J =16.3 Hz, 1H), 6.28(s, 1H), 7.02(dd, J =8.5, 2.0 Hz, 1H), 7.31(d, J =8.5 Hz, 1H), 7.49(d, J =2.0 Hz, 1H), 7.51(s, 1H), 7.58(d, J =8.6 Hz, 1H), 7.97(m, 1H), 8.31(d, J =8.6 Hz, 1H), 8.79(s, 1H), 9.72(br s, 2H), 11.18(s, 1H)ppm; MS(ISP周线): m/z 478(M+H)。

表1: 由C-6羧酸衍生的酰胺类似物

实施例	名称	m/z [M+H]
787	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸乙基酰胺	492
788	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸二甲基酰胺	492
789	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸苄基酰胺	554
790	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸(2-羟基-乙基)-酰胺	508
791	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸双-(2-羟基-乙基)-酰胺	552
792	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-(吗啉-4-羰基)-哌嗪-2-酮	534
793	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸甲基氨基甲酰基甲基-酰胺	535

下列化合物用上述方法制备。

实施例	名称	m/z [M+H]
794	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-氧代-哌嗪-2-甲酸	458

795	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-氧代-哌嗪-2-甲酸甲酯	472
796	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-氧代-哌嗪-2-甲酸酰胺	457
797	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-氧代-哌嗪-2-甲酸乙基酰胺	458
798	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-(4-甲基-哌嗪-1-羰基)-哌嗪-2-酮	540

实施例799

(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲酯

将(±)-1-(3-氨基-4-氯基-苄基)-4-(6-氯-苯并[b]噻吩-2磺酰基)-6-氧代-哌嗪-2-甲酸甲酯(42 mg, 0.08 mmol)，实施例99、1,3,5-三嗪(40 mg, 0.48 mmol)、冰醋酸(30 mg, 0.48 mmol)的纯乙醇(1 mL)溶液保持回流16小时。此反应混合物经浓缩，然后溶解于水/乙腈，通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1% TFA; 梯度: 0% B至60% B在30分钟内]得到17 mg(32%)的标题化合物，为一种白色固体。

^{1}H NMR(300 MHz, d_6-DMSO) δ 3.47(m, 1H), 3.67(s, 3H), 3.71(d, J =16.1 Hz, 1H), 4.00(d, J =16.5 Hz, 1H), 4.05(m, 1H), 4.52(m, 1H), 4.72(ABq, Δ_{AB} =248 Hz, J_{AB} =16.5 Hz, 2H), 7.57(m, 2H), 8.05(d, J =8.6 Hz, 1H), 8.20(s, 1H), 8.23(d, J =8.5 Hz, 1H), 8.35(d, J =1.9 Hz, 1H), 8.49(s, 1H), 8.72(s, 1H), 9.57(br s, 2H)ppm; MS(离子喷雾): m/z 546(M+H)。

实施例800

(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸

将水(1 mL)加入到(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲酯(20 mg, 0.03 mmol), 实施例799, 的THF/甲醇1: 1混合物(2 mL)溶液中。室温下, 再加入氢氧化锂一水合物(15 mg, 0.35 mmol)。16小时后, 此反应混合物用水稀释, 通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1 % TFA; 梯度: 0% B至60% B在30分钟内]得到12 mg(63%)的标题化合物, 为一种白色固体。

^{1}H NMR(300 MHz, d_6-DMSO) δ 3.69(d, J =16.0 Hz, 1H), 3.97(d, J =16.0 Hz, 1H), 4.08(d, J =11.7 Hz, 1H), 4.18(d, J =16.2 Hz, 1H), 4.31(d, J =2.7 Hz, 1H), 5.20(d, J =16.2 Hz, 1H), 7.47(d, J =8.7 Hz, 1H), 7.52(s, 1H), 7.58(dd, J =8.6, 1.9 Hz, 1H), 8.06(d, J =8.7 Hz, 1H), 8.16(d, J =8.6 Hz, 1H), 8.19(s, 1H), 8.34(d, J =1.9 Hz, 1H), 8.54(s, 1H), 8.77(brs, 1H)ppm; MS(离子喷雾): m/z 532(M+H)。

实施例801

(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸酰胺

向含(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸(45 mg, 0.08 mmol), 实施例800、N-甲基吗啉(18 mg, 0.18 mmol)、HATU(35 mg, 0.09 mmol)的无水DMF(1 mL)混合物中, 加入NH_3(7N在甲醇中, 2滴, 约0.5 mmol)。此多相混合物室温下搅拌16小时, 然后浓缩至干。残余物溶解于水, 通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1% TFA; 梯度: 0% B至60% B在30分钟内]得到25 mg(46%)的标题化合物, 为一种白色固体。 ^{1}H NMR(300 MHz, d_6-DMSO) δ 3.63(d, J =16.0 Hz, 1H), 4.01(m, 4H), 5.17(d, J =16.6 Hz, 1H), 7.58(m, 3H), 8.08(d, J =8.6 Hz,

1H)，8.17(s，1H)，8.26(d，J =8.6 Hz，1H)，8.34(d，J =1.9 Hz，1H)，8.74(s，1H)，9.63(br s，2H)ppm；MS(ISP周线)：m/z 531(M+H)。

下列化合物用上述方法制备。

实施例	名称	m/z [M+H]
802	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸乙酯	560
803	(+/-)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸	531
804	(+/-)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸甲基酰胺	544
805	(+/-)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸乙基酰胺	558
806	(+/-)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸二甲基酰胺	558
807	(+/-)-1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(吗啉-4-羰基)-哌嗪-2-酮	600

实施例808

(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲酯

A. (±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲酯

向(±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-2-甲酸甲酯(1.17g，2.6mmol)，实施例784，部分B、5-氯噻吩-2-基

氧基乙酸(0.5g, 2.6mmol), 实施例24和N-甲基吗啉(0.58g, 5.72mmol)的无水DMF(10mL)溶液中, 室温下加入HATU(1.09g, 2.86mmol). 1.5小时后, 将此反应混合物用二氯甲烷(100ml)和碳酸氢钠水溶液(100mL)稀释, 并分层。将此有机相用二氯甲烷(100mL)洗涤4次, 并将合并的有机相用盐水洗涤1次, 用硫酸钠干燥, 过滤并浓缩。将此粗品酰胺通过快速硅胶色谱纯化(己烷/乙酸乙酯, 4:1至1:2)得到1.5g的标题化合物, 其直接用于下步反应。1H NMR(300MHz, $CDCl_3$, 旋光异构体的约2:1混合物)主要的旋光异构体: δ 3.55(d, J=15.2Hz, 1H), 3.60(m, 1H), 3.69(m, 5H), 4.37(d, J=17.7Hz, 1H), 4.62(m, 2H), 4.79(d, J=13.3Hz, 1H), 5.35(d, J=15.2Hz, 1H), 6.05(d, J=3.9Hz, 1H), 6.52(m, 2H), 6.84(d, J=8.1Hz, 1H), 7.18-7.49(m, 11H), 7.76(m, 1H)ppm; MS(ISP周线): m/z 627(M+H)。

B. (±)-1-(3-氨基-4-氰基-苄基)-4-(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲基酯

将浓盐酸(12M, 0.5 mL)在0℃下加入到(±)-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲酯(1.5 g, 2.39 mmol)的4:1甲醇/THF(25 mL)溶液中。1.5小时后, 此反应混合物经浓缩至干, 然后在EtOAc/碳酸氢钠水溶液的1: 1混合物(200 mL) 之间分配, 分层。水相用乙酸乙酯萃取, 然后将合并的有机相用盐水洗涤, 用无水硫酸钠干燥, 过滤并浓缩。粗品残余物进行硅胶色谱处理(己烷/EtOAc, 4:1至1: 2)得到934 mg(84%, 两步)的标题化合物。^1H NMR(300 MHz, $CDCl_3$, 旋光异构体的约2 : 1混合物)所选峰: δ 3.16(约dd, J 14.0, 3.8 Hz, 1H), 3.68(s, 3H), 3.96(约dd, J =3.8, 2.0 Hz, 1H), 4.17(d, J =17.7 Hz, 1H), 4.45(br s, 2H), 4.62(m, 2H), 4.87(d, J =14.1 Hz, 1H), 5.21(d, J =15.1 Hz, 1H), 6.07(m, 1H), 6.51(d, J =3.8 Hz, 1H), 6.57(d, J =7.9 Hz, 1H), 6.62(br s, 1H), 7.35(d, J =7.9 Hz, 1H)ppm; MS(ISP周线); 463(M+H)。

C. (±)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙

酰基]-6-氧代-哌嗪-2-甲酸甲酯

将含(±)-1-(3-氨基-4-氯基-苄基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲酯(110 mg, 0.25 mmol)、1,3,5-三嗪(207 mg, 2.55 mmol)、冰醋酸(157 mg, 2.55 mmol)的纯乙醇(5 mL)溶液保持回流16小时。此反应混合物经浓缩至干,然后通过反相HPLC纯化[缓冲液A: 水w/0.1% TFA; 缓冲液B: 乙腈 w/0.1% TFA; 梯度: 0% B至60% B在30分钟内]得到50 mg(32%)的标题化合物, 为一种白色固体。^{1}H NMR(300 MHz, d_6-DMSO) δ 3.34-3.89(m, 2H), 3.60(s, 3H), 4.14-4.54(m, 3H), 4.64(br d, J =14.4 Hz, 1H), 4.78-5.11(m, 3H), 6.19(d, J =4.1 Hz, 1H), 6.73(d, J =4.1 Hz, 1H), 7.64(s, 1H), 7.65(d, J =9. 0 Hz, 1H), 8.34(d, J =9. 0 Hz, 1H), 8.79(s, 1H), 9.71(br s, 2H)ppm; MS(离子喷雾): m/z 490(M+H)。

实施例809

(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲基酰胺

将水(1 mL)加入到(±)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲酯(20 mg, 0.03 mmol), 实施例808, 的THF/甲醇的1: 1混合物(2 mL)溶液中。室温下, 再加入氢氧化锂一水合物(3 mg, 0.07 mmol)。16小时后, 此反应混合物用水稀释, 通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1 % TFA; 梯度: 0% B至60% B在30分钟内]得到25 mg(> 100 %)的 有关的酸, 冷冻后为一种白色固体, 其直接用于下步反应。向(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸(12 mg, 0.02 mmol)、N-甲基吗啉(19 mg, 0.19 mmol)、HATU(22 mg, 0.05 mmol)的无水DMF(1 mL)混合物中, 加入$MeNH_2$盐酸盐(5 mg, 0.19 mmol)。此反应混合物室温下搅拌1小时, 然后浓缩至干。残余物溶解于水, 通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1 % TFA; 梯度: 0% B至60% B在30分钟

内]得到7 mg(58%)的标题化合物，为一种白色固体。

^{1}H NMR(300 MHz, d_6-DMSO)旋转异构体的混合物：δ 2.51(m, 3H), 4.07-4.54(m, 6H), 4.87(m, 2H), 5.10(m, 1H), 6.18(m, 1H), 6.74(m, 1H), 7.62(m, 2H), 8.06(br s, 1H), 8.32(br d, J =8.8Hz, 1H), 8.78(s, 1H), 9.61(br s, 2H)ppm; MS(ISP周线)：489(M+H)。

下列化合物用上述方法制备。

实施例	名称	m/z [M+H]
810	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸乙基酰胺	503

实施例811

(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸

将水(0.5 mL)加入到(±)-1-(3-氨基-4-氰基-苄基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸甲酯(35 mg, 0.08 mmol)，实施例808，部分B，的THF/甲醇的1：1混合物(1 mL)溶液中。室温下，再加入氢氧化锂一水合物(4 mg, 0.10 mmol)。16小时后，加入另一批氢氧化锂一水合物(4 mg, 0.10 mmol)并将此反应混合物再搅拌2小时，然后用水稀释，通过反相HPLC纯化[缓冲液A：水w/0.1 % TFA；缓冲液B：乙腈 w/0.1 % TFA；梯度：0% B至60% B在30分钟内]得到40 mg(95%)的有关酸，冻干后为一种白色固体，其直接用于下步反应。MS(ISP周线)：m/z 449(M+H)。

将(+/-)-1-(3-氨基-4-氰基-苄基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸(20 mg, 0.03 mmol)、1,3,5-三嗪(28 mg, 0.34 mmol)、冰醋酸(20 mg, 0.34 mmol)的纯乙醇(6 mL)溶液保持回流16小时。此反应混合物经浓缩至干，然后通过反相HPLC纯化[缓

冲液A：水w/0.1 % TFA；缓冲液B：乙腈 w/0.1 % TFA；梯度：0% B至60% B在30分钟内]得到15 mg(75%)的标题化合物，为一种白色固体。^{1}H NMR(300 MHz, d_6-DMSO) δ 3.75-4.38(m, 5H), 4.67(d, J =14.8 Hz, 1H), 4.79(d, J =15.3 Hz, 1H), 4.95(m, 1H), 5.09(br d, J =16.0 Hz, 1H), 6.18(m, 1H), 6.71(m, 1H), 7.64(m, 2H), 8.31(d, J =8.5 Hz, 1H), 8.75(s, 1H), 9.64(br s, 2H)ppm；MS(ISP周线)：m/z 476(M+H)。

实施例812

4-丙-2-炔基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 2-(2-氧代-4-丙-2-炔基-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

将2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(4.3 g, 13.0 mmol)，实施例69，的乙腈(250 mL)溶液冷却至0℃。将碳酸钾(1.98 g, 14.3 mmol)加入到此反应混合物中，接着炔丙基溴(1.55g, 13.0 mmol)。将混合物缓慢升温至室温，维持至通过TLC观察起始物完全反应(约8小时)。将混合物浓缩至干，然后在碳酸氢钠水溶液(200 mL)、二氯甲烷(200 mL)之间分配，分层。水相用二氯甲烷(100 mL)萃取两次，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行快速硅胶色谱纯化(二氯甲烷至5%甲醇/二氯甲烷)得到3.38 g(70%)的标题化合物，为一种浅黄色固体。^{1}H NMR(300 MHz, $CDCl_3$) δ 1.69(s, 9H), 2.34(t, J =2.4 Hz, 1H), 2.89(m, 2H), 3.42(s, 2H), 3.45(d, J =2.4 Hz, 2H), 3.52(m, 2H), 4.95(d, J =1.4 Hz, 2H), 6.42(br s, 1H), 7.88(dd, J =5.8, 0.8 Hz, 1H), 8.41(d, J =5.8 Hz, 1H), 8.78(d, J =0.8 Hz, 1H)ppm；MS(E1)：m/z 368(M^+)。

B. 4-丙-2-炔基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

向2-(2-氧代-4-丙-2-炔基-哌嗪-1-基甲基)-吡咯并[3,2c]吡啶-1-甲酸叔丁酯(1.3 g, 3.53 mmol)的二氯甲烷(100 mL)溶液中，在0℃下加入TFA(20 mL)。6小时后，此反应混合物经浓缩至干，然后在碳

酸氢钠水溶液(500 mL)、二氯甲烷(200 mL)之间分配，分层。水相用二氯甲烷(100 mL)萃取四次，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行快速硅胶色谱纯化(二氯甲烷至10% 甲醇/二氯甲烷)得到616 mg(65%)的标题化合物，为一种浅黄色固体。^{1}H NMR(300 MHz, $CDCl_3$) δ 2.27(约t, J =2.4 Hz, 1H), 2.76(m, 2H), 3.33(s, 2H), 3.83(d, J =2.4 Hz, 2H), 3.45(m, 2H), 4.57(s, 2H), 6.47(s, 1H), 7.23(d, J =5.7 Hz, 1H), 8.28(d, J =5.7Hz, 1H), 8.85(d, J =0.9 Hz, 1H), 9.34(br s, 1H)ppm; MS(El): m/z 268(M^+)。

实施例813

1,4-双-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 2-{4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙-2-炔基]-2-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

将含2-(2-氧代-4-丙-2-炔基-哌嗪-1-基甲基)-吡咯并[3,2c]吡啶-1-甲酸叔丁酯(100 mg, 0.27 mmol)，实施例812、(3-碘代吡啶-4-基)-氨基甲酸叔丁酯(87 mg, 0.27 mmol)，实施例69，部分B、Et_3N(110 mg, 1.08 mmol)、$(PH_3P)_4PdC_{L2}$(10 mg, 0.013 mmol)、CuI(1 mg, 0.008 mmol)的无水DMF(5 mL)溶液室温下搅拌。5小时后，此反应混合物用EtOAc(50 mL)、水(50 mL)稀释，分层。水层用乙酸乙酯(25 mL)萃取两次，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩。粗品残余物进行快速硅胶色谱纯化(二氯甲烷至10% 甲醇 二氯甲烷)得到77 mg(51 %)的标题化合物，为无色油状物。^{1}H NMR(300 MHz, $CDCl_3$, 约2: 1旋转异构体的混合物)主要的旋转异构体: δ 1.53(s, 9H), 1.69(s, 9H), 2.98(m, 2H), 3.49(s, 2H), 3.56(m, 2H), 3.78(s, 2H), 4.98(s, 2H), 6.43(s, 1H), 7.89(m, 1H), 8.09(m, 2H), 8.34(m, 1H), 8.41(m, 1H), 8.75(m, 1H)ppm; MS(ISP周线): m/z 561(M+H)。

B. 2-[4-(1-叔丁氧羰基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-2-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

将1,8-二氮杂双环[5.4.0]十一碳-7-烯(42 mg, 0.27 mmol)加入到2-{4-[3-(4-叔丁氧羰基氨基-吡啶-3-基)-丙-2-炔基]-2-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(77 mg, 0.14 mmol)的无水乙腈(10 mL)悬浮液中，将混合物升温至50℃。4小时后，此反应混合物经浓缩至干，残余物在二氯甲烷(50 mL)、水(50 mL)之间分配，分层。水层用二氯甲烷(25 mL)萃取两次，合并后的有机相用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩,得到85 mg标题化合物，为一种粗品固体，其不经纯化直接使用。^{1}H NMR(300 MHz, $CDCl_3$) δ 1.68(s, 9H), 1.70(s, 9H), 2.91(m, 2H), 3.41(s, 2H), 3.49(m, 2H), 4.26(s, 2H), 4.95(d, J =1.1 Hz, 2H), 6.39(d, J =0.7 Hz, 1H), 6.68(d, J =0.7 Hz, 1H), 7.86(m, 1H), 8.41(m, 1H), 8.76(br s, 1H), 8.82(br s, 1H)ppm; MS(El): m/z 561(M+H)。

C. 1,4-双-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

向2-[4-(1-叔丁氧羰基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-2-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(85 mg, 0.14mmol)的二氯甲烷(5 mL)溶液中，在0℃下加入TFA(1 mL)，溶液缓慢升温至室温。16小时后，此反应混合物经浓缩至干，用水稀释，通过反相HPLC纯化[缓冲液A: 水w/0.1 % TFA; 缓冲液B: 乙腈 w/0.1 % TFA; 梯度: 0% B至45% B在30分钟内]得到35 mg(36%, 两步)的标题化合物，为一种淡黄色、冻干的固体。

^{1}H NMR(300 MHz, d_6-DMSO) δ 2.80(m, 2H), 3.25(s, 2H), 3.37(m, 2H), 3.93(s, 2H), 4.76(s, 2H), 6.88(s, 1H), 6.94(s, 1H), 7.85(d, J =6.6 Hz, 1H), 7.89(d, J =6.6 Hz, 1H), 8.37(d, J =6.7Hz, 1H), 8.38(d, J =6.7 Hz, 1H), 9.17(s, 1H), 9.19(s, 1H), 12.80(s, 1H), 12.96(s, 1H), 14.91(br s, 2H)ppm; MS(离子喷雾): m/z 361(M+H)。$C_{23}H_{25}ClN_4OS$ MS m/z: 441, 443。

实施例814

2-氨基-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲

基]-苯甲腈

A. {1-[3-二苯亚甲基-氨基)-4-氰基-苄基]-2-氧代-哌啶-4-基}-乙酸乙基酯

氢化钠(140 mg, 3.51 mmol)加入到(2-氧代-哌啶-4-基)-乙酸乙基酯(500 mg, 2.70 mmol)的10 mL THF的冷却溶液中。搅拌45分钟后,加入2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(1.43 g, 3.82 mmol),实施例13,将此反应搅拌过夜。 除去THF,残余物在在250mL乙酸乙酯中回收。过量的氢化钠用5mL水停止反应,接着进行正常的水处理。粗品产物进行硅胶色谱处理(50% EtOAc/己烷)得到{1-[3-二苯亚甲基-氨基)-4-氰基-苄基]-2-氧代-哌啶4-基}-乙酸乙基酯(732 mg, 57%),为一种亮黄色固体。$C_{30}H_{29}N_3O_3$ MS m/z: 480, 482。元素分析理论值$C_{30}H_{29}N_3O_3$: C, 75.13; H, 6.09; N, 8.76。实测值C, 73.01; H, 6.02; N, 8.46。

B. {1-[3-二苯亚甲基-氨基)-4-氰基-苄基]-2-氧代-哌啶-4-基}-乙酸

向{1-[3-二苯亚甲基-氨基)-4-氰基-苄基]-2-氧代-哌啶-4-基}乙酸乙基酯(732 mg, 1.53 mmol)的5 mL的THF溶液中,加入1N氢氧化钠(1.53 ml, 1.53 mmol)。搅拌4小时,除去THF,加入EtOAc(500 mL)。将此反应混合物酸化至pH为6,接着进行正常的水处理。分离所需的羧酸(571 mg, 83% 收率),为一种白色固体。

C. N-(2-氨基-5-氯-苯基)-2-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-2-氧代-哌啶-4-基}-乙酰胺。

向{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-2-氧代-哌啶-4-基}-乙酸(190 mg, 0.422 mmol)的THF(5 mL)和二氯甲烷(3 mL)的浆液中,加入三乙胺(0.09 ml, 0.633 mmol)。将此溶液冷却至0℃,加入存在于甲苯中的1 M 氯代甲酸异丙酯(0.422 mL, 0.422 mmol)。将此均匀的混合物升温至室温,然后加入4-氯-1,2-亚苯基-二胺(150 mg, 1.06 mmol)。此反应室温下搅拌过夜。除去挥发性溶剂,将所得残余物进行色谱处理(SiO_2,5% 甲醇/EtOAc)得到N-(2-氨基-5-氯-苯

基)-2-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-2-氧代-哌啶-4-基}-乙酰胺(200 mg, 82% 收率)。$C_{34}H_{30}ClN_5O_2$ MS m/z: 576, 578。

D. 2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基}-苯甲腈

将此乙酰胺(200 mg, 0.35 mmol)溶解于2 mL的乙酸中, 回流3小时。 除去乙酸, 在乙酸乙酯中回收残余物, 用饱和碳酸氢钠洗涤。浓缩溶剂得到2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基}-苯甲腈(200 mg, 100% 收率), 其不经纯化即可使用。$C_{34}H_{28}ClN_5O_5$ MS m/z: + 558, 560。

E. 2-氨基-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基]-苯甲腈盐酸盐

将上述苯甲腈(220 mg, 0.36 mmol)溶解于5 mL的甲醇中。向冰冷的甲醇溶液中通入氢氯酸接着加入3滴水。室温下搅拌1小时后, 除去甲醇。所得白色固体用乙酸乙酯研磨。高真空下干燥后,得到2-氨基-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基]-苯甲腈盐酸盐(145.6 mg, 87% 收率), 为一种白色固体。$C_{21}H_{20}ClN_5O$: MS m/z: 394, 396。

实施例815

4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基]苯甲腈

向冰冷的4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基]-苯甲腈(127 mg, 0.336 mmol)的10 mL的甲醇溶液中通入氢氯酸。该溶液中还含有3A分子筛。此反应在-30℃下保存48小时。 将此甲醇在旋转蒸发器中浓缩。加入新鲜甲醇(15 mL), 接着通入氨气流。此反应加热回流2.5小时。此反应混合物室温下过滤。从母液中除去甲醇。将所得残余物通过反相HPLC纯化(0-50 % ACN/H_2O)。分离产物, 为一种白色固体, 熔点为105-110℃。$C_{21}H_{22}ClN_5O$ MS m/z: 396, 398。元素分析理论值$C_{21}H_{22}ClN_5O \cdot 2C_2HF_3O_2$: C, 48.13; H, 3.88; N, 11.22。

实测值：C，45.05；H，3.52；N，9.89。

实施例816

1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-基甲基)哌啶-2-酮

向2-氨基-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基]-苯甲腈盐酸盐(143 mg，0.308 mmol)，实施例814，部分E，在2 mL的乙醇的溶液中，加入三乙胺(0.05 mL，0.366 mmol)、冰醋酸(0.02mL，0.366 mmol)、三嗪(15 mg，0.183 mmol)。将所得混合物回流过夜。用旋转蒸发器除去挥发性溶剂，残余物通过反相HPLC纯化(0-50% 乙腈/H_2O)。分离所需产物(110 mg，55% 收率)，为一种白色粉末，熔点为128-132℃。$C_{22}H_{21}ClN_6O$ MS m/z：421，423。元素分析理论值$C_{22}H_{21}ClN_6O$：C，48.12；H，3.57；N，12.95。实测值：C，45.79；H，3.68；N，11.94。^1H NMR(CD_3OD) δ：8.67(s，1H)；8.31(d，1 H，J =4.0 Hz)；7.83-7.55(m，5H)；4.93-4.73(m，2H)；3.48-3.42(m，2H)；3.31-3.21(m，2H)；2.71-2.58(m，2H)；2.43-2.33(m，1H)；2.07-2.01(m，1H)；1.82 -1.69(m，1H)。

实施例817

4-(6-氯-1H-苯并咪唑-2-基甲基)-1-(2,4-二氨基-喹唑啉-7-基甲基)-哌啶-2-酮

将2-氨基-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基]-苯甲腈 盐酸盐(70 mg，0.15 mmol)，实施例814，部分E、吡啶(1.0 mL)、新鲜制备的氯甲酰胺盐酸盐(150 mg，1.33 mmol)置于密封的试管中，加热至200℃。所得混合物加热24小时。 粗品反应混合物直接通过反相HPLC纯化(0-50% ACN/H_2O)。分离产物(53 mg，45%收率)，为一种黄褐色固体。$C_{22}H_{22}ClN_7O$ MS m/z：436，438。元素分析理论值$C_{22}H_{22}ClN_7O$：C，43.23；H，3.24；N，12.60。实测值：C，43.16；H，3.44；N，13.40。

实施例818

1-(4-氨基-2-甲基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-基甲基)-哌啶-2-酮

将氯化氢气流间歇地通过冰冷的2-氨基-4-[4-(6-氯-1H-苯并咪唑-2-基甲基)-2-氧代-哌啶-1-基甲基]-苯甲腈盐酸盐(57 mg, 0.123 mmol), 实施例814, 部分E、乙腈(0.03 mL, 0.93 mmol)在1.5 mL的二噁烷的混合物中, 通入6小时。除去二噁烷; 残余物通过反相HPLC纯化(0-40 % ACN/H_2O)。分离所需产物(9.5 mg, 12% 收率), 为一种澄清蜡状物。$C_{23}H_{23}ClN_6O$ MS m/z: 435, 437。

下列化合物用如上所述方法制备。

实施例	名称	m/z [M+H]
819	(3S,5R)-4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-3,5-二甲基-2-氧代-哌嗪-1-基甲基]-苯甲腈	441,443
820	(3S,5S)-4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-3,5-二甲基-2-氧代-哌嗪-1-基甲基]-苯甲腈	441,443
821	4-{4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3,5-二甲基-2-氧代-哌嗪-1-基甲基}-苯甲腈	431,433
822	(3R,5S)-4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-3,5-二甲基-2-氧代-哌嗪-1-基甲基]-苯甲腈	441,443

实施例823

2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]-N-[2-(3H-咪唑-4-基)-乙基]乙酰胺

A. 4-叔丁氧羰基甲基-3-氧代-哌嗪-1-甲酸苄酯

向3-氧代哌嗪-1-甲酸苄酯(4.68g, 20mmol)的20 mL DMF溶液中, 在0℃下加入氢化钠(60%, 880 mg, 22 mmol)。将此悬浮液室温下搅拌1小时。加如入溴代乙酸叔丁基酯(4.68 g, 24 mmol)。所得混合物室温下搅拌过夜。用乙酸乙酯(200 mL)稀释后, 将混合物用盐水(3 x 50

mL)洗涤。得自浓缩有机相的粗品残余物在硅胶上进行色谱(30% 乙酸乙酯/己烷)得到5.57 g(80%)的4-叔丁氧羰基甲基-3-氧代哌嗪-1-甲酸苄酯，为一种白色固体。

B. (2-氧代-哌嗪-1-基)乙酸叔丁基酯

将4-叔丁氧羰基甲基-3-氧代哌嗪-1-甲酸苄酯(2.0g, 5.75 mmol)溶解于20 mL的甲醇和2 mL的乙酸中。加入钯(5%)碳(100 mg)，并将此反应混合物在氢气氛下搅拌过夜。将混合物过滤并浓缩。加入乙酸乙酯，用1N氢氧化钠将混合物中和至pH 7。有机层经浓缩，得到(2-氧代-哌嗪-1-基)乙酸叔丁基酯(1.22g)。

C. [4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]乙酸叔丁基酯

向(2-氧代-哌嗪-1-基)乙酸叔丁基酯(1.22 g, 5.7 mmol)的10 mL的二氯甲烷溶液中，加入三乙胺(1.2 mL, 8.55 mmol)，6-氯苯并噻吩磺酰基氯(1.52 g, 5.7 mmol)。在室温下将此反应混合物搅拌过夜。进行快速柱色谱(50 % 乙酸乙酯/己烷)得到2.3 g(92%)的[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]乙酸叔丁基酯。

D. [4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]乙酸

将[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]乙酸叔丁基酯(500mg, 1.13mmol)溶解于1mL的三氟乙酸和3mL的二氯甲烷中。将溶剂与甲苯共沸。分离[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]乙酸(438mg)，为白色固体。

E. 2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]-N-[2-(3H-咪唑-4-基)-乙基]乙酰胺

向[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代哌嗪-1-基]乙酸(47mg, 0.12mmol)的2mL四氢呋喃浆液中，加入三乙胺(0.025mL, 0.18mmol)。将此混合物冷却至0℃，并加入存在于甲苯中的1M氯甲酸异丙基酯溶液(0.12mL, 0.12mmol)。将此混合物搅拌15分钟并加入组胺(13.3mg, 0.12mmol)。将此混合物室温下搅拌过夜。进行反相HPLC(AcCN/H_2O/TFA)得到2-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-氧代

哌嗪-1-基]-N-[2-(3H-咪唑-4-基)-乙基]乙酰胺三氟乙酸盐(17mg, 25%), 为固体。mp 77-82℃; MS m/z 482 (M+H)。

用实施例823的方法由适当的起始物制备下列化合物。

实施例	名称	m/z [M+H]
824	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-吡啶-4-基-乙酰胺	465, 467
825	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-吡啶-3-基甲基-乙酰胺	479, 481
826	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-哌啶-4-基-乙酰胺	471, 473
827	N-(1-亚氨基氨基甲酰基-哌啶-4-基)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-乙酰胺	513, 515
828	5-(2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-乙酰基氨基}-乙基)-咪唑-1-甲酸乙酯	554, 556
829	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-嘧啶-4-基-乙酰胺	466, 468
830	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-苯基-乙酰胺	464, 466
831	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(9H-嘌呤-6-基)-乙酰胺	506, 508
832	N-(4-氨基-2-甲基-嘧啶-5-基甲基)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-乙酰胺	509, 511
833	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(3-咪唑-1-基-丙基)-乙酰胺	496, 498

834	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-[2-(1-甲基-1H-咪唑-4-基)-乙基]-乙酰胺	496, 498
835	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(2-吡啶-4-基-乙基)-乙酰胺	493, 495
836	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-[2-(3-甲基-3H-咪唑-4-基)-乙基]-乙酰胺	496, 498
837	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(2-吡啶-2-基-乙基)-乙酰胺	493, 495
838	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(2-吡啶-3-基-乙基)-乙酰胺	493, 495
839	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(2-咪唑-1-基-乙基)-乙酰胺	482, 484
840	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-[2-(1-甲基-1H-吡咯-2-基)-乙基]-乙酰胺	495, 497
841	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-[2-(5-甲基-1H-咪唑-4-基)-乙基]-乙酰胺	496, 498
842	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(4-二甲基氨基-[1, 3, 5]三嗪-2-基)-乙酰胺	510, 512
843	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-甲基-N-吡啶-4-基-乙酰胺	479, 481
844	N-[2-(2-氨基-吡啶-4-基)-乙基]-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-乙酰胺	508, 510
845	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-[2-(4-甲基-噻唑-5-基)-乙基]-乙酰胺	513, 515

846	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(2-噻唑-4-基-乙基)-乙酰胺	499, 501
847	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-(3-胍基-丙基)-乙酰胺三氟乙酸盐	487, 489
848	N-(3-氨基-丙基)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-乙酰胺	445, 447
849	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-[2-(2-巯基-1H-咪唑-4-基)-乙基]-乙酰胺	514, 516
850	N-[2-(2-氨基-噻唑-4-基)-乙基]-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-乙酰胺	514, 516
851	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-甲基-N-(2-吡啶-4-基-乙基)-乙酰胺	507, 509
852	2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-N-[2-(2-甲硫基-1H-咪唑-4-基)-乙基]-乙酰胺	528, 530

实施例853

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[3-(3H-咪唑-4-基)-丙基]哌嗪-2-酮

A. 3-氧代-4-[3-(3-三苯甲基-3H-咪唑-4-基)-烯丙基-哌嗪-1-甲酸苄酯

将3-氧代-哌嗪基-1-甲酸苄酯(702 mg, 3.0 mmol)溶解于二甲基甲酰胺(10 mL), 并冷却至0℃。加入氢化钠(60%, 148 mg, 3.7 mmol), 接着加入5-(3-氯-丙烯基)-1-三苯甲基-1H-咪唑(473 mg, 1.2 mmol)。将所得混合物室温下放置过夜。高真空下除去大部分二甲基甲酰胺。此反应混合物用乙酸乙酯(250 mL)稀释, 用水停止反应。分层, 用乙酸乙酯(2x 100 mL)进行萃取, 用硫酸镁干燥。残余物经过滤并浓缩后进行硅胶色谱处理(50% EtOAc/己烷)得到3-氧代-4-[3-(3-三苯

甲基-3H-咪唑-4-基)-烯丙基-哌嗪-1-甲酸苄酯(360 mg)，为所需的产物。

B. 4-[3-(3-叔丁氧羰基-3H-咪唑-4-基)-烯丙基]-3-氧代-哌嗪-1-甲酸苄酯

将3-氧代-4-[3-(3-三苯甲基-3H-咪唑-4-基)-烯丙基-哌嗪-1-甲酸苄酯(360 mg, 0.62 mmol)在30%三氟乙酸的二氯甲烷(10 mL)溶液中剧烈搅拌。搅拌3小时，除去三苯甲基。真空下除去挥发性溶剂，粗品产物在二氯甲烷(10 mL)中回收。将吡啶(0.5 ml)、二叔丁基二碳酸酯(176 mg, 0.81 mmol)加入到此溶液中，并将所得混合物搅拌过夜。将此反应混合物浓缩并通过快速柱色谱纯化(SiO_2, 20% EtOAc/己烷)得到4-[3-(3-叔丁氧羰基-3H-咪唑-4-基)-烯丙基]-3-氧代-哌嗪-1-甲酸苄酯(100 mg)。

C. 5-{3-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-丙基}-咪唑-1-甲酸叔丁酯

将钯/炭(10 %, 15 mg)加入到4-[3-(3-叔丁氧基羰基-3H-咪唑-4-基)-烯丙基]-3-氧代-哌嗪-1-甲酸苄酯(50 mg, 0.114 mmol)的5 mL的甲醇溶液中。此反应混合物在氢气氛下搅拌过夜。滤除钯，用旋转蒸发器除去挥发性溶剂。将粗品产物(50 mg, 0.114 mmol)再溶解于二氯甲烷(5 mL)。加入三乙胺(0.06 ml, 0.43 mmol)6-氯-苯并[b]噻吩-2-磺酰基氯(39 mg, 0.15 mmol)，并将所得混合物搅拌过夜。粗品产物直接通过快速柱色谱纯化(SiO_2, 30% EtOAc/己烷)得到5-{3-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-丙基}-咪唑-1-甲酸叔丁酯(30 mg)。

D. 4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[3-(3H-咪唑-4-基)-丙基]-哌嗪-2-酮：

将5-{3-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基]-丙基}-咪唑-1-甲酸叔丁酯(30 mg, 0.055 mmol)在30 %三氟乙酸的二氯甲烷(2 mL)溶液中剧烈搅拌。搅拌3小时后完成此反应。 用旋转蒸发器除去挥发性溶剂，将胶状固体用乙醚研磨几次得到4-(6-氯-苯并

[b]噻吩-2-磺酰基)-1-[3-(3H-咪唑-4-基)-丙基]-哌嗪-2-酮三氟乙酸盐(30 mg)，为一种黄色固体。$C_{18}H_{19}ClN_4O_3S_2$(m/z)+：439，441。元素分析理论值$C_{18}H_{19}ClN_4O_3S_2 \cdot C_2HF_3O_2$：C，43.44；H，3.65；N，10.13。实测值C，42.03；H，3.55；N，8.26。

下列化合物用如上所述方法制备。

实施例	名称	m/z [M+H]
854	4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-哌啶-1-甲腈	470,472 Cl花样
855	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(3-哌嗪-1-基-丙基)-哌嗪-2-酮	457,459 Cl花样
856	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(3-吡啶-4-基-丙基)-哌嗪-2-酮	450,452 Cl花样
857	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-哌啶-4-基-丁基)-哌嗪-2-酮	470,472 Cl花样
858	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(2-哌啶-4-基-乙基)-哌嗪-2-酮	442
859	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(3-哌啶-4-基-丙基)-哌嗪-2-酮	456

实施例860

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-[4-(6-甲氧基吡啶-3-基)-苄基]-哌嗪-2-酮

A. 3-甲氧基甲基-4-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-氧代-哌嗪-1-甲酸苄酯

此标题化合物用实施例66，部分A的方法制备，用5-(4-溴甲基-苯基)-2-甲氧基-吡啶代替4-溴甲基甲苯腈，并用2-甲氧基甲基-3-氧代哌嗪基-1-甲酸苄酯代替3-氧代哌嗪基-1-甲酸苄酯。MS(ISP)m/z 476，(M+H)。

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-[4-(6-甲

氧基-吡啶-3-基)苄基]-哌嗪-2-酮

通过将3-甲氧基甲基-4-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-氧代-哌嗪-1-甲酸苄酯如实施例75，部分C所述脱保护制备此标题化合物。粗品胺在如实施例123所述与3-(5-氯-噻吩-2-基)-(E)-丙烯酸，实施例25偶联。MS(ISP)m/z 516，518,(M+H)，Cl花样。

按照实施例860的方法制备下列化合物。

实施例	名称	m/z [M+H]
861	4'-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-联苯基-2-甲腈	522,524 Cl花样
862	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-氯-3-羟基-苄基)-哌嗪-2-酮	471,473 Cl花样
863	1-苄基-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮	421,423 Cl花样
864	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-氯-苄基)-哌嗪-2-酮	455,457 Cl花样
865	4-[(4-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2-酮	516,518 Cl花样
866	4-[(5-氯-噻吩-3-基氧基)-乙酰基]-1-[4-(6-羟基-吡啶-3-基)-苄基]-3-(S)-甲氧基甲基-哌嗪-2-酮	502,504 Cl花样
867	4-[(5-氯-噻吩-3-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2-酮	516,518 Cl花样
868	4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-[4-(6-羟基-吡啶-3-基)-苄基]-3-(S)-甲氧基甲基-哌嗪-2-酮	502,504 Cl花样

869	4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-甲基-哌嗪-2-酮	482
870	4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-3-(S)-甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	468
871	1-联苯基-4-基甲基-4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-3(S)-乙基-6-甲基-哌嗪-2-酮	
872	4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-1-[4-(6-羟基-吡啶-3-基)-苄基]-3-(S)-甲氧基甲基-哌嗪-2-酮	498,500 Cl花样
873	4-[3-(5-氯-噻吩-2-基)-(E)-丙烯酰基]-3-(S)-甲氧基甲基-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2-酮	512,514 Cl花样

实施例874

1-(3-氨基-1H-吲唑-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮

A. 2-氨基-4-(2-氧代-哌嗪-1-基甲基)-苯甲腈

向4-(3-氨基-4-氰基-苄基)-3-氧代-哌嗪-1-甲酸苄酯盐酸盐(4.0 g, 10.0mmol)的甲醇(45 ml)和二氯甲烷(10 ml)溶液中，加入10% Pd碳(0.6 g)。将混合物在氢气氛下搅拌2小时，通过硅藻土板过滤。将滤液浓缩，残余物通过柱色谱纯化，用存在于甲醇/二氯甲烷的10% 7M NH_3得到标题化合物(1.62 g, 7.0 mmol)。^1H NMR(DMSO, 300MHz) δ 7.34(d, 1H), 6.64(s, 1H), 6.46(d, 1H), 6.04(bs, 2H), 4.40(s, 2H), 3.28(s, 2H), 3.14(m, 2H), 2.87(m, 2H), 2.77(bs, 1H)。MS(离子喷雾): m/z 231 $(M+H)^+$。

B. 2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-2-氧代-哌嗪-1-基甲基]-苯甲腈

向2-氨基-4-(2-氧代-哌嗪-1-基甲基)-苯甲腈(0.345 g, 1.5 mmol)的DMF(2 ml)的冷溶液(0℃)中，加入细粉无水碳酸钾(0.311 g, 2.25 mmol)，搅拌20分钟。向此混合物中加入2-溴甲基苯并[b]噻吩(0.392 g, 1.5 mmol)的DMF(3 ml)溶液，移除冷却浴，搅拌2小时。此反应混合物经高真空浓缩，残余物通过柱色谱纯化，用55% EtOAc/5% 甲醇/己烷洗脱得到标题化合物(0.477 g, 1.16 mmol)，为一种白色固体。^{1}H NMR(DMSO, 300MHz) δ 8.06(d, 1H), 7.78(d, 1H), 7.37(m, 3H), 6.64(s, 1H), 6.44(d, 1H), 6.09(bs, 2H), 4.42(s, 2H), 3.88(s, 2H), 3.21(m, 4H), 2.72(m, 2H)。MS(离子喷雾): m/z 411, 413$(M+H)^+$, Cl花样。

C. 1-(3-氨基-1H-吲唑-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-哌嗪-2-酮

向2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-2氧代-哌嗪-1-基甲基]-苯甲腈(0.365 g, 0.89 mmol)的浓盐酸(2.1 ml)冷溶液(0℃)中，滴加亚硝酸钠(0.068 g, 0.98 mmol)的H_2O(0.2 ml)溶液。将此反应混合物加入到氯化锡(II)二水合物(1.61 g, 7.12 mmol)的浓盐酸(0.62 ml)和H_2O(3 ml)的冷溶液(0℃)中。通过真空过滤收集沉淀，高真空下干燥。粗品固体通过柱色谱纯化，用存在于甲醇/二氯甲烷中的10% 7M NH_3洗脱得到标题化合物(0.144 g, 0.34 mmol)，为一种黄色固体。^{1}H NMR(DMSO, 300MHz) δ 11.35(bs, 1H), 8.05(d, 1H), 7.78(d, 1H), 7.64(d, 1H), 7.37(m, 2H), 7.08(s, 1H), 6.78(d, 1H), 5.75(s, 1H), 5.40(bs, 1H), 4.58(s, 2H), 3.88(s, 2H), 3.20(m, 4H), 2.70(bt, 2H)。MS(离子喷雾): m/z 426$(M+H)^+$。元素分析理论值 $C_{21}H_{20}N_5OSCl$; $(H_2O)_{0.25}$: C, 58.6; H, 4.8; N, 16.3。实测值C, 58.6; H, 4.7; N, 15.9。M. P. =246-248℃。

实施例875

1-(3-氨基-1H-吲唑-6-基甲基)-4-[3-(5-氯-噻吩-2-基)]-哌嗪-2-酮

A. 2-氨基-4-{4-3-(5-氯-噻吩-2-基)-烯丙基]-2-氧代-哌嗪-1-基甲

基}-苯甲腈

按照与实施例874，部分B基本上相同的方法，使用2-(3-溴-丙烯基)-5-氯-噻吩，得到标题化合物。 MS(El)：m/z 386，388(M⁺)，Cl花样。

B. 1-(3-氨基-1H-吲唑-6-基甲基)-4-[3-(5-氯-噻吩-2-基)]-哌嗪-2-酮

按照与实施例874，部分C基本上相同的方法得到标题化合物。^{1}H NMR(DMSO，300MHz) δ 11.32(bs，1H)，7.62(d，1H)，7.06(s，1H)，7.02(d，1H)，6.96(d，1H)，6.78(d，1H)，6.67(d，1H)，5.96(m，1H)，5.32(bs，2H)，4.57(s，2H)，3.19(bt，2H)，3.12(m，4H)，2.64(bt，2H)。MS(El)：m/z 401，403(M⁺)，Cl花样。元素分析理论值$C_{19}H_{20}ClN_5OS$：C，56.8；H，5.0；N，17.4。实测值C，56.6；H，4.8；N，17.2。M.P. =167-169℃。

实施例876

1-(3-氨基-1H-吲唑-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)哌嗪-2-酮

A. 2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-苯甲腈

按照与实施例874，部分B基本上相同的方法，不同的是使用6氯-苯并[b]噻吩-2-磺酰基氯，实施例1，得到标题化合物。 MS(离子喷雾)：m/z 461，463(M+H)⁺，Cl花样。

B. 1-(3-氨基-1H-吲唑-6-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

按照与实施例874，部分C基本上相同的方法，得到标题化合物。^{1}H NMR(DMSO，300MHz) δ 11.29(s，1H)，8.35(s，1H)，8.18(s，1H)，8.08(d，1H)，7.58(m，2H)，7.05(s，1H)，6.70(d，1H)，5.30(bs，2H)，4.56(s，2H)，3.84(s，2H)，3.40(m，2H)，3.30(m，2H)。MS(离子喷雾)：m/z 476，478(M+H)⁺，Cl花样。元素分析理论值$C_{20}H_{18}ClN_5O_3S_2$：

C, 50.5; H, 3.8; N, 14.7. 实测值C, 50.3; H, 3.6 ; N, 14.5. M. P. =274-276℃。

下列化合物用上述方法制备。

实施例	名称	m/z
877	4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-2-(S)-甲基-3,6-二氧代-哌嗪-1-基甲基]-苯甲腈	441,443 Cl花样
878	4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-2-(R)-甲基-3,6-二氧代-哌嗪-1-基甲基]-苯甲腈	441,443 Cl花样
879	3-[4-(6-氯-苯并[b]噻吩-2-基甲基)-2,5-二氧代-哌嗪-1-基甲基]-苯甲腈	427,429 Cl花样
880	4-[4-(6-氯-苯并[b]噻吩-2-基甲基)-2,5-二氧代-哌嗪-1-基甲基]-苯甲腈	427,429 Cl花样

实施例881

5-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯

A. 5-氯-吲哚-1-甲酸叔丁酯:

向NaH(60%, 1.0 g, 25.2 mmol)的无水THF(50 mL)悬浮液中，在0℃下加入5-氯-吲哚(2.73 g, 18.0 mmol)。20分钟后，加入二叔丁基二碳酸酯(4.71 g, 21.6 mmol)并将此反应混合物在0℃下维持4小时。此反应混合物在乙醚(100 mL)、饱和氯化铵水溶液(100 mL)之间分配，分层。水相用乙醚(2 x 50 mL)萃取两次，然后将合并后的有机萃取物用盐水洗涤一次，无水硫酸镁干燥，过滤并浓缩。粗品产物进行快速硅胶色谱纯化(己烷/EtOAc, 30:1to 20: 1)得到4.0 g(89%)的5-氯-吲哚-1-甲酸叔丁酯，为无色固体。^{1}H NMR(300 MHz, $CDCl_3$) δ 1.66(s, 9H), 6.50(d, J =3.5 Hz, 1H), 7.27(m, 1H), 7.52(s, 1H), 7.60(d, J =3.3 Hz, 1H), 8.06(d, J =8.6 Hz, 1H)ppm。

B. 5-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯

向5-氯-吲哚-1-甲酸叔丁酯(4.0 g, 15.9 mmol)的无水THF(60 mL)

溶液中，在-78℃，用注射器滴加存在于戊烷的中1.7M t-BuLi(11.2 mL，19.0 mmol)。在-78℃下1小时后，向此反应混合物中通入5-10分钟的SO_2气体。将此反应混合物升温至室温，然后真空浓缩至干。再将所得固体悬浮于己烷(80 mL)中，冷却至-60℃，滴加SO_2C_{L2}(2.6 g，19.0 mmol)。

16小时后，此反应混合物经浓缩至干，残余物在EtOAc(100 mL)、碳酸氢钠水溶液(100 mL)之间分配。分层，有机相用盐水洗涤一次，用无水硫酸镁干燥，过滤并浓缩。粗品产物进行快速硅胶色谱纯化(己烷/EtOAc，100:1至30：1)得到3.35 g(60%)的5-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯，为一种米黄色固体。^{1}H NMR(300 MHz，$CDCl_3$) δ 1.73(s，9H)，7.52(dd，J =9.1，2.0 Hz，1H)，7.60(s，1H)，7.69(d，J =2.0 Hz，1H)，8.19(d，J =9.1 Hz，1H)ppm。

实施例882

6-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯

A. 6-氯-吲哚-1-甲酸叔丁酯

向NaH(60%，0.41 g，10.3 mmol)的无水THF(20 mL)悬浮液中，在0℃下加入6-氯-吲哚(1.2 g，7.4 mmol)。10分钟后，加入二叔丁基二碳酸酯(1.93 g，8.88 mmol)并将此反应混合物缓慢升温至室温，过夜。此反应混合物经浓缩至干，残余物在乙醚(100 mL)、饱和氯化铵水溶液(100 mL)之间分配，分层。水相用乙醚萃取两次(2 x 50 mL)，然后将合并的有机萃取物用盐水洗涤一次，用无水硫酸镁干燥，过滤并浓缩。粗品产物进行快速硅胶色谱纯化(己烷/EtOAc，10：1)得到6.0 g(82%)的6-氯-吲哚-1-甲酸叔丁酯，为无色固体。^{1}H NMR(300 MHz，$CDCl_3$) δ 1.66(s，9H)，6.52(d，J =3.6 Hz，1H)，7.19(dd，J =8.3，1.8 Hz，1H)，7.45(d，J=8.3Hz，1H)，7.56(d，J=3.6Hz，1H)，8.18(s，1H)ppm。

B. 6-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯

向6-氯-吲哚-1-甲酸叔丁酯(2.1 g，8.34 mmol)的无水THF(30 mL)

溶液中，在-78℃下用注射器滴加存在于戊烷中的1.7 M t-BuLi(6 mL, 10.2 mmol)。在-78℃下1小时后，向此反应混合物中通入5-10分钟的SO_2气体。此反应混合物升温至室温，然后真空浓缩至干。所得固体再悬浮于己烷(80 mL)中，冷却至-60℃，滴加SO_2C_{L2}(0.81 g, 10.0 mmol)。16小时后，此反应混合物经浓缩至干，残余物在乙醚(100 mL)、碳酸氢钠水溶液(100 mL)之间分配。分层，有机相用盐水洗涤一次，用无水硫酸镁干燥，过滤并浓缩。粗品产物进行快速硅胶色谱纯化(己烷/EtOAc, 100:1至30: 1)得到5.34 g(64%)的6-氯-2-氯磺酰基-吲哚-1-甲酸叔丁酯，为米色固体。 ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.74(s, 9H), 7.35(dd, J=8.5, 1.8Hz, 1H), 7.63(m, 2H), 8.31(m, 1H) ppm。

实施例883

3-(5-氯噻吩-2-基)-3-氧代-丙酸叔丁基酯

将乙酸叔丁基酯(2.90g, 25mmol)0.25M THF溶液滴加到双(三甲基硅烷基)氨化钾(100ml的0.5M甲苯溶液)和5-氯噻吩-2-甲酸乙酯(Lancaster)(4.77g, 25mmol)的50ml的冷(-78℃)THF溶液中。将此反应在1小时内室温至0℃。在0℃再搅拌1小时后，将此反应倒入100ml的1M HCl溶液中。用盐水萃取有机层并真空蒸发。将粗品残余物通过快速柱色谱纯化，用5%乙酸乙酯/己烷洗脱得到产物(4.54g, 17mmol)，为油状物。^{1}H NMR($CDCl_3$, 300 MHz) δ 7.53(d, 1H), 6.98(d, 1H), 3.78(3, 2H), 1.50(s, 9H)。

实施例884

6-氯-苯并呋喃甲酸甲酯

A. 4-氯-2-羟基-苄醇

向存在于200ml THF中的7 g $LiAlH_4$中，分批加入15 g的4-氯水杨酸。将所得混合物加热回流1小时，冷却，在室温下搅拌21小时。 滴加存在于THF(50 ml)中的水(7 ml)，接着加入1N盐酸(250 ml)、浓盐

酸(50 ml)、乙酸乙酯(200 ml)。在硅藻土板上过滤后分为两层，有机层用盐水洗涤，用硫酸镁干燥，浓缩。褐色油状物溶解于亚丙基醚并在硅胶短柱上过滤。浓缩后在环己烷中结晶此固体，过滤，洗涤，干燥得到4-氯-2-羟基-苄醇，为一种白色固体(9.7 g，70% 收率)。$C_7H_7ClO_2$ MS(M^+)m/z：158，160，Cl花样。

B. 乙基-(2-羟基甲基-5-氯-苯氧基)-乙酸酯

向4-氯-2-羟基-苄醇(9.7 g，61.3 mmol)的100 mL的DMF溶液中，加入碳酸钾(17 g，123.1 mmol)，所得悬浮液室温下搅拌15分钟。加入溴乙酸乙酯(7.96 ml，67 mmol)，将混合物在室温下搅拌两天。将混合物倒入500 mL的水，用乙酸乙酯(500 ml)萃取。分离乙酸乙酯层，用水(500 ml)、盐水(500ml)洗涤，用硫酸镁干燥。浓缩后，得到乙基-(2-羟基甲基-5-氯-苯氧基)-乙酸酯，为一种白色固体(13.7 g，91 % 收率)。$C_{11}H_{13}ClO_4$，MS(M^+)m/z：244，246，Cl花样。

C. 乙基-(2-甲酰基-5-氯-苯氧基)-乙酸酯

将乙基-(2-羟基甲基-5-氯-苯氧基)-乙酸酯(2.44 g，10 mmol)溶解于40 mL的氯仿中。分两批加入活化的氧化锰(IV)(8.7 g，100 mmol)，将所得悬浮液在室温下搅拌5小时。 在硅藻土板上过滤后，并浓缩得到乙基-(2-甲酰基-5-氯-苯氧基)-乙酸酯(2.18 g，90% 收率)，为一种浅黄色油状物。$C_{11}H_{11}ClO_4$，MS($M+H)^+$：243，Cl花样。

D. 甲基-6-氯-苯并呋喃甲酸

将镁(1.2 g，50 mmol)溶解于40 ml的甲醇中。加入乙基-(2甲酰基-5-氯-苯氧基)-乙酸酯(2.1 g，8.65 mmol)的15 mL的甲醇溶液并将所得混合物加热回流1小时，冷却，倒入1N盐酸(150ml)中。室温下搅拌后滤出黄色固体，用水彻底洗涤，干燥。得到甲基-6-氯-苯并呋喃甲酸，为一种黄色固体(0.835 g，46 % 收率)。

$C_{10}H_7ClO_3$，MS(M^+)：210，Cl花样

实施例885

2-环戊基-3-氧代-哌嗪-1-甲酸苄酯

如实施例41所述制备此标题化合物，用CBZ-1-氨基环戊基-1-甲酸代替Cbz-O-甲基-丝氨酸。^{1}H NMR(CD_3OD, 300MHz) δ 7.32(m, 5H), 5.12(s, 2H), 3.71(m, 2H), 3.28(m, 2H), 2.17(m, 4H), 1.8(m, 4H)。MS(离子喷雾)m/z 289, (M+H)。

实施例886

(+/-)-顺式-4-苄氧基羰基-十氢喹喔啉基-2-酮

A. (+/-)-顺式-十氢喹喔啉基-2-酮

将顺-1,2-二氨基环己烷(4.1 g, 36 mmol)溶解于150 mL的水。在10℃下滴加5分钟的存在于50mL水中噁氯乙酸(3.4 g, 36 mmol)，然后在10℃下滴加存在于30ml水中的碳酸钾(7.9 g, 57 mmol)。将此反应混合物缓慢升温至室温，搅拌24小时。 将此溶液在90℃下加热2小时，浓缩。将所得固体在沸腾的甲苯(100ml)中回收，热过滤，浓缩，得到(+/-)-顺式-十氢喹喔啉基-2-酮(0.8 g, 14% 收率)，为一种白色固体。

$C_8H_{14}N_2O$, MS(M+H)$^+$: 155

B. (+/-)-顺式-4-苄氧基羰基-十氢喹喔啉基-2-酮

将(+/-)-顺式-十氢喹喔啉基-2-酮(0.8 g, 5.19 mmol)悬浮于 25 ml H_2O中。然后滴加碳酸氢钠(0.87 g, 10.35 mmol)并将此反应混合物冷却至10℃。将氯代甲酸苄酯(1 ml, 6.68 mmol)滴加到 剧烈搅拌的混合物中。20小时后室温下滤出固体，用水彻底洗涤，空气干燥。得到标题化合物(1.46g, 98 % 收率)，为一种白色固体。

$C_{16}H_{20}N_2O_3$, MS(M+H)$^+$: 289

实施例887

5-甲基-3-氧代-2-丙基-哌嗪-1-甲酸叔丁酯

A. [1-(甲氧基-甲氧基-1-甲基-氨基甲酰基]-氨基甲酸苄酯

向N-Cbz-1-丙氨酸(12.9 g, 66.7 mmol)和N,O-二甲基羟基胺盐酸盐(7.2 g, 73.8 mmol)的二氯甲烷(200mL)溶液中，加入TBTU(21.43

g, 66.7 mmol)、二异丙基乙胺(25.9 g, 231.5 mmol)。6小时后，溶液用二氯甲烷(200mL)稀释，并用1N HCl、H_2O、饱和NaCl洗涤。有机层用硫酸镁干燥，过滤并浓缩，得到标题化合物，为一种油。MS(EI)m/z 266, (M^+)。

B. [1-甲基-2-氧代-乙基]-氨基甲酸苄酯

向[1-(甲氧基-甲氧基1-甲基-氨基甲酰基]-氨基甲酸苄酯(66.7 mmol)的THF(160mL)溶液中，在0℃下滴加氢化锂铝的1.0M THF溶液(81.1 mmol, 81.1 mL)。20分钟后，滴加1N硫酸氢钾。此溶液用H_2O(200mL)稀释，用1N硫酸氢钾将pH调节至3。所得溶液用乙醚萃取。乙醚萃取物用水和饱和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩，得到标题化合物(12g, 66 mmol)的标题化合物。 MS(EI)m/z 177, (M^+)。

C. 2-[2-苄氧基羰基氨基-丙基氨基]-戊酸甲基酯

向[1-甲基-2-氧代-乙基]-氨基甲酸苄酯(12.3 g, 69 mmol)、正缬氨酸甲基酯盐酸盐(11.6 g, 69mmol)的甲醇(300mL)溶液中，加入二异丙基乙胺(9.4 g, 73 mmol)和2滴乙酸。10分钟后，加入ZnC_{L2}(9.46 g, 69mmol)、氰基硼氢化钠(8.72g, 14 mmol)。溶液室温下搅拌16小时。然后浓缩此溶液。 将残余物溶解于EtOAc和1N $KHSO_4$。将此有机层用1N硫酸氢钾、水和饱和氯化钠洗涤。有机层用硫酸镁干燥，过滤，浓缩。粗品产物通过柱色谱纯化，用20% EtOAc/己烷至40% EtOAc/己烷梯度洗脱。得到标题化合物(8.6 gm, 26.6 mmol)，为一种泡沫。MS(离子喷雾)m/z 323, (M+H)。

D. 5-甲基-3-氧代-2-丙基-哌嗪-1-甲酸叔丁酯

向2-[2-苄氧基羰基氨基-丙基氨基]-戊酸甲基酯(6.6g, 20.5 mmol)的甲醇(100mL)溶液中，加入4滴AcOH和0.65g 10% Pd/C。将此反应的气氛换为氢气。此反应搅拌过夜。然后过滤此溶液得到澄清溶液。溶液经浓缩，残余物溶解于乙醇。将溶液加热回流2小时。此后浓缩此醇溶液。 残余物溶解于二氯甲烷(60 mL)，并加入BOC2O(3.3 g, 15.1 mmol)，接着加入DMAP(0.16 g, 1.3 mmol)。16小时后，此反应

用二氯甲烷(150mL)稀释，用1N 硫酸氢钾、H_2O和饱和氯化钠洗涤。有机层用硫酸镁干燥，过滤并浓缩，得到标题化合物(3.1 g，12.1 mmol)，为一种白色固体。^1H NMR($CDCl_3$，300MHz) δ 7.78(s，1H)，4.36(m，1H)，4.02(m，1H)，3.48(m，2H)，2.49(m，1H)，1.77(m，1H)，1.55(m，1H)，1.39(s，9H)，1.02(d，3H)，0.8(m，3H)。MS(离子喷雾)m/z 257，(M+H)。

实施例888

4-[4-氨基-喹唑啉-7-基甲基]-5-甲基-3-氧代-2-丙基-哌嗪

A. 3-[3-氨基-4-氰基苄基]-2-丙基-5-甲基-3-氧代-哌嗪-1-甲酸叔丁酯

向5-甲基-3-氧代-2-丙基-哌嗪-1-甲酸叔丁酯(3.07 g，12 mmol)，如实施例所述制备887，的THF(150 mL)溶液中，加入t-BuOK(1.3 g，11 mmol)。将此溶液室温下搅拌25分钟。此后，此反应混合物冷却至0℃，加入2-氨基-4-溴甲基-苯甲腈(2.9 g，11.3 mmol)和18-C-6(15 mg)。将溶液升温至室温，搅拌16小时。此后，加入0.5 mL的饱和氯化铵溶液。浓缩此溶液。 残余物通过柱色谱纯化，用20% EtOAc/二氯甲烷洗脱得到标题化合物，为一种白色固体。

MS(离子喷雾)m/z 387，(M+H)。

B. 4-[4-氨基-喹唑啉-7-基甲基]-5-甲基-3-氧代-2-丙基-哌嗪-1-甲酸叔丁酯

向3-[3-氨基-4-氰基苄基]-2-丙基-5-甲基-3-氧代-哌嗪-1-甲酸叔丁酯(1.16 g，3.0 mmol)的乙醇(30 mL)溶液中，加入乙酸(0.55 g，9.0 mmol)和三嗪(0.73 g，9.0 mmol)。将此溶液回流过夜。此后，浓缩此溶液。 残余物通过柱色谱纯化用5%甲醇/二氯甲烷洗脱得到标题化合物(0.91 g)，为一种白色固体。

MS(离子喷雾) m/z 414，(M+H)。

C. 4-[4-氨基-喹唑啉-7-基甲基]-5-甲基-3-氧代-2-丙基-哌嗪

向4-[4-氨基-喹唑啉-7-基甲基]-5-甲基-3-氧代-2-丙基-哌嗪-

1-甲酸叔丁基-酯(0.91 g, 2.2 mmol)所EtOAc(40 mL)溶液中，在0℃下通入5分钟的HCl(气体)。此后，溶液室温下搅拌15分钟。浓缩此溶液。残余物通过柱色谱纯化，用1: 5: 100 NH_4OH/甲醇/二氯甲烷洗脱。得到标题化合物(0.5 g)，为一种白色固体。^1H NMR(300 MHz, CDOD) δ 8.40(s, 1H), 8.04(d, 1H), 7.52(s, 1H), 7.36(m, 1H), 5.10(d, 1H), 4.45(d, 1H), 3.55(m, 2H), 3.10(m, 1H), 2.81(m, 1H), 1.90(m, 1H), 1.72(m, 1H), 1.44(m, 2H), 1.29(d, 3H), 0.96(m, 3H)。

MS(离子喷雾)m/z 314, (M+H)。

实施例889

(R)-3-甲氧基甲基-5-氧代-哌嗪-1-甲酸烯丙基酯

A. (S)-2-苄氧基羰基氨基-3-甲氧基-丙酸甲基酯

将Z-L-丝氨酸(30 g, 0.126 mol)的无水DMF(500 mL)溶液冷却至0℃。在约20分钟内分批加入氢化钠(60%, 11.05 g, 0.28 mol)加入，将混合物搅拌1小时。加入碘代甲烷(23.5 mL, 0.38 mol)，将混合物在0℃搅拌30分钟，然后在室温下搅拌2.5小时，此时TLC表明起始物彻底反应。加入水(1200 mL)，将混合物用乙醚(4 x 200 mL)萃取。合并的有机萃取物用盐水(2 x 200 mL)洗涤，用无水硫酸钠干燥并浓缩得到30 g的粗品(S)-2苄氧基羰基氨基-3-甲氧基-丙酸甲基酯，为一种浅黄色油状物。

B. (R)-(1-羟基甲基-2-甲氧基-乙基)-氨基甲酸苄酯

在-40℃下将氯化钙(16.63 g, 149.8 mmol)加入到硼氢化钠(11.33 g, 299.6 mmol)的乙醇(300 mL)搅拌悬浮液中。将此多相混合物升温至-20℃，搅拌1小时。然后通过转移导管加入存在于纯乙醇(250mL)中的(S)-2-苄氧基羰基氨基-3-甲氧基-丙酸甲基酯(20 g, 74.9 mmol)。将此多相混合物在-20℃搅拌3小时。此反应用水(400 mL)停止反应，小心地用1.0M盐酸酸化。水层水层用二氯甲烷萃取(4 x 200 mL)，合并后的有机相用盐水(200 mL)洗涤，用无水硫酸钠干燥并浓缩得到无色油状物。将混合物吸附到硅胶上，进行硅胶色谱处理(己烷:

EtOAc, 4:1> 2:1> 1:1> 1: 2)得到11.5 g(64%)的(R)-(1-羟基甲基-2-甲氧基-乙基)-氨基甲酸苄酯，为无色油状物。

C. (S)-(1-甲酰基-2-甲氧基-乙基)-氨基甲酸苄酯

向DMSO(3.56 mL, 50.21 mmol)的无水二氯甲烷(50 mL)溶液中，在-78℃下用注射器加入2.0 M草酰氯的二氯甲烷(12.55 mL, 25.1 mmol)溶液。将混合物在-78℃下搅拌10分钟，然后通过转移导管加入(R)-(1-羟基甲基-2-甲氧基-乙基)-氨基甲酸苄酯(5 g, 20.92 mmol)的无水二氯甲烷(100 mL)溶液。将混合物在-78℃下搅拌30分钟。加入三乙胺(14.6 mL, 104.6 mmol)，将混合物置于0℃浴中。此反应在10分钟内反应彻底。将混合物用饱和$NaHSO_4$(200 mL)停止反应，产物水层用二氯甲烷萃取(4 x 100 mL)。合并的有机萃取物用盐水(100 mL)洗涤，用硫酸钠干燥，并浓缩得到(S)-(1-甲酰基-2-甲氧基-乙基)-氨基甲酸苄酯，为黄色油状物，其不经进一步纯化直接使用。^{1}H NMR(300 MHz, $CDCl_3$) δ 3.32(s, 3H), 3.63(dd, J=9. 6, 4.5 Hz, 1H), 3.93(dd, J=9. 6, 3.3 Hz, 1H), 4.36(m, 1H), 5.13(s, 2H), 5.68(br d, 1H), 7.29-7.37(m, 5H), 9.60(s, 1H)ppm。

D. (R)-(2-苄氧基羰基氨基-3-甲氧基-丙基氨基)-乙酸甲酯

向甘氨酸甲基酯HCl(10.51 g, 83.68 mmol)的无水甲醇(100 mL)溶液中，在0℃下加入(S)-(1-甲酰基-2-甲氧基-乙基)-氨基甲酸苄酯(20.92 mmol)的无水甲醇(20 mL)溶液。将此溶液在0℃下搅拌10分钟，然后加入存在于THF(31.38 mL, 31.38 mmol)的1.0 M $NaBH_3CN$，限制将多相混合物升温至室温，过夜搅拌。将混合物经浓缩至干，然后在碳酸氢钠(200 mL)、EtOAc(200 mL)之间分配。分层，水层用乙酸乙酯萃取两次(100 mL)，合并后的有机相用盐水(100 mL)洗涤，用硫酸钠干燥，并浓缩得到黄色油状物，将其吸附到硅胶上，进行色谱处理(二氯甲烷 => 1 % 甲醇/二氯甲烷=> 2% 甲醇/二氯甲烷)得到3.9 g(60%)的R-(2-苄氧基羰基氨基-3-甲氧基-丙基氨基)-乙酸甲酯，为一种浅黄色油状物。^{1}H NMR(300 MHz, $CDCl_3$) δ 1.73(br s, 1H), 2.71(dd, J =12.1, 5.7 Hz, 1H), 2.84(dd, J =12.2, 5.7 Hz, 1H), 3.32(s, 3H),

3.39(d, J =8.6 Hz, 2H), 3.40-3.52(m, 2H), 3.70(s, 3H), 3.82(m, 1H), 5.09(s, 2H), 5.35(br d, 1H), 7.25-7.35(m, 5H)ppm. 质谱(离子喷雾): m/z 331(M+H)。

E. (R)-6-甲氧基甲基-哌嗪-2-酮

将(R)-(2-苄氧基羰基氨基-3-甲氧基-丙基氨基)-乙酸甲酯(3.9 g, 12.58 mmol)溶解于甲醇(约200 mL)中, 并在活性炭存在下升温脱色1小时。将混合物通过硅藻土过滤, 浓缩澄清的滤液。 残余物再溶解于甲醇(160 mL), 置于Parr瓶中. 加入钯碳(10%, 800 mg), 将混合物45psi氢化5小时。再加入钯碳(250 mg), 在45psi下混合物反应16小时。将混合物通过硅藻土过滤并浓缩得到1.5 g(83%)的(R)-6-甲氧基甲基-哌嗪-2-酮, 为黄色固体, 其不经进一步纯化直接使用。^{1}H NMR(300 MHz, $CDCl_3$) δ 1.77(br s, 1H), 2.70(dd, J =13.1, 7.2 Hz, 1H), 3.07(dd, J =13.1, 4.5 Hz, 1H), 3.26(dd, J =9.1, 7.7 Hz, 1H), 3.33(s, 3H), 3.37-3.45(m, 3H), 3.61(m, 1H), 6.51(br s, 1H)ppm.

F. (R)-3-甲氧基甲基-5-氧代-哌嗪-1-甲酸烯丙基酯

将(R)-6-甲氧基甲基-哌嗪-2-酮(2.3 g, 16.0 mmol)溶解于无水二氯甲烷(60 mL)中, 冷却至0℃。加入三乙胺(3.4 mL, 24.0 mmol), 5分钟后加入氯甲酸烯丙基酯(2.0 mL, 19.2 mmol)。将混合物在2小时升温至室温, 此时TLC分析表明此反应反应完全时。将混合物在水(100 mL)、二氯甲烷(100 mL)之间分配, 分层。水相用二氯甲烷萃取两次(2 x 75 mL), 合并后的有机相用盐水(100 mL)洗涤, 用无水硫酸钠干燥并浓缩得到粗品产物, 其进行快速硅胶色谱纯化(二氯甲烷至1%, 2%, 4% 甲醇/二氯甲烷)得到3.41 g(93%)的(R)-3-甲氧基甲基-5-氧代哌嗪-1-甲酸烯丙基酯, 为无色油状物。^{1}H NMR(300 MHz, $CDCl_3$) δ 3.26(dd, J =9.3, 7.4 Hz, 1H), 3.31(s, 3H), 3.36(m, 1H), 3.63(m, 1H), 3.76(m, 1H), 4.07(ABq, Δ_{AB} =39.9 Hz, J_{AB} =18.5 Hz, 2H), 4.58(d, J =5.59 Hz, 2H), 5.21(m, 2H), 5.88(m, 1H), 7.05(br, 1H)ppm。

实施例890

6-异丙基-哌嗪-2-酮

A. (R)-2-苄氧基羰基氨基-3-甲基-硫代丁酸S-乙基酯

向(R)-2-苄氧基羰基氨基-3-甲基-丁酸(5.0 g, 20.0 mmol)的无水二氯甲烷(20 mL)溶液中，加入DMAP(258 mg, 2.0 mmol)，接着加入冷的EtSH(1.6 mL, 22.0 mmol)。一批加入二环己基碳二亚胺(4.5 g, 22.0 mmol)，30分钟后此反应完全。通过真空过滤除去固体物质，将滤液浓缩。粗品产物进行快速硅胶色谱纯化(己烷至8:1己烷/EtOAc)得到(R)-2-苄氧基羰基氨基-3甲基-硫代丁酸S-乙基酯(5.21 g, 88%)，为无色油状物。^{1}H NMR(300 MHz, $CDCl_3$) δ 0.85(d, J =6.8 Hz, 3H), 0.98(d, J =6.8 Hz, 3H), 1.23(t, J =7.5 Hz, 3H), 2.27(m, 1H), 2.88(q, J=7.5Hz, 2H), 4.35(dd, J=9. 5, 4.6Hz, 1H), 5.13(s, 2H), 5.25(brd, J=9. 5Hz, 1H), 7.30-7.36(m, 5H)ppm。

B. (R)-(1-甲酰基-2-甲基-丙基)-氨基甲酸苄酯

向(R)-2-苄氧基羰基氨基-3-甲基-硫代丁酸S-乙基酯(5.2 g, 17.6 mmol)的丙酮(100 mL)溶液中，加入钯碳(10%, 233 mg)。将此多相混合物冷却至0℃，快速加入Et_3SiH(8.4 mL, 53 mmol)。30分钟后，此反应混合物通过硅藻土垫过滤，浓缩澄清的滤液成残余物，其在己烷(200 mL)、乙腈(300 mL)之间分配。分层，ACN 相用己烷洗涤一次己烷(100 mL)，然后浓缩得到粗品(R)-(1-甲酰基-2-甲基-丙基)-氨基甲酸苄酯(4.13 g)，其不经纯化直接使用。^{1}H NMR(300 MHz, $CDCl_3$) δ 2.30(m, 1H), 4.31(m, 1H), 5.09(s, 2H), 5.45(br, 1H), 7.30-7.45(m, 5H), 9.65(s, 1H)ppm。

C. (R)-(2-苄氧基羰基氨基-3-甲基-丁基氨基)-乙酸乙基酯

向粗品(R)-(1-甲酰基-2-甲基-丙基)-氨基甲酸苄酯(4.13 g, 17.6 mmol)的无水甲醇(100 mL)溶液中，在0℃下加入甘氨酸乙基酯盐酸盐(9.5 g, 70.4 mmol)。10分钟后，加入存在于 THF(27 mL, 27 mmol)的1.0 M $NaCNBH_3$，多相反应混合物升温至室温，过夜。此反应混合物经浓缩，残余物在乙醚(200 mL)、饱和碳酸氢钠水溶液(200 mL)之间

分配。分层，水层用乙醚萃取两次(2 x 200 mL)。合并的有机萃取物用盐水洗涤，用无水硫酸钠干燥，过滤并浓缩得到粗品产物，其进行快速硅胶色谱纯化(己烷/EtOAc，2:1to 1: 1)，得到4.2 g(74%)的(R)-(2-苄氧基羰基氨基-3-甲基-丁基氨基)-乙酸乙基酯，为无色油状物。^{1}H NMR(300 MHz，$CDCl_3$) δ 0.89(d，J =7.0 Hz，3H)，0.92(d，J =7.0 Hz，3H)，1.25(t，J =8.4 Hz，3H)，1.62(br s，1H)，1.80(m，1H)，2.65-2.70(m，2H)，3.37(ABq，Δ_{AB}=32.3Hz，J_{AB}=17.4Hz，2H)，4.16(q，J=8.4Hz，2H)，5.14(s，2H)，7.28-7.36(m，5H)ppm。质谱(离子喷雾)：m/z 323(M+H)。

D. (R)-6-异丙基-哌嗪-2-酮

向 Parr反应器中的存在于甲醇(130 mL)的(R)-(2-苄氧基羰基氨基-3-甲基-丁基氨基)乙酸乙基酯(4.2 g，13.0 mmol)中，加入钯碳(10%，396 mmol)。此反应用40psi氢气压加压并在室温下摇动4小时。然后，将此反应混合物通过硅藻土板过滤，将滤液浓缩，得到1.77 g(95%)的(R)-6-异丙基-哌嗪-2-酮，为米黄色固体，其不经进一步纯化直接使用。^{1}H NMR(300 MHz，$CDCl_3$) δ 0.93(d，J =6.8 Hz，3H)，0.97(d，J =6.8 Hz，3H)，1.68(sept，J =6.7 Hz，1H)，2.67(dd，J =12.8，8.9 Hz，1H)，3.09-3.22(m，2H)，3.46(ABq，Δ_{AB}=34.3 Hz，J_{AB} =17.5 Hz，2H)，5.97(br s，1H)ppm。

实施例891

9-(4-氨基喹唑啉-7-基甲基)-6,9-二氮杂-螺[4,5]癸-10-酮

此标题化合物按照实施例75所述制备，用环戊基-3-氧代-哌嗪-1-甲酸苄酯，实施例885，代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。^{1}H NMR(CD_3OD，300MHz) δ 8.38(s，1H)，8.09(d，1H)，7.56(s，1H)，7.39(d，1H)，4.72(s，2H)，3.38(m，2H)，3.07(m，2H)，2.21(m，2H)，1.72(m，6H)。

实施例892

(+/-)-顺式-4-苄氧基羰基-十氢喹喔啉基-2-酮

A. (+/-)-顺式-十氢喹喔啉基-2-酮

将顺-1,2-二氨基环己烷(4.1 g, 36 mmol)溶解于150 mL的H_2O。在5分钟内在10℃下滴加存在于50mL水中的氯乙酸(3.4 g, 36 mmol),然后在10℃滴加存在于30mL水中的碳酸钾(7.9 g, 57 mmol)。此反应混合物缓慢升温至室温,搅拌24小时。将此溶液在90℃加热2小时,浓缩。将所得固体在沸腾的甲苯(100ml)中回收,热过滤,浓缩得到(+/-)-顺式-十氢喹喔啉基-2-酮(0.8g, 收率14%),为白色固体。

$C_8H_{14}N_2O$, MS$(M+H)^+$: 155

B. (+/-)-顺式-4-苄氧基羰基-十氢喹喔啉基-2-酮

将(+/-)-顺式-十氢喹喔啉基-2-酮(0.8g, 5.19mmol)悬浮于25ml水中。加入碳酸氢钠(0.87g, 10.35mmol),并将此反应混合物冷却至10℃。向剧烈搅拌的混合物中滴加氯甲酸苄酯(1ml, 6.68mmol)。室温下20小时后,滤出固体,用水彻底洗涤,空气干燥。得到标题化合物(1.46g, 收率98%),为白色固体。

$C_{16}H_{20}N_2O_3$, MS$(M+H)^+$: 289

实施例893

(+/-)-顺式-1-(4-氨基-喹唑啉-7-基甲基)-十氢喹喔啉基-2-酮

此标题化合物用实施例75所述的方法制备,用(+/-)-顺式-4-苄氧基羰基-十氢喹喔啉基-2-酮(实施例892)代替2-甲氧基甲基-3-氧代-哌嗪-1-甲酸苄酯。

$C_{17}H_{21}N_5O$, MS$(M+H)^+$: 312

实施例894

(+/-)-反式-4-苄氧基羰基-十氢喹喔啉基-2-酮

A. (+/-)-反式-十氢喹喔啉基-2-酮

将(+/-)-反式-1,2-二氨基环己烷(22.84 g, 200 mmol)溶解于600

mL的H_2O中。在30分钟内在10℃下滴加存在于200mL水中的氯乙酸(18.8 g, 200 mmol)，然后在10℃下滴加存在于120mL水中的碳酸钾(44 g, 320 mmol)。此反应混合物缓慢升温至室温，搅拌24小时。将此溶液在90℃加热2小时，浓缩。所得固体在沸腾的乙醇(800 ml)中回收，热过滤，浓缩。 米黄色固体在沸腾的甲苯(1000 ml)重结晶，干燥得到(1)(9.72 g, 31% 收率)，为一种白色固体。

$C_8H_{14}N_2O$, MS$(M+H)^+$: 155

B. (+/-)-反式-4-苄氧基羰基-十氢喹喔啉基-2-酮

将(+/-)-反式-4-苄氧基羰基-十氢喹喔啉基-2-酮(0.8 g, 5.19 mmol)悬浮于25 mL的水中。加入碳酸氢钠(0.87 g, 10.35 mmol)并将此反应混合物冷却至10℃。将氯代甲酸苄酯(1 ml, 6.68 mmol)滴加到剧烈搅拌的混合物。 5小时后室温下滤出固体，用水彻底洗涤，空气干燥。得到标题化合物(1.33 g, 89 % 收率)，为一种白色固体。

实施例895

(+/-)-反式-1-(4-氨基-喹唑啉-7-基甲基)-十氢喹喔啉基-2-酮

此标题化合物按照实施例75所述制备，用反式-4苄氧基羰基-十氢喹喔啉基-2-酮(实施例894)代替2-甲氧基甲基-3-氧代哌嗪-1-甲酸苄酯。

$C_{17}H_{21}N_5O$, MS$(M+H)^+$: 312

实施例896

4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮

A. [1-(2,2-二甲氧基-乙基氨基甲酰基)-3-(S)-甲硫基-丙基]-氨基甲酸苄酯

向(L)-N-苄氧基羰基-甲硫氨酸(25g, 88.2 mmol)的400 mL的二氯甲烷溶液中，加入TBTU(28.3 g, 88.2 mmol)，接着加入NEt_3(36.6 ml, 264 mmol)和氨基乙醛二甲基缩醛(10.6 ml, 69.7 mmol)。将溶液搅

拌16小时，用H_2O、1N盐酸、饱和碳酸氢钠水溶液、盐水洗涤，用硫酸镁干燥并浓缩。所得粗品产物通过柱色谱纯化，用1 % 甲醇：二氯甲烷至5% 甲醇：二氯甲烷的梯度液洗脱。得到标题化合物(23.3 g，71% 收率)，为一种白色固体。

$C_{17}H_{26}N_2O_5S$ MS $(M+H)^+$:371

B. 4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)-3,4-二氢-1H-吡嗪-2-酮

向[1-(2,2-二甲氧基-乙基氨基甲酰基)-3-(S)-甲硫基-丙基]氨基甲酸苄酯(23.3 g，63 mmol)的甲苯(300 ml)溶液中，加入对甲苯磺酸一水合物(1.14 g，6.3 mmol)。所得溶液在70℃下搅拌4小时，冷却，用水、盐水洗涤，用硫酸镁干燥并浓缩。所得粗品产物通过柱色谱纯化，用2% 甲醇：二氯甲烷至5% 甲醇：二氯甲烷的梯度页洗脱。得到标题化合物(17.9 g，93% 收率)，为油状物。

$C_{15}H_{18}N_2O_3S$ MS$(M+H)^+$：307

C. 4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮

向4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)-3,4-二氢-1H-吡嗪-2-酮(0.3 g，1 mmol)的二氯甲烷溶液中，加入Et_3SiH(1.57 ml，10 mmol)。将所得溶液冷却至0℃，滴加CF_3CO_2H(2.2 ml，30 mmol)。将混合物室温下搅拌16小时，用饱和碳酸氢钠水溶液、盐水洗涤。溶液用硫酸镁干燥，浓缩。所得粗品产物通过在硅胶上进行柱色谱纯化，用50% AcOEt：己烷至100 % AcOEt的梯度液洗脱。得到标题化合物(0.138 g，46 % 收率)，为油状物。

$C_{15}H_{20}N_2O_3S$ MS$(M+H)^+$ ：309

实施例897

1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮

A. 4-苄氧基羰基-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮

向4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮(1.15 g，3.74 mmol)的10 ml的DMF溶液中，在0℃下加入氢化钠(164 mg，60%

在油中，4.12 mmol)。将此溶液搅拌10分钟，然后滴加存在于25mL DMF的2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(2.6 g，52%，3.74 mmol)。所得混合物搅拌20小时室温下，用乙酸乙酯稀释，用水、饱和碳酸氢钠水溶液、盐水洗涤。溶液用硫酸镁干燥，浓缩。所得粗品产物通过在硅胶上进行柱色谱纯化，用2% 甲醇：二氯甲烷洗脱。得到标题化合物(1.8 g，80 % 收率)，为粘稠油状物。

$C_{36}H_{34}N_4O_3S$ MS(M+H)$^+$：603

B. 4-苄氧基羰基-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮

向4-苄氧基羰基-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮(1.8 g，3 mmol)的20 mL的乙酸乙酯溶液中，加入浓盐酸(10滴)、H_2O(10滴)。将所得混合物搅拌1小时，倾析乙酸乙酯溶液，用饱和碳酸氢钠水溶液、水、盐水洗涤。溶液用硫酸镁干燥，浓缩。所得粗品产物通过柱色谱纯化，在硅胶上用1% 甲醇：二氯甲烷洗脱。得到标题化合物(1.17 g，89% 收率)，为一种黄色泡沫。

$C_{23}H_{26}N_4O_3S$ MS(M+H)$^+$：439

C. 1-(4-氨基-喹唑啉-7-基甲基)-4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)哌嗪-2-酮

向4-苄氧基羰基-1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮(1.17 g，2.67 mmol)的15 mL的乙醇溶液中，加入1,3,5-三嗪、冰醋酸(3.1 ml，53.4 mmol)。将所得溶液回流20小时，真空浓缩。残余物溶解于乙酸乙酯，用1N盐酸、饱和碳酸氢钠水溶液、水、盐水洗涤。此溶液用硫酸镁干燥，浓缩。所得粗品产物通过柱色谱纯化，用5% 甲醇：二氯甲烷至10% 甲醇：二氯甲烷梯度洗脱。得到标题化合物(489 mg，39% 收率)，为一种黄色固体。

$C_{24}H_{27}N_5O_3S$ MS(M+H)$^+$ ：466。

D. 1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-(2-甲硫基-乙基)-哌嗪-2-

酮

将1-(4-氨基-喹唑啉-7-基甲基)-4-苄氧基羰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮(100 mg, 0.215 mmol)溶解于5 mL的30%溴化氢乙酸溶液中。将混合物搅拌1小时，用乙醚稀释。倾析掉乙醚，所得固体用乙醚彻底洗涤。所得粗品产物通过柱色谱纯化，用二氯甲烷/甲醇/NH_4OH(30%在水中)的 4/2/1混合物洗脱。用5% 甲醇：二氯甲烷至10%甲醇：二氯甲烷的梯度洗脱。所得产物通过另一个柱色谱纯化，用20%甲醇：二氯甲烷至50% 甲醇：二氯甲烷梯度洗脱。得到标题化合物(30 mg, 42 % 收率)，为米黄色固体。

$C_{16}H_{25}N_5OS$ MS $(M+H)^+$：332。

下列化合物用上述方法制备，用实施例101的方法，与氨基-喹唑啉基和适当的磺酰氯偶联。

实施例	名称	m/z (M+H)
898	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮	513
899	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基-哌嗪-2-酮	530
900	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮	514
901	(R/S)1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-氧代-哌嗪-2-甲酸乙酯	544
902	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮	515
903	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮	514
904	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮	513

905	(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-八氢-喹喔啉-2-酮	542
906	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮	515,517 Cl花样
907	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-哌嗪-2-酮	471
908	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-哌嗪-2-酮	471
909	[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-(S)-基]-乙酸	546
910	[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪基-2-(S)-基]-乙酸叔丁基酯	602
911	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮	516
912	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸(2-吡咯烷基-1-基-乙基)-酰胺	628
913	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸2-吡咯烷基-1-基-乙基酯	629
914	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮	532
915	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮	532
916	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-磺酸(4-氯-苯基)-酰胺	491

下列化合物可以用上述模板制备，用实施例101的方法将与氨基-

喹唑啉、适当的磺酰基氯偶联。

实施例	名称
917	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸2-咪唑-1-基-乙基酯
918	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸2-吗啉-4-基-乙基酯
919	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸吡咯烷基-2-基甲基酯
920	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-甲酸2-甲基氨基-乙基酯
921	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基-哌嗪-2-酮
922	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基-哌嗪-2-酮
923	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基-哌嗪-2-酮
924	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基-哌嗪-2-酮
925	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基-哌嗪-2-酮
926	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮
927	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮
928	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮
929	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮

930	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮
931	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮
932	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮
933	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮
934	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲基-哌嗪-2-酮
935	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲基-哌嗪-2-酮
936	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮
937	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮

下列化合物用上述方法制备，用实施例268的方法与氨基-喹唑啉基、适当的烷基化试剂偶联。

实施例	名称	m/z(M+H)
938	1-(4-氨基-喹唑啉-7-基甲基)-4-(2-氯-咪唑并[1,2-a]吡啶-7-基甲基)-哌嗪-2-酮	422
939	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3(S)-(2-甲硫基-乙基)-哌嗪-2-酮	495
940	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	470,472 Cl花样

941	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-噻吩并[2,3-b]吡啶-2-基甲基)-(S)-3-丙基-哌嗪-2-酮	481,483 Cl花样
942	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代(S)-2-丙基-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯	563,565 Cl花样
943	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-(S)-3-丙基-哌嗪-2-酮	463,465 Cl花样
944	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-基甲基)-3(S)-丙基-哌嗪-2-酮	464
945	9-(4-氨基-喹唑啉-7-基甲基)-6-[3-(5-氯-噻吩-2-基)-烯丙基]-6,9-二氮杂-螺[4.5]癸-10-酮	468
946	(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-八氢-喹喔啉-2-酮	468,470 Cl花样
947	(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-八氢-喹喔啉-2-酮	475,477 Cl花样
948	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-3(S)-异丁基-哌嗪-2-酮	477,479 Cl花样
949	1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-3(S)-异丁基-哌嗪-2-酮	489,491 Cl花样
950	3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基甲基]-苯甲腈	434
951	(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-八氢-喹喔啉-2-酮	475,477 Cl花样
952	(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-八氢-喹喔啉-2-酮	468,470 Cl花样
953	(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-(7-氯-异喹啉-3-基甲基)-八氢-喹喔啉-2-酮	487,489 Cl花样

954	2-[4-(4-氨基-喹唑啉-7-基甲基)-1-(7-氯-异喹啉-3-基甲基)-3-氧代-哌嗪基-2-(S)-基]-N-甲基-乙酰胺	504,506 Cl花样
955	2-[4-(4-氨基-喹唑啉-7-基甲基)-1-(7-氯-异喹啉-3-基甲基)-3-氧代-哌嗪基-2-(S)-基]-乙酰胺	490,492 Cl花样
956	2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-3-氧代-哌嗪基-2-(S)-基}-乙酰胺	471,473 Cl花样
957	2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-3-氧代-哌嗪基-2-(S)-基}-N-甲基-乙酰胺	485,487 Cl花样
958	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3(S)-异丁基-哌嗪-2-酮	470,472 Cl花样
959	(s)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-6-甲氧基甲基-哌嗪-2-酮	458,460 Cl花样
960	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-氨基-噻吩并[3,2-d]嘧啶-6-基甲基)-3(S)-甲氧基甲基-哌嗪-2-酮	465
961	1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-4-(4-嘧啶-4-基-苄基)-哌嗪-2-酮	470
962	4-[4-(2-氨基-嘧啶-4-基)-苄基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	485
963	3-氨基-5-[4-(4-氨基-喹唑啉-7-基甲基)-2(S)-甲氧基甲基-3-氧代-哌嗪-1-基甲基]-噻吩-2-甲腈	438
964	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮	472

实施例965

3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-苯甲腈

向1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮，实施例75，(50 mg，0.16 mmol)、3-氰基肉桂酸(29 mg，0.17 mmol，由3-氰基苯甲醛制备)的1 mL的DMF溶液中，加入N,N-二异丙基乙基胺(0.07 mL，0.38 mmol)，接着加入2-(1H-苯并三唑-1-基)-1,1,3,3-四甲基四氟硼酸脲(TBTU)(59 mg，0.18 mmol)。将所得混合物在室温下搅拌16小时，浓缩此溶液。粗品产物通过RP-HPLC纯化，用10% 乙腈/H_2O(0.1% TFA)至60% 乙腈/H_2O(0.1% TFA)梯度洗脱30分钟，合并适当的产物馏份，冻干得到标题化合物(73 mg，0.13 mmol)，为一种白色固体。^1H NMR(d_6-DMSO，300 MHz) δ 9.72(bs，2H)，8.78(s，1H)，8.40(s，1H)，8.35(d，1H)，8.04(m，1H)，7.83(d，1H)，7.60(m，4H)，7.46(d，1H)，5.25-4.44(m，4H，旋转异构体)，4.02(m，1H)，3.66(m，1H)，3.51-3.40(m，3H)，3.27(s，3H)。ISP MS，$[M+H]^+$=457。

实施例966

3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪基 1-基]-3-氧代-丙烯基}-苯甲腈

将3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-苯甲腈(68 mg，0.12 mmol)溶解于9 mL的2:1乙醇/二氯甲烷中。此溶液冷却至0℃，向溶液中通入5分钟的HCl气体。除去冰浴并将此反应混合物室温下搅拌过夜。此后，浓缩此溶液。残余物溶解于10 mL的甲醇中。此溶液冷却至0℃，向此溶液中通入5分钟的NH_3气体。此反应混合物加热回流2小时。此后，浓缩此溶液。残余物通过RP-HPLC纯化，用10% 乙腈/H_2O(0.1% TFA)至60% 乙腈/H_2O(0.1% TFA))梯度洗脱30分钟。将适当的馏份冻干得到标题化合物(55 mg，0.08 mmol)，为一种固体。^1H NMR(d_6-DMSO，300 MHz) δ 9.75(bs，2H)，9.36(bs，4H)，8.80(s，1H)，8.42(s，1H)，8.13(m，1H)，8.10(m，1H)，7.79(d，1H)，7.62(m，4H)，7.42(m，1H)，

5.20-4.46(m, 4H, 旋转异构体), 4.03(m, 1H), 3.86(m, 1H), 3.56-3.34(m, 3H), 3.28(s, 3H)。ISP MS, $[M+H]^+$=474。

实施例967

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-羟基-苯基)-丙烯酰基]-(3S)丙基-哌嗪-2-酮

此标题化合物按照实施例123所述制备, 用4-羟基-肉桂酸和1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮(实施例75)。

^{1}H NMR(d_6-DMSO, 300 MHz) δ 9.88(s, 1H), 9.68(bs, 2H), 8.80(s, 1H), 8.36(d, 1H), 7.58(m, 4H), 7.48(d, 1H), 7.07(d, 1H), 6.76(d, 2H), (m, 3H, 旋转异构体), 3.62-3.25(m, 4H), 1.87(m, 2H), 1.32(m, 2H), 0.89(t, 3H)。ISP MS, $[M+H]^+$=446。

实施例968

1-(4-氨基-喹唑啉-7-基甲基)-4-3-(3-氯-苯基)-丙烯酰基]-(3S)-丙基哌嗪-2-酮

此标题化合物按照实施例123所述制备, 用3-氯-肉桂酸和1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮(实施例75)。

^{1}H NMR(d_6-DMSO, 300 MHz) δ 9.64(bs, 2H), 8.78(s, 1H), 8.36(d, 1H), 7.96(m, 1 H, 旋转异构体), 7.66(m, 2H), 7.53(m, 2H), 7.40(m, 3H), 5.10-4.42(m, 3H, 旋转异构体), 3.65(m, 1H), 3.52-3.22(m, 3H), 1.90(m, 2H), 1.33(m, 2H), 0.90(t, 3H)。ISP MS, $[M+H]^+$=464。

实施例969

1-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(5氯-噻吩-2-基)-丙烷-1,3-二酮

此标题化合物由Witzeman和Nottingham. (J. Org. Chem. 1991, 56, 1713.)公开方法的改良形式制备。将1-(4-氨基喹唑啉-7-基甲

基)-3-丙基哌嗪-2-酮(0.299 g, 1mmol)、3-(5-氯-噻吩-2-基)-3-氧代-丙酸叔丁酯(0.287 g, 1.1 mmol)溶解于10 ml吡啶中。将含所得溶液的此烧瓶置于预加热至125℃的油浴中。将此反应在氮气流下加热搅拌1小时直到大部分吡啶蒸发。将残留的吡啶真空蒸发。残余物用快速柱色谱进行纯化，用5% 甲醇/二氯甲烷至10% 甲醇/二氯甲烷梯度洗脱得到产物(0.48 g, 0.98 mmol)。该产物可以用二氯甲烷/己烷重结晶得到黄色固体。M. P. 120-5℃(分解)。MS(离子喷雾)m/z 486, (M+H)。

实施例970

1-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(5-氯-噻吩-2-基)-2-氟-丙烷-1,3-二酮

通过Differding和Ofner.的方法(Synlett 1991, 187.)制备。将1-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(5-氯-噻吩-2-基)-丙烷-1,3-二酮(0.486 g, 1 mmol)的40 ml THF溶液滴加到冰冷的NaH(0.16g的60%氢化钠, 4mmol)和5ml THF中。在0℃将此混合物搅拌1小时后，滴加N-氟苯磺酰亚胺(Aldrich)(0.378g, 1.2mmol)的10ml THF溶液。将此反应室温下搅拌过夜，之后用冰醋酸(0.23ml, 2.240g, 4mmol)停止反应。真空蒸发挥发物并将此残余物通过快速柱色谱纯化，用5%甲醇/二氯甲烷至10%甲醇/二氯甲烷梯度洗脱，得到白色固体产物。将此产物可以用THF/己烷重结晶。M.P. 194-6℃。MS(离子喷射) M/z 504, (M+H)。

实施例971

1-(4-氨基喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮

向1-(4-氨基喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮(29mg, 0.057mmol)的1ml二氯

甲烷溶液中，在0℃下加入3-氯过苯甲酸(14mg，71%，0.057mmol)。将所得混合物室温下搅拌2小时，浓缩。将此产物通过RP-HPLC纯化，用10% 乙腈/H_2O(0.1% TFA)至80% 乙腈/H_2O(0.1% TFA)梯度洗脱。将所收集的适当馏份冻干得到标题化合物，为一种白色固体(63 mg，33 %收率)。

$C_{22}H_{24}N_5O_4S_2Cl\cdot CF_3CO_2H(M+H)^+$:506

实施例972

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(s)-(2-甲亚磺酰基-乙基)-哌嗪-2-酮

于0℃向1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(s)-(2-甲磺酰基-乙基)-哌嗪-2-酮(29mg，0.057mmol)的1ml CH_2Cl_2溶液中加入3-氯过苯甲酸(14mg，71%，0.057mmol)于室温搅拌所得混合物2小时，浓缩。用RP-HPLC洗脱纯化产物，洗脱梯度为10% CH_3CN/H_2O (0.1% TFA)-80% CH_3CN/H_2O (0.1% TFA)。冷冻干燥适当收集的馏分，得到白色固状标题化合物(10mg，27%产率)。

$C_{22}H_{24}N_5O_4S_2Cl\cdot CF_3CO_2H(M+H)^+$:522

实施例973

1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(S)(2-甲磺酰基-乙基)-哌嗪-2-酮

向1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基-3-(S)-(2-甲硫基-乙基)-哌嗪-2-酮(29 mg，0.057 mmol)的1 ml二氯甲烷溶液中，在0℃下加入3-氯过苯甲酸(28 mg，71 %，0.114 mmol)。将所得混合物在室温下搅拌2小时，浓缩。将此产物通过RP-HPLC纯化，用10% 乙腈/H_2O(0.1% TFA)至80% 乙腈/H_2O(0.1% TFA)洗脱。将所收集的适当馏份冻干得到标题化合物，为一种白色固体(25 mg，67 % 收率)。

$C_{22}H_{24}N_5O_5S_2CL\cdot CF_3CO_2H(M+H)^+$：538

用上述方法和模板，以及实施例123描述的方法，与氨基喹唑啉基团偶联，制备下列化合物。

实施例	名称	m/z(M+H)
974	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-二甲基氨基甲基-哌嗪-2-酮	449,451 Cl花样
975	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并-[b]噻吩-2-羰基)-(3S)-甲氧基甲基-哌嗪-2-酮	496
976	1-(4-氨基-2-甲基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮	488,490 Cl花样
977	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-羰基)-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	492,494 Cl花样
978	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-羰基)-3(S)-(2-甲硫基-乙基)-哌嗪-2-酮	510,512 Cl花样
979	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯苯并[b]-噻吩-2-羰基)-(S)-3-丙基-哌嗪-2-酮	494,496 Cl花样
980	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并[b]-噻吩-2-羰基)-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	508,510 Cl花样
981	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]-噻吩-2-羰基)-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	508,510 Cl花样
982	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	484,486 Cl花样

983	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	488, 490 Cl花样
984	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基)-丙烯酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	484, 486 Cl花样
985	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	488, 490 Cl花样
986	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-苯并呋喃-2-羰基)-3(S)-丙基-哌嗪-2-酮	478, 480 Cl花样
987	3-{2-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-基]-2-氧代-乙基}-苯甲腈	462
988	3-{2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-2-氧代-乙基}-苯甲腈	418
989	4-[3-(4-氨基-环己基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-丙基-哌嗪-2-酮	451
990	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-羰基)-(S)-3-丙基-哌嗪-2-酮	494, 496 Cl花样
991	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并呋喃-2-羰基)-3(S)-丙基-哌嗪-2-酮三氟乙酸酯	478, 480 Cl花样
992	1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(3-氯-苯基)-丙烷-1, 3-二酮	480
993	4-[(5-氨基-吡啶-2-基氧基)-乙酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(S)-3-甲氧基甲基-哌嗪-2-酮	452
994	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(R)-甲氧基甲基-哌嗪-2-酮	476, 478 Cl花样
995	3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-3-氧代-丙基}-苯甲腈	432

996	3-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代-丙基}-苯甲腈	476
997	1-(4-氨基-喹唑啉-7-基甲基)-4-(4-咪唑-1-基-苯甲酰基)-3(S)-丙基-哌嗪-2-酮	470
998	(6-{2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-甲氧基甲基-3-氧代-哌嗪-1-基]-2-氧代-乙氧基}-吡啶-3-基)-氨基甲酸叔丁酯	552
999	(4aRS,8aSR)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-八氢-喹喔啉-2-酮	486,488 Cl花样
1000	(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-八氢-喹喔啉-2-酮	486,488 Cl花样
1001	(4aRS,8aRS)-1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-八氢-喹喔啉-2-酮	482,484 Cl花样
1002	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-6-氧代-1,6-二氢-吡啶-3-基)-丙烯酰基]-(S)-3-丙基-哌嗪-2-酮	481,483 Cl花样
1003	1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-基]-3-(4-羟基-苯基)-丙烷-1,3-二酮	462
1004	2-{4-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-]-丙烯酰基]-3-氧代-哌嗪基-2-(S)-基}-乙酰胺	485,487 Cl花样
1005	2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-氧代-哌嗪基-2-(S)-基}-乙酰胺	485,487 Cl花样

1006	2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-氧代-哌嗪基-2-(S)-基}-乙酰胺	489, 491 Cl花样
1007	{4-(4-氨基-喹唑啉-7-基甲基)-1-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-氧代-哌嗪基-2-(S)-基}-乙酸甲酯	504, 506 Cl花样
1008	2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-氧代-哌嗪基-2-(S)-基}-N-甲基-乙酰胺	499, 501 Cl花样
1009	2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-氧代-哌嗪基-2-(S)-基}-N-甲基-乙酰胺	503, 505 Cl花样
1010	2-{4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-氧代-哌嗪基-2-(S)-基}-N-甲基-乙酰胺	499, 501 Cl花样
1011	4-{3-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-苯磺酰胺	511
1012	N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲氧基甲基-3-氧代-哌嗪-1-基]-3-氧代-丙基}-吡啶-2-基)-乙酰胺	492
1013	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氨基-[1, 3, 4]噻二唑-2-基硫基)-乙酰基]-(S)-3-丙基-哌嗪-2-酮	473
1014	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氨基-[1, 3, 4]噻二唑-2-基硫基)-乙酰基]-(S)-3-甲氧基甲基-哌嗪-2-酮	475
1015	3-[4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-羰基]-苯甲腈	448

1016	1-(4-氨基-喹唑啉-7-基甲基)-4-[(哌啶-3-基氧基)-乙酰基]-哌嗪-2-酮	399
1017	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-4-羟基-苯基)-(E)-丙烯酰基]-(3S)-甲氧基甲基-哌嗪-2-酮	482
1018	(3S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-羟基-萘-2-羰基)-3-丙基-哌嗪-2-酮	470
1019	(3S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-羟基-1H-吲哚-2-羰基)-3-丙基-哌嗪-2-酮	459
1020	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-羟基-苯氧基)-乙酰基]-(3S)-甲氧基甲基-哌嗪-2-酮	452
1021	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-羟基-苯基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	460
1022	N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-(S)-丙基-哌嗪-1-基]-3-氧代-丙烯基}-吡啶-2-基)-乙酰胺	488
1023	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	488, 490 Cl花样
1024	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	482, 484 Cl花样
1025	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3,6-双-甲氧基甲基-哌嗪-2-酮	
1026	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	478, 480 Cl花样

1027	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	484, 486 Cl花样
1028	4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	478
1029	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(S)-2-丙基-哌嗪-1-基]-N-(5-氯-噻吩-2-基)-2-氧代-乙酰胺	487, 489 Cl花样
1030	2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-N-(5-氯-噻吩-2-基)-2-氧代-乙酰胺	445, 447 Cl花样
1031	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-3-基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	484, 490 Cl花样
1032	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	484, 490 Cl花样
1033	2-[4-(4-氨基-喹唑啉-7-基甲基)-(S)-2-甲氧基甲基-3-氧代-哌嗪-1-基]-N-(5-氯-噻吩-2-基)-2-氧代-乙酰胺	489, 491 Cl花样
1034	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-甲氧基甲基-哌嗪-2-酮	476
1035	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3, 4-二羟基-苯基)-(E)-丙烯酰基]-(3S)-甲氧基甲基-哌嗪-2-酮	464
1036	4-[3-(6-氨基-吡啶-3-基)-丙酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮	450
1037	4-[3-(6-氨基-吡啶-3-基)-丙酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-丙基-哌嗪-2-酮	448

1038	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3-(S)-羟基甲基-哌嗪-2-酮	458, 460 Cl花样
1039	N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-丁基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-6-甲基-吡啶-2-基)-乙酰胺	516
1040	N-(5-{3-[4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-丁基-3-氧代-哌嗪-1-基]-3-氧代-丙烯基}-吡啶-2-基)-乙酰胺	502
1041	4-[3-(6-氨基-2-甲基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-丁基-哌嗪-2-酮	474
1042	1-[4-(4-氨基喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-3-(5-氯-噻吩-2-基)-丙烷-1, 3-二酮	444
1043	4-[3-(3-氨基-4-氯-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮	481
1044	4-[3-(3-氨基-5-氯-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮	481
1045	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-3-基氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	488, 490 Cl花样
1046	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-(R)-6-甲基-(S)-3-丙基-哌嗪-2-酮	488, 490 Cl花样
1047	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯亚磺酰基)-乙酰基]-(3-S)-丙基-哌嗪-2-酮	500
1048	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-羟基-苯氧基)-乙酰基]-(3S)-甲氧基甲基-哌嗪-2-酮	452
1049	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-苯硫基)-乙酰基]-哌嗪-2-酮	442

1050	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯亚磺酰基)-乙酰基]-(3S)-甲氧基甲基-哌嗪-2-酮	502
1051	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-羟基-苯基)-(E)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	448
1052	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-羟基-苯基)-(E)-丙烯酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮	448
1053	1-(4-氨基-喹唑啉-7-基甲基)-4-[(4-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-羟基甲基-哌嗪-2-酮	462, 464 Cl花样
1054	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-(S)-羟基甲基-哌嗪-2-酮	458, 460 Cl花样
1055	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3, 6-双-甲氧基甲基-哌嗪-2-酮	521
1056	(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)乙酰基]-6-甲氧基甲基-哌嗪-2-酮	476
1057	4-[(6-氨基-嘧啶-4-基氧基)-乙酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-甲氧基甲基-哌嗪-2-酮	453
1058	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯磺酰基)-乙酰基]-哌嗪-2-酮	474
1059	1-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基]-3-(4-氯-苯基)-丙烷-1, 3-二酮	438
1060	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3-氯-苯硫基)-乙酰基]-哌嗪-2-酮	442
1061	4-[3-(6-氨基-2-甲基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3-(S)-丙基-哌嗪-2-酮	460
1062	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-3-羟基-丙烯酰基]-哌嗪-2-酮	438

1063	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-二甲基氨基-苯基)-丙烯酰基]-(3S)-丙基-哌嗪-2-酮	473
1064	3-(S)-6-(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-嘧吩-2-基氧基)-乙酰基]-6-羟基甲基-3-甲氧基甲基-哌嗪-2-酮	506
1065	4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-异丁基-哌嗪-2-酮	460
1066	4-[3-(2-氨基-嘧啶-5-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-丙基-哌嗪-2-酮	447
1067	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-羟基-苯基)-丙烯酰基]-(3S)-丙基-哌嗪-2-酮	446
1068	4-[3-(3-氨基-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮	447
1069	4-[3-(4-氨基-3-氯-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-甲氧基甲基-哌嗪-2-酮	481
1070	1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡嗪-2-基氧基)-乙酰基]-(S)-3-甲氧基甲基-哌嗪-2-酮	472, 474 Cl花样
1071	1-(4-氨基-喹唑啉-7-基甲基)-4-[(6-氯-吡嗪-2-基氧基)-乙酰基]-(S)-3-丙基-哌嗪-2-酮	470, 472 Cl花样
1072	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-异丁基-哌嗪-2-酮	484, 486 Cl花样
1073	1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-异丁基-哌嗪-2-酮	488, 490 Cl花样
1074	1-(4-氨基-喹唑啉-7-基甲基)-4-[(2-氨基-噻唑-4-基)-乙酰基]-(S)-3-丙基-哌嗪-2-酮	440
1075	(+/-)-1-(4-氨基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-氧代-哌嗪-2-甲酸乙酯	504, 506 Cl花样

1076	4-[3-(4-氨基-苯基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-(3S)-丙基-哌嗪-2-酮	445
1077	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3,4-二氯-噻吩-2-基氧基)-乙酰基]-(S)-3-丙基-哌嗪-2-酮	508,510,512, Cl_2花样
1078	1-(4-氨基-喹唑啉-7-基甲基)-4-[(3,4-二氯-噻吩-2-基氧基)-乙酰基]-(S)-3-甲氧基甲基-哌嗪-2-酮	510,512,514, Cl_2花样
1079	4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-(4-氨基-喹唑啉-7-基甲基)-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮	462
1080	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮	486,488 Cl花样
1081	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-(2-甲氧基-乙基)-哌嗪-2-酮	486,488 Cl花样

实施例1082

4-(4-氨基-喹唑啉-7-基甲基)-(S)-5-甲基-3-氧代-(S)-2-丙基哌嗪-1-甲酸(4-氯-苯基)-酰胺

向4-[4-氨基-喹唑啉-7-基甲基]-5-甲基-3-氧代-2-丙基-哌嗪(12 mg, 0.04 mmol, 实施例888)的2 mL的DMF溶液中, 加入4-氯苯基异氰酸酯(9 mg, 0.06 mmol)。在100℃下搅拌1小时, 浓缩此溶液。 粗品产物通过RP-HPLC纯化, 用10% 乙腈/H_2O(0.1 % TFA)至70% 乙腈/H_2O(0.1 % TFA)梯度洗脱, 合并适当的产物馏份, 冻干得到标题化合物(16 mg, 0.03 mmol), 为一种白色固体。^1H NMR(d_6-DMSO, 300 MHz) δ 9.74(bs, 2H), 8.77(m, 2H), 8.35(m, 1H), 7.56(m, 2H), 7.46(d, 2H), 7.21(d, 2H), 5.00-4.38(m, 3H, 旋转异构体), 4.20(m, 1H, 旋

转异构体)，3.58(m，1H，旋转异构体)，3.10(m，1H)，1.86(m，2H)，1.33(m，2H)，1.08(m，3H，旋转异构体)，0.90(t，3H)。ISP MS，$[M+H]^+$=467，469(Cl 花样)。

实施例1083

4-(4-氨基-喹唑啉-7-基甲基)-(S)-5-甲基-3-氧代-(S)-2-丙基哌嗪-1-甲酸(5-氯-噻吩-2-基)酰胺

将5-氯-噻吩-2-羰基叠氮化物(28 mg，0.15 mmol，实施例38)、4-[4-氨基-喹唑啉-7-基甲基]-5-甲基-3-氧代-2-丙基-哌嗪，实施例888，(26 mg，0.08 mmol)的3 mL的无水DMF化合物在100℃下加热1小时。将所得混合物真空浓缩。粗品产物通过RP-HPLC纯化，用10% 乙腈/H_2O(0.1% TFA)至70% 乙腈/H_2O(0.1% TFA)梯度洗脱，合并适当的产物馏份，冻干得到标题化合物(18 mg，0.03 mmol)，为一种白色固体。^1H NMR(d_6-DMSO，300 MHz) δ 9.96(bs，1H)，9.70(bs，2H)，8.72(s，1H)，8.22(d，1H)，7.55(d，1H)，7.50(s，1H)，6.68(d，1H)，6.37(d，1H)，4.99-4.38(m，3H，旋转异构体)，4.15(m，1H，旋转异构体)，3.58(m，1H，旋转异构体)，3.10(m，1H)，1.85(m，2H)，1.32(m，2H)，1.07(m，3H，旋转异构体)，0.88(t，3H)。ISP MS，$[M+H]^+$=473，475(Cl花样)。

用上述方法、模板，与氨基-喹唑啉偶联，制备了下列实施例：

实施例	名称	m/z(M+H)
1084	4-(4-氨基-喹唑啉-7-基甲基)-2(S)-异丁基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	466
1085	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-羟基甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	440
1086	(2S)-4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-甲酸(5-溴-噻唑-2-基)-酰胺	504

1087	(2S)-4-(4-氨基-喹唑啉-7-基甲基)-2-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-氯-噻唑-2-基)-酰胺	462
1088	(2S)-4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-甲酸(5-氯-噻唑-2-基)-酰胺	460
1089	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(4-羟基-苯基)-酰胺	437
1090	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-甲基氨基甲酰基甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	481
1091	4-(4-氨基-喹唑啉-7-基甲基)-2-(S)-氨基甲酰基甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	467
1092	(4aRS,8aRS)-4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-八氢-喹喔啉-1-甲酸(4-氯-苯基)-酰胺	465
1093	4-(4-氨基-喹唑啉-7-基甲基)-2(S)-(2-甲硫基-乙基)-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	485,487 Cl花样
1094	4-(4-氨基-喹唑啉-7-基甲基)-(2S)-甲氧基甲基-3-氧代-哌嗪-1-甲酸(5-氯-呋喃-2-基)-酰胺	445
1095	(2S)-4-(4-氨基-喹唑啉-7-基甲基)-2-甲氧基甲基-3-氧代-(5-溴-噻唑-2-基)-酰胺哌嗪-1-甲酸	506
1096	N-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-(S)-2-丙基-哌嗪-1-羰基]-4-氯-苯磺酰胺	517,519 Cl花样

用上述模板与氨基-喹啉或氨基-噌啉，以及实施例718-721描述的方法：

实施例	名称	m/z(M+H)
1097	1-(S)-4-(4-氨基-喹啉-7-基甲基)-3-氧代-2-丙基-哌嗪-1-甲酸(4-氯-苯基)-酰胺	452
1098	1-(S)-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-丙基-哌嗪-2-酮	455

1099	1-(S)-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-4-氧基-3-丙基-哌嗪-2-酮	471
1100	1-(S)-4-(4-氨基-喹啉-7-基甲基)-2-甲氧基甲基-3-氧代-2-(4-氯-苯基)-酰胺哌嗪-1-甲酸	425
1101	(S)-4-(4-氨基喹啉-7-基甲基)-2-甲氧基甲基-3-氧代-2-(5-氯噻吩-2-基)-酰胺哌嗪-1-甲酸	460
1102	1-(S)-4-(4-氨基-喹啉-7-基甲基)-2-甲基-3-氧代-2-哌嗪-1-甲酸苯基酰胺	390
1103	1-(S)-4-(4-氨基-喹啉-7-基甲基)-2-甲基-3-氧代-2-哌嗪-1-甲酸(4-氯-苯基)-酰胺	454
1104	1-(S)-4-(4-氨基-噌啉-7-基甲基)-2-甲基-3-氧代-哌嗪-1-甲酸(4-氯-苯基)-酰胺	425
1105	1-(S)-(4-氨基-噌啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3-甲基-哌嗪-2-酮	442
1106	1-(4-氨基-噌啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-甲基-哌嗪-2-酮	428

用适当的酮基哌嗪和磺酰氯，用上述方法制备下列化合物。在CHIRALPAK AD 10 □m柱上分离消旋体。

实施例	名称	m/z(M+H)
1107	4-[2-(5-氯-噻吩-2-基)-乙磺酰基]-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(+)-甲酸甲酯	598,600 Cl花样
1108	4-[2-(5-氯-噻吩-2-基)-乙磺酰基]-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(-)-甲酸甲酯	598,600 Cl花样
1109	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(+)-甲酸酰胺	504,506 Cl花样

1110	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-(-)-甲酸酰胺	504,506 Cl花样
1111	4-[2-(5-氯-噻吩-2-基)-乙磺酰基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	481,483 Cl花样
1112	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	505,507 Cl花样
1113	4-[2-(5-氯-噻吩-2-基)-乙磺酰基]-6-羟基基甲基-1-(1-甲基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	481,483 Cl花样
1114	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-羟基甲基-1-(1-甲基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	505,507 Cl花样
1115	4-(5-氯-1H-吲哚-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	444
1116	4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	488,490 Cl花样
1117	4-(7-甲氧基-萘-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	451
1118	4-(苯并[b]噻吩-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	427

烷基氮杂吲哚类的代表性合成:

实施例1119

4-[4-(5-氯-噻吩-2-基)-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)哌嗪-2-酮

A. 4-(5-氯-噻吩-2-基)-苯甲醛

将4-甲酰基苯基硼酸(1.37 g, 9.15 mmol)、2-溴-5-氯噻吩(1 mL,

9.15 mmol)、2M Na_2CO_3(9 mL, 18.3 mmol)、$Pd(PPH_3)_4$(0.53 mg, 0.46 mmol)在DME(30 mL)中加热回流4小时，之后将此反应混合物真空浓缩，在乙酸乙酯中回收。有机溶液用水(x2)，然后用盐水洗涤，用硫酸镁干燥，过滤并浓缩至干。粗品残余物通过色谱纯化，用5% EtOAc/己烷作为洗脱剂，得到黄色固体(1.8 g, 8.1 mmol)，为标题化合物。

EI MS $[M]^+$=222,224, Cl花样。

B. 2-{4-[4-(5-氯-噻吩-2-基)-苄基]-2-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯

向2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(0.10 g, 0.30 mmol)的乙腈(5 mL)溶液中，加入4-(5-氯-噻吩-2-基)-苯甲醛(0.067 g, 0.30 mmol)，接着加入三乙酰氧基硼氢化物(0.13 g, 0.60 mmol)、冰醋酸(1滴)。将所得混合物室温下搅拌过夜，然后倒入EtOAc中，用水(x2)和盐水洗涤。有机层用硫酸镁干燥，过滤并浓缩至干，然后通过柱色谱纯化，用乙酸乙酯作为洗脱剂，得到标题化合物(0.90 g, 0.17 mmol)。ESI MS $[M+H]^+$=537。

C. 4-[4-(5-氯-噻吩-2-基)-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

将2-{4-[4-(5-氯-噻吩-2-基)-苄基]-2-氧代-哌嗪-1-基甲基}-吡咯并[3,2-c]吡啶-1-酸叔丁酯(0.90 g, 0.17 mmol)在30% TFA/二氯甲烷(8 mL)中搅拌1小时，然后浓缩至干，通过RP-HPLC纯化，用10-100% 乙腈/0.1% TFA 水作为洗脱剂。收集适当的馏份，冻干得到标题产物，为一种无定形白色固体(0.44 mg, 0.08 mmol)。

实施例	名称	m/z(M+H)
1120	4-[3-(5-氯-噻吩-2-基)-苄基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	479
1121	4-[3-(5-氯-噻吩-2-基)-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	437

1122	4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	438
1123	4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	480
1124	4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	482
1125	4-[2-(4-氯-苯基)-1H-吲哚-3-基甲基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	512
1126	4-[6-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	482
1127	4-[4-(5-氯-噻吩-2-基)-苄基]-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	481
1128	4-[6-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	438
1129	4-(5-氯-[2,3']联噻吩基-5'-基甲基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	443
1130	4-(5'-氯-[2,2']联噻吩基-5-基甲基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	487
1131	4-[2,2']联噻吩基-5-基甲基-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	453
1132	4-(5-氯-[2,3']联噻吩基-5'-基甲基)-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	485

1133	4-[6-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	480
1134	4-[3-(5-氯-噻吩-2-基)-4-氟-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	455
1135	4-[5-(3-氯-苯基)-呋喃-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	421
1136	4-[4-(5-氯-噻吩-2-基)-苄基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	437
1137	4-[3-(5-氯-噻吩-2-基)-4-氟-苄基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	497
1138	4-[4-(5-氯-噻吩-2-基)-苄基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	479
1139	4-[5-(3-氯-苯基)-呋喃-2-基甲基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	463
1140	4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	429,431 Cl花样
1141	4-(5-氯-1H-吲哚-2-基甲基)-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	436
1142	4-(5'-氯-[2,2']联噻吩基-5-基甲基)-3-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	485,487 Cl花样
1143	4-[4-(5-氯-噻吩-2-基)-苄基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	481

1144	4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	482

用上述模板制备下列化合物，用实施例860的描述及所述的磺酰基化、烷基化或酰胺偶联反应的方法，与氨基-甲基-喹唑啉、喹唑啉酮、羟基-喹啉、氧代-1,6-二氢-吡啶苄基、6-甲氧基-吡啶-3-基)-苄基或3-咪唑-1-基-苄基偶联。

实施例	名称	m/z(M+H)
1145	1-(4-氨基-2-甲基-喹唑啉-7-基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-丙基-哌嗪-2-酮	487
1146	7-{4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-2-氧代-(S)-3-丙基-哌嗪-1-基甲基}-3H-喹唑啉-4-酮	471,473 Cl花样
1147	7-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-2-氧代-(S)-3-丙基-哌嗪-1-基甲基}-3H-喹唑啉-4-酮	475,477 Cl花样
1148	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-(S)-6-甲基-(S)-3-丙基-哌嗪-2-酮	484,486 Cl花样
1149	4-[3-(5-氯-噻吩-2-基)-烯丙基]-(S)-3-乙基-1-(4-羟基-喹啉-7-基甲基)-哌嗪-2-酮	442,444 Cl花样
1150	7-{4-[3-(5-氯-噻吩-2-基)-烯丙基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-2H-异喹啉-1-酮	457
1151	7-[4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基]-2H-异喹啉-1-酮	477,479 Cl花样
1152	4-(5-氯-1H-吲哚-2-基甲基)-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	489,491 Cl花样

1153	4-(5-氯-1H-吲哚-2-基甲基)-3-(S)-甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	561,563 Cl花样
1154	6-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-3-甲基-3H-喹唑啉-4-酮	491,493 Cl花样
1155	6-(4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-3H-喹唑啉-4-酮	477,479 Cl花样
1156	4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	473,475 Cl花样
1157	4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	459,461 Cl花样
1158	4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-甲基-哌嗪-2-酮	487,489 Cl花样
1159	4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	501,503 Cl花样
1160	4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2-酮	473,475 Cl花样
1161	4-(7-氯-异喹啉-3-基甲基)-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	515,517 Cl花样
1162	4-(7-氯-异喹啉-3-基甲基)-3-(S)-甲氧基甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	503
1163	4-[3-(6-氨基-吡啶-3-基)-丙酰基]-3-(S)-甲氧基甲基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	476

1164	(S)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-6-甲氧基甲基-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2-酮	516
1165	4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-3(S)-异丁基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	510
1166	4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-(3-咪唑-1-基-苄基)-3-(S)-甲氧基甲基-哌嗪-2-酮	475,477 Cl花样
1167	4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-异丁基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	514
1168	4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-3(S)-异丁基-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2-酮	486
1169	4-[3-(6-氨基-吡啶-3-基)-丙烯酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	472
1170	4-[(5-氯-噻吩-3-基氧基)-乙酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	500,502 Cl花样
1171	4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	500,502 Cl花样
1172	4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	496,498 Cl花样
1173	4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	496,498 Cl花样

1174	4-[3-(4-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	510,512 Cl花样
1175	4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	514,516 Cl花样
1176	4-[3-(5-氯-噻吩-2-基)-丙烯酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	510,512 Cl花样
1177	4-[(5-氯-噻吩-3-基氧基)-乙酰基]-1-[4-(6-甲氧基-吡啶-3-基)-苄基]-3-(S)-丙基-哌嗪-2-酮	514,516 Cl花样

实施例1178

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮

A: 4-氰基甲基-哌嗪-1-甲酸叔丁酯

向部分溶解的哌嗪-1-甲酸叔丁酯(2.0g, 10mmol)的THF (30 mL)溶液中加入60%的氢化钠(0.44g, 11mmol)。将所得溶液搅拌5分钟，然后加入溴乙腈(0.9mL, 13mmol)。将该反应液搅拌4小时。加入甲醇(1mL)并将溶液浓缩，残余物用EtOAc稀释并用1N HCl、H_2O、$NaHCO_3$洗涤，然后将溶液用$MgSO_4$干燥。将滤液浓缩并用硅胶柱对粗品产物进行色谱处理(50% EtOAc/PE-EtOAc)得到4-氰基甲基-哌嗪-1-甲酸叔丁酯。^1H NMR (300MHz, $CDCl_3$) δ 4.41 (s, 2H), 4.16 (s, 2H), 3.75 (t, 2H), 3.51 (t, 2H), 1.47 (s, 9H)。

B: 哌嗪-1-基-乙腈

向30% TFA/CH_2Cl_2 (10mL)溶液中加入4-氰基甲基-哌嗪-1-甲酸叔丁酯(1.7g, 6.8mmol)并将此反应液搅拌14小时。将此反应液浓缩并用

硅胶色谱进行处理(1%氢氧化铵/7%甲醇/CH_2Cl_2)分离出游离碱形式的哌嗪-1-基-乙腈。^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (s, 2H), 3.54 (s, 2H), 3.45 (t, 2H), 3.13 (t, 2H)。

C: [4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-1-基]-乙腈

向哌嗪-1-基-乙腈(0.32g, 2.3mmol)和三乙胺(350mg, 3.4mmol)的溶液中于0℃下加入6-氯-苯并[b]噻吩-2-磺酰氯(615mg, 2.3mmol)。将此反应液升温至室温并搅拌4小时。将此反应液用CH_2Cl_2稀释, 用1N盐酸、碳酸氢钠洗涤并用硫酸镁干燥。将溶液浓缩并将残余物用PE研磨, 用乙醚研磨, 抽真空得到不经进一步纯化即可使用的[4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-1-基]-乙腈。^1H NMR (300 MHz, $CDCl_3$) δ 7.89-7.84 (m, 3H), 7.48 (dd, 1H), 4.36 (s, 2H), 3.92 (s, 2H), 3.64-3.61 (m, 2H), 3.57-3.54 (m, 2H); MS (离子喷雾) 444 $(M+H)^+$。

D: 2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-1-基]-硫代乙酰胺

将[4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-1-基]-乙腈(1.2 g, 3.2mmol)的悬浮液与二异丙基乙基胺(0.65 g, 5.0mmol)在用硫化氢气体饱和的乙醇中的溶液一起加热4小时。将此反应液冷却、过滤、用冷乙醇洗涤得到2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-1-基]硫代乙酰胺。^1H NMR (300 MHz, DMSO-d_6) δ 9.71 (bs, 1H), 9.01 (bs, 1H), 8.35 (d, 1H), 8.21 (s, 1H), 8.08 (d, 1H), 7.59 (dd, 1H), 4.15 (s, 2H), 3.73 (s, 2H), 3.43 (s, 4H)。

E: 2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮

向甲苯/叔丁醇(1:1)溶液中加入2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-1-基]-硫代乙酰胺(180 mg, 0.45mmol)和3-溴-环己烷-1,2-二酮(135 mg, 0.80mmol)。将此反应液于90℃加热4小时然后浓

缩，将粗品产物溶于CH_2Cl_2并用碳酸氢钠洗涤。将溶液浓缩并用1%甲醇/EtOAc纯化得到2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.47 (dd, 1H), 4.80 (s, 2H), 3.91 (s, 2H), 3.61 (t, 2H), 3.43 (t, 2H), 3.05 (t, 2H), 2.65 (t, 2H), 2.24 (dt, 2H); MS（离子喷雾） 496 $(M+H)^+$.

利用相应的α-卤代酮，可以制得如下产物:

实施例1179

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4-甲基-噻唑-5-甲酸甲基酰胺

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 5.69 (br, 1H), 4.74 (s, 2H), 3.91 (s, 2H), 3.63-3.59 (m, 2H), 3.49-3.43 (m, 2H), 2.94 (d, 3H), 2.61 (s, 3H); MS（离子喷雾） 499 $(M+H)^+$。

实施例1180

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4-甲基-噻唑-5-甲酸二甲基酰胺

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 3H), 7.46 (dd, 1H), 4.76 (s, 2H), 3.90 (s, 2H), 3.62-3.59 (m, 2H), 3.46-3.42 (m, 2H), 3.03 (br, 6H), 2.37 (s, 3H); MS（离子喷雾） 513 $(M+H)^+$。

实施例1181

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-吡啶-4-基-噻唑-2-基甲基)-哌嗪-2-酮氢溴酸盐

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br, 2H), 7.83-7.80 (m, 3H), 7.77 (br, 2H), 7.66 (s, 1H), 7.44 (dd, 1H), 4.87 (s, 2H), 3.96 (s,

2H), 3.70-3.66 (m, 2H), 3.52-3.49 (m, 2H); MS(离子喷雾) 505 $(M+H)^+$。

实施例1182

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸酰胺

^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.84 (br, 1H), 5.60 (br, 1H), 4.85 (d, 1H), 4.66 (d, 1H), 3.91 (s, 2H), 3.64-3.52 (m, 3H), 3.47-3.44 (m, 2H), 2.76-2.62 (m, 2H), 2.41-2.33 (m, 1H), 1.93-2.81 (m, 3H); MS(离子喷雾) 525 $(M+H)^+$.

实施例1183

{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸甲酯

^1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1 H), 7.11 (s, 1 H), 4.80 (s, 2H), 3.93 (s, 2H), 3.78 (s, 2H), 3.73 (s, 3H), 3.61-3.57 (m, 2H), 3.47-3.44 (m, 2H); MS(离子喷雾) 500 $(M+H)^+$。

实施例1184

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸乙酯

^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.86-7.81 (m, 3H), 7.46 (dd, 1H), 4.86 (s, 2H), 4.41 (q, 2H), 3.93 (s, 2H), 3.63-3.59 (m, 2H), 3.48-3.44 (m, 2H), 1.39 (t, 3H); MS(离子喷雾) 500 $(M+H)^+$。

实施例1185

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4-甲

基-噻唑-5-甲酸甲酯

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.83 (m, 3H), 7.47 (dd, 1H), 4.76 (s, 2H), 3.93 (s, 2H), 3.84 (s, 3H), 3.64-3.60 (m, 2H), 3.49-3.45 (m, 2H) 2.66 (s, 3H); MS(离子喷雾) 500 $(M+H)^+$。

实施例1186

1-(4-叔丁基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1 H), 6.79 (s, 1 H), 4.81 (s, 2H), 3.93 (s, 2H), 3.61-3.58 (m, 2H), 3.48-3.44 (m, 2H), 1.29 (s, 9H); MS(离子喷雾) 484 $(M+H)^+$。

实施例1187

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(5-氯-噻吩-2-基)-噻唑-2-基甲基]-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.81 (m, 3H), 7.45 (dd, 1H), 7.18 (s, 1H), 7.13 (d, 1H), 6.86 (d, 1H), 4.81 (s, 2H), 3.95 (s, 2H), 3.67-3.64 (m, 2H), 3.52-3.48 (m, 2H); MS (离子喷雾) 544 $(M+H)^+$。

实施例1188

1-[4-(4-溴-苯基)-噻唑-2-基甲基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 3H), 7.70 (ddd, 2H), 7.53 (ddd, 2H), 7.45 (dd, 1H), 7.38 (s, 1H), 4.86 (s, 2H), 3.96 (s, 2H), 3.68-3.65 (m, 2H), 3.51-3.48 (m, 2H); MS(离子喷雾) 582 $(M+H)^+$。

实施例1188

1-[4-(3-溴-苯基)-噻唑-2-基甲基]-4-(6-氯-苯并[b]噻吩-2-磺酰

基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, 1H), 7.83-7.80 (m, 3H), 7.73 (dd, 1H), 7.48-7.40 (m, 3H), 7.28 (dd, 1H), 4.86 (s, 2H), 3.96 (s, 2H), 3.69-3.65 (m, 2H), 3.52-3.48 (m, 2H); MS(离子喷雾) 582 $(M+H)^+$。

实施例1189

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-甲基-噻唑-2-基甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.80 (m, 3H), 7.45 (dd, 1H), 6.79 (s, 1H), 4.78 (s, 2H), 3.92 (s, 2H), 3.59-3.56 (m, 2H), 3.47-3.43 (m, 2H), 2.38 (s, 3H); MS(离子喷雾) 442 $(M+H)^+$。

实施例1190

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-吡啶-3-基-噻唑-2-基甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (dd, 1H), 8.58 (dd, 1H), 8.11 (ddd, 1H), 7.83-7.79 (m, 3H), 7.43 (dd, 1H), 7.33 (dd, 1H), 4.86 (s, 2H), 3.95 (s, 2H), 3.67-3.64 (m, 2H), 3.51-3.47 (m, 2H); MS(离子喷雾) 505 $(M+H)^+$。

实施例1191

1-(5-乙酰基-4-甲基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.45 (dd, 1H), 4.75 (s, 2H), 3.92 (s, 2H), 3.65-3.61 (m, 2H), 3.48-3.45 (m, 2H), 2.65 (s, 3H), 2.61 (s, 3H); MS(离子喷雾) 499 $(M+H)^+$。

实施例1192

3-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-3-甲基-丁酸乙酯

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.85 (s, 1H), 4.80 (s, 2H), 3.98 (q, 2H), 3.92 (s, 2H), 3.60-3.57 (m, 2H), 3.46-3.43 (m, 2H), 2.66 (s, 2H), 1.40 (s, 6H), 1.12 (t, 3H); MS (离子喷雾) 556 $(M+H)^+$。

实施例1193

1-(4-金刚烷-1-基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 6.74 (s, 1 H), 4.81 (s, 2H), 3.93 (s, 2H), 3.60-3.57 (m, 2H), 3.48-3.44 (m, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80-1.71 (m, 6H); MS (离子喷雾) 562 $(M+H)^+$。

实施例1194

1-(4-金刚烷-1-基-噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 6.74 (s, 1H), 4.81 (s, 2H), 3.93 (s, 2H), 3.60-3.57 (m, 2H), 3.48-3.44 (m, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80-1.71 (m, 6H); MS (离子喷雾) 562 $(M+H)^+$。

实施例1195

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-苯基-噻唑-2-基甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.79 (m, 5H), 7.45-7.31(m, 5H), 4.87 (s, 2H), 3.95 (s, 2H), 3.69-3.65 (m, 2H), 3.51-3.47 (m, 2H); MS (离子喷雾) 504 $(M+H)^+$。

实施例1195

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(4-羟基-苯基)-噻唑-2-基甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.78 (m, 3H), 7.63 (ddd, 2H), 7.41 (dd, 1H), 7.17 (s, 1H), 6.83 (ddd, 1H), 4.81 (s, 2H), 3.92 (s, 2H), 3.68-3.61 (m, 2H), 3.48-3.44 (m, 2H); MS(离子喷雾) 520 $(M+H)^+$。

实施例1196

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(4-羟基-苯基)-噻唑-2-基甲基]-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.79 (m, 3H), 7.43 (dd, 1H), 7.36-7.34 (md, 3H), 7.25 (m, 1H), 6.83 (dd, 1H), 6.10 (br, 1H), 4.86 (s, 2H), 3.95 (s, 2H), 3.68-3.64 (m, 2H), 3.50-3.47 (m, 2H); MS(离子喷雾) 520 $(M+H)^+$。

实施例1197

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 4.80 (s, 2H), 3.91 (s, 2H), 3.61-3.58 (m, 2H), 3.46-3.43 (m, 2H), 2.72 (bm, 4H), 1.83 (bs, 4H); MS(离子喷雾) 482 $(M+H)^+$。

实施例1198

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.47 (dd, 1H), 4.83 (s, 2H), 3.92 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H),

3.18 (s, 3H), 3.10 (s, 3H); MS (离子喷雾) 499 $(M+H)^+$。

实施例1199

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸乙酯

^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.46 (dd, 1H), 4.81 (s, 2H), 4.17 (q, 2H), 3.91 (s, 1H), 3.89 (s, 1H), 3.80 (t, 0.5), 3.60-2.52 (m, 2.5H), 3.45-3.36 (m, 2H), 2.78-2.68 (m, 2H), 2.16-1.77 (m, 4H), 1.25 (t, 3H); MS (离子喷雾) 554 $(M+H)^+$。

实施例1200

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-苯甲酸

^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 1H), 7.80-7.76 (m, 3H), 7.55-7.35 (m, 5H), (s, 2H), 3.94 (s, 2H), 3.55 (m, 2H), 3.43 (m, 2H); MS (离子喷雾) 548 $(M+H)^+$。

实施例1201

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(2-羟基-苯基)-噻唑-2-基甲基]-哌嗪-2-酮

^1H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.82-7.79 (m, 3H), 7.55 (dd, 1H), 7.45-7.40 (m, 2H), 7.24 (d, 1 H), 6.97-6.89 (m, 2H), 4.87 (s, 2H), 3.95 (s, 2H), 3.61 (m, 2H), 3.50 (m, 2H); MS (离子喷雾) 520 $(M+H)^+$。

实施例1202

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-吡啶-2-基-噻唑-2-基甲基)-哌嗪-2-酮

^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.99 (d, 1H), 7.96 (s,

1H), 7.83-7.74 (m, 4H), 7.43 (dd, 1H), 7.23-7.19 (m, 1H), 4.88 (s, 2H), 3.94 (s, 2H), 3.65 (m, 2H), 3.48 (m, 2H); MS (离子喷雾) 505 $(M+H)^+$。

实施例1203

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-苯甲酰胺

^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.84-7.79 (m, 2H), 7.61-7.55 (m, 2H), 7.48-7.37 (m, 4H), 5.86 (d (宽峰), 2H), 4.83 (s, 2H), 3.92 (s, 2H), 3.65 (m, 2H), 3.47 (m, 2H); MS (离子喷雾) 547 $(M+H)^+$。

利用上面描述的方法可以制得如下化合物;

实施例1204

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4,5,6,7-四氢-噻唑并[5,4-c]吡啶-2-基甲基)-哌嗪-2-酮

实施例1205

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(5-甲基-4,5,6,7-四氢-噻唑并[5,4-c]吡啶-2-基甲基)-哌嗪-2-酮

实施例1206

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4,5,6,7-四氢-噻唑并[4,5-c]吡啶-2-基甲基)-哌嗪-2-酮

实施例1207

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(5-甲基-4,5,6,7-四氢-噻唑并[4,5-c]吡啶-2-基甲基)-哌嗪-2-酮

实施例1208

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,7-二氢-5H-噻唑并[4,5-c]吡啶-6-酮

按照上面描述的方法制备下面的化合物。

实施例	名称	MS (m/z) (M+H)
1209	(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-4,5,6,7-四氢-苯并噻唑-4-甲酸酰胺	569
1210	(R)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮	526
1211	(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸乙酯	544/546
1212	(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-4-甲基-噻唑-5-甲酸二甲基酰胺	557
1213	(R)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-1-(4-吡啶-3-基-噻唑-2-基甲基)-哌嗪-2-酮	549
1214	(R)-3-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-基}-3-甲基-丁酸乙酯	600
1215	(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸	516
1216	(R)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺	543

1217	(S)-2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-(3S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-4,5,6,7-四氢-苯并噻唑-4-甲酸酰胺	513
1218	(S)-2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-(3S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基)-噻唑-4-甲酸乙酯	488
1219	(S)-2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-噻唑-4-甲酸二甲基酰胺	487
1220	(S)-(2-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-噻唑-4-基)-乙酸甲酯	488
1221	(S)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3(S)-甲氧基甲基-1-(4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮	470

实施例1222

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-羟基-4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮

向2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮(7mg, 0.01mmol)的乙醇(1mL)悬浮液中加入硼氢化钠(3mg, 0.08mmol)。反应15分钟后将此反应液用EtOAc稀释并用1N盐酸、碳酸氢钠和盐水洗涤。将溶液用硫酸镁干燥然后浓缩得到4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(4-羟基-4,5,6,7-四氢-苯并噻唑-2-基甲基)-哌嗪-2-酮。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 3H), 7.46 (dd, 1H), 4.83-4.81 (m, 1H), 4.76 (s, 1H), 4.75 (s, 1H), 3.92 (s, 1H), 3.91 (s, 1H), 3.62-3.55 (m, 2H), 3.47-3.41 (m, 2H), 2.76-2.62 (m, 2H), 2.05-1.78 (m, 4H); MS(离子喷雾)498 $(M+H)^+$。

实施例1223

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮肟

将2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮(24mg, 0.05mmol)、羟胺盐酸盐(20 mg, 0.3mmol)、乙酸钠(20 mg, 0.3 mmol)和乙醇(2mL)混合并搅拌3.5小时。将该反应液用CH_2Cl_2稀释并用氯化铵、碳酸氢钠洗涤然后浓缩得到2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮肟。^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.34 (d, 1H), 8.20 (s, 1H), 8.07 (d, 1H), 7.59 (dd, 1H), 4.70 (s, 2H), 3.87 (s, 2H), 3.49 (s, 4H), 2.74 (t, 2H), 2.61 (t, 2H), 1.81 (dt, 2H); MS(离子喷雾)511 $(M+H)^+$。

实施例1224a

1-(4-氨基-苯并噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮和

实施例1224b

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-5,6,7,8-四氢-噻唑并[4,5-c]吖庚因-4-酮

将2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-6,7-二氢-5H-苯并噻唑-4-酮(60mg, 0.12mmol)溶于$CHCl_3$ (4mL)并在剧烈搅拌下加入硫酸(0.5mL)。加入叠氮化钠(25mg 0.4mmol)并将此反应液搅拌1.75小时。然后将该反应液滴加到迅速搅拌中的碳酸钾/水/二氯甲烷混合物中。分出有机相并用水洗涤、用硫酸镁干燥然后浓缩。将残余物经柱色谱纯化(硅胶, 2%-6%的MeOH/CH_2Cl_2)得到两种产物的混合物。

较快洗脱的产物是Semler-Wolff芳构化产物, 1-(4-氨基-苯并噻唑-2-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-2-酮。^{1}H NMR

(300 MHz, DMSO-d_6) δ 8.32 (d, 1H), 8.21 (s, 1H), 8.07 (d, 1H), 7.59 (dd, 1H), 7.08 (t, 1H), 6.98 (d, 1H), 6.13 (d, 1H), 5.59 (s, 2H), 4.84 (s, 2H), 3.93 (s, 2H), 3.54 (s, 4H); MS(离子喷雾) 493 $(M+H)^+$。

较慢洗脱的产物是扩环的内酰胺2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-5,6,7,8-四氢-噻唑并[4,5-c]吖庚因-4-酮。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.47 (dd, 1H), 6.47 (bs, 1H), 4.80 (m, 2H), 3.91 (s, 2H), 3.65-3.61 (m, 2H), 3.46-3.42 (m, 2H), 3.37-3.32 (m, 2H), 3.07 (t, 2H) 2.17-2.10 (m, 2H); MS (离子喷雾) 511 $(M+H)^+$。

实施例1225

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺

A: 2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基-甲酸

将2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基-甲酸乙酯(75mg, 0.15mmol)的溶液溶于THF/MeOH-3:1(2mL)并加入1N氢氧化钠(0.5mL)。将此反应液搅拌2小时然后用EtOAc稀释并用2N盐酸洗涤。将有机相用硫酸镁干燥然后浓缩得到2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基甲酸。^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 8.04 (d, 1H), 7.57 (dd, 1H), 4.74 (s, 2H), 3.87 (s, 2H), 3.49 (s, 4H); MS(离子喷雾) 471 $(M)^+$。

B: 2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺

向2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基-甲酸(14mg, 0.03mmol)的N-甲基吡咯烷酮 (0.3 mL)

溶液中加入TBTU (0.05mmol)、二异丙基乙基胺(0.06mmol)和二甲胺盐酸盐(0.06)。将此反应液搅拌3小时，补加相同量的TBTU、DIEA和胺。将此反应液搅拌1小时然后将浓缩，经柱色谱(硅胶，2% MeOH/EtOAc)纯化得到2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸二甲基酰胺。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.47 (dd, 1H), 4.83 (s, 2H), 3.92 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 3.18 (s, 3H), 3.10 (s, 3H); MS (离子喷雾) 499 $(M+H)^+$。

在上面的反应中使用另外的胺可以分离出如下产物:

实施例1226

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(吡咯烷基-1-羰基)-噻唑-2-基甲基]-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.87-7.81 (m, 3H), 7.47 (d, 1H), 4.81 (s, 2H), 3.92 (s, 2H), 3.82 (m, 2H), 3.72-3.61 (m, 4H), 3.46 (m, 2H), 1.97-1.87 (m, 4H); MS (离子喷雾) 525 $(M+H)^+$。

实施例1227

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(吗啉-4-羰基)-噻唑-2-基甲基]-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 4H), 7.46 (dd, 1H), 4.82 (s, 2H), 3.93 (s, 2H), 3.88-3.67 (m, 8H), 3.61 (m, 2H), 3.46 (m, 2H); MS (离子喷雾) 541 $(M+H)^+$。

实施例1228

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(哌嗪-1-羰基)-噻唑-2-基甲基]-哌嗪-2-酮

TFA盐的形式：^{1}H NMR (300 MHz, $CDCl_3$) δ 9.9 (s (broad), 1H), 7.99 (s, 1H), 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 4.80 (s, 2H), 4.39-3.96 (m (broad), 4H), 3.90 (s, 2H), 3.59 (m, 2H), 3.47 (m, 2H), 3.28 (s (broad), 4H); MS (离子喷雾) 540 $(M+H)^+$。

实施例1229

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸N',N'-二甲基-肼

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.86-7.80 (m, 3H), 7.46-7.43 (m, 1H), 4.77 (s, 2H), 3.92 (s, 2H), 3.83 (m, 2H), 3.52 (m, 2H), 3.21 (s, 6H); MS (离子喷雾) 514 $(M+H)^+$。

实施例1230

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸(2-羟基-乙基)-甲基-酰胺

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.46 (dd, 1H), 4.81 (s, 2H), 4.68 (t, 1H), 3.94 (s, 2H), 3.72 (m, 2H), 3.64-3.54 (m, 4H), 3.49 (m, 2H), 3.08 (s, 3H); MS (离子喷雾) 529 $(M+H)^+$。

实施例1231

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-[4-(3-羟基-吡咯烷基-1-羰基)-噻唑-2-基甲基]-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H), 7.87-7.82 (m, 3H), 7.45 (dd, 1 H), 4.85 (s, 2H), 4.62-4.55 (m, 1H), 4.08-3.42 (m, 10H). 2.12-1.92 (m, 2H); MS (离子喷雾) 541 $(M+H)^+$。

实施例1232

2-(4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸甲氧基-甲基-酰胺

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86-7.81 (m, 3H), 7.45 (dd, 1H), 4.85 (s, 2H), 3.92 (s, 2H), 3.72 (s, 3H), 3.62 (m, 2H), 3.45 (m, 2H), 3.39 (s, 3H); MS (离子喷雾) 515 $(M+H)^+$。

实施例1233

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸异丙基-甲基-酰胺

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.66 (m, 1H), 7.45 (dd, 1H), 4.95-4.89 (m, 0.5), 4.82 (s, 2H), 4.38-4.22 (m, 0.5), 3.91 (s, 2H), 3.68-3.59 (m, 2H), 3.48-3.42 (m, 2H), 2.92 (s (broad), 3H), 1.24-1.15 (m, 6H); MS (离子喷雾) 527 $(M+H)^+$。

实施例1234

({2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-羰基}-甲基-氨基)-乙酸乙酯

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.81 (m, 4H), 7.46 (dd, 1H), 4.83 (s, 1H), 4.75 (s, 1H), 4.44 (s, 1H), 4.26-4.13 (m, 3H), 3.91 (s, 1H), 3.63-3.58 (m, 2H), 3.46-3.43 (m, 2H), 3.31 (s, 1.5), 3.15 (s, 1.5), 1.32-1.22 (m, 3H); MS (离子喷雾) 571 $(M+H)^+$。

实施例1235

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-酰胺

MS (离子喷雾) 471 $(M+H)^+$。

实施例1236

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸甲基酰胺

MS (离子喷雾) 485 $(M+H)^+$。

实施例1237

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-甲酸异丙基酰胺

MS（离子喷雾）513 $(M+H)^+$。

将{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸甲酯在前面所采用的条件下用氢氧化钠处理可得到如下产物:

实施例1238

{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸

^1H NMR (300 MHz, $CDCl_3$+ CD_3OD) δ 7.90-7.87 (m, 3H), 7.47 (dd, 1H), 7.17 (s, 1H), 4.80 (s, 2H), 3.93 (s, 2H), 3.75 (s, 2H), 3.60-3.58 (m, 2H), 3.50-3.48 (m, 2H); MS（离子喷雾）486 $(M+H)^+$。

用所示的胺在前述条件下形成酰胺键得到如下产物

实施例1239

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酰胺

MS（离子喷雾）485 $(M+H)^+$。

实施例1240

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-N-甲基-乙酰胺

MS（离子喷雾）499 $(M+H)^+$。

实施例1241

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-

噻唑-4-基}-N-异丙基-乙酰胺

MS（离子喷雾）527 $(M+H)^+$。

实施例1242

2-{2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-N,N-二甲基-乙酰胺

MS（离子喷雾）513 $(M+H)^+$。

实施例1243

2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,7-二氢-5H-噻唑并[5,4-c]吡啶-6-酮

A: 5-苄氧羰基氨基-3-氧代-戊酸乙酯

将Cbz-β-丙氨酸(5.0g, 21.6mmol)溶于THF(10mL)。向该溶液中滴加羰基二咪唑(3.5g, 21.6mmol)的THF(50mL)溶液并搅拌16小时。然后将该溶液通过旋转蒸发减少到约30mL。向另一个经烘箱干燥的烧瓶中加入异丙基氯化镁的THF(2M)溶液(16.2mL, 32mmol)，将其冷却至0℃然后滴加丙二酸单乙酯(4.28g, 32.4mmol)。将该溶液于0℃搅拌30分钟，升温至25℃并继续搅拌30分钟，最后升温至40℃加热30分钟。然后将烧瓶内的物质冷却至0℃并向其中滴加第一个烧瓶内的物质。将此反应液逐渐升温至25℃，继续搅拌4小时。将此反应液倒入100mL冰冷的1N磷酸中并搅拌30分钟。将该溶液用乙酸乙酯萃取(3x100mL)。然后将合并的有机层先用饱和碳酸氢钠洗涤(3x100mL)，然后用盐水(3x100mL)洗涤。将有机层用硫酸镁干燥，过滤，然后旋转蒸发成油状物得到5-苄氧羰基氨基-3-氧代-戊酸乙酯。产物不经进一步的纯化直接使用。^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.25 (bm, 1H), 5.06 (s, 2H), 4.17 (q, 2H), 3.42 (m, 5H), 2.78 (t, 2H), 1.25 (t, 3H); MS（离子喷雾）294 $(M+H)^+$。

B: 5-苄氧羰基氨基-4-溴-3-氧代-戊酸乙酯

将5-苄氧羰基氨基-3-氧代-戊酸乙酯(1.0g, 3.4mmol)溶于冰乙酸(10mL)并向其中加入过溴溴化吡啶(1.1g, 3.4mmol)。将此反应液搅拌16小时后倒入水(100mL)中, 用乙酸乙酯萃取(2x100mL)。将有机层合并并用水(2x100mL)和盐水(2x100mL)洗涤。将有机层用硫酸镁干燥, 过滤然后旋转蒸发得到油状物。将粗品产物通过快速硅胶色谱纯化, 用25%乙酸乙酯/己烷洗脱得到5-苄氧羰基氨基-4-溴-3-氧代-戊酸乙酯。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 5H), 5.27 (m, 1H), 5.09 (s, 2H), 4.67 (t, 1H), 4.17 (q, 2H), 3.72 (m, 4H), 1.27 (t, 3H); MS (离子喷雾) 372 $(M+H)^+$。

C: {5-(苄氧羰基氨基-甲基)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸乙酯

将2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-哌嗪-1-基]-硫代乙酰胺(200mg, 0.5mmol)和5-苄氧羰基氨基-4-溴-3-氧代-戊酸乙酯(370mg, 1.0mmol)在甲苯/叔丁醇(1:1, 5mL)的混合物中的悬浮液于90℃加热16小时。将反应液浓缩并经柱色谱纯化(硅胶, 2% MeOH/CH_2Cl_2)得到{5-(苄氧羰基氨基-甲基)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸乙酯。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.45 (dd, 1 H), 7.32 (s, 5H), 7.45 (bt, 1H), 5.07 (s, 2H), 4.73 (s, 2H), 4.42 (d, 2H), 4.13 (q, 2H), 3.90 (s, 2H), 3.76 (s, 2H), 3.61-3.55 (m, 2H), 3.50-3.43 (m, 2H), 1.24 (t, 3H); MS (离子喷雾) 677 $(M+H)^+$。

D: {5-氨基甲基-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基)-噻唑-4-基}-乙酸乙酯

将{5-(苄氧羰基氨基-甲基)-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸乙酯(40mg, 0.06mmol)用30%的HBr/HOAc (1mL)处理7小时。向其中加入乙醚

(10mL)，将所得沉淀物用乙醚洗涤两次。将所得的盐在EtOAc (15mL)和碳酸氢钠溶液(10mL)之间进行分配。将有机相用碳酸氢钠和盐水(2x10mL)洗涤，用硫酸镁干燥然后浓缩得到{5-氨基甲基-2-[4-(6-氯-苯并哌嗪-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸乙酯。^{1}H NMR (300 MHz, DMSO) δ 8.32 (d, 1H), 8.17 (s, 1H), 8.08-8.02 (m, 2H), 7.57 (dd, 1H), 4.62 (s, 2H), 4.02 (q, 2H), 3.81 (s, 2H), 3.74(s, 2H), 3.64 (s, 2H), 3.48-3.35 (m, 4H), 2.48 (t, 3H); MS (离子喷雾) 543 (M+H)$^+$。

E: 2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,7-二氢-5H-噻唑并[5,4-c]吡啶-6-酮

将{5-氨基甲基-2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-噻唑-4-基}-乙酸乙酯(12mg, 0.02mmol)于70℃下在乙醇(3mL)中加热3天。将形成的沉淀过滤得到2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-4,7-二氢-5H-噻唑并[5,4-c]吡啶-6-酮。^{1}H NMR (300 MHz, DMSO) δ 8.31 (d, 1H), 8.08-8.02 (m, 2H), 7.55(dd, 1H), 4.67(s, 2H), 4.36(s (broad), 2H), 3.84 (s, 2H), 3.60-3.54 (m, 4H), 3.38(t, 2H); MS (LC/MS-ESI) 496 (M+H)$^+$。

实施例1244

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-哌啶-4-基甲基-哌嗪-2-酮

A: 4-羟基甲基-哌啶-1-甲酸叔丁酯

将六氢异烟酸(19.6g, 76mmol)溶于THF(200mL)并冷却至0℃，然后在10分钟内分批加入氢化锂铝。将反应液于25℃搅拌16小时。然后将反应液冷却至0℃，依次向其中滴加水(6mL)和15%氢氧化钠(6mL)。20分钟后，加入水(18mL)并将此反应液搅拌30分钟。将反应液过滤，将滤液浓缩并用己烷重结晶得到4-羟基甲基-哌啶-1-甲酸叔丁酯。Mp 67-75℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (bd, 2H), 3.50 (d, 2H), 2.70 (dd, 2H), 1.73-1.60 (m, 3H), 1.45 (s, 9H), 1.14 (ddd, 2H);

MS（离子喷雾）216 $(M+H)^+$。

B: 4-溴甲基-哌啶-1-甲酸叔丁酯

将4-羟基甲基-哌啶-1-甲酸叔丁酯(2.30g, 10.7mmol)和四溴化碳(4.43g, 13.4mmol)的CH_2Cl_2 (40mL)溶液冷却至0℃。向其中加入三苯膦(4.21g, 16.0mmol)并将此反应液于25℃搅拌1小时。将反应液浓缩并向残余物中加入乙醚。将混合物过滤并用乙醚洗涤。将滤液浓缩并经柱色谱纯化(硅胶, 20% EtOAc/己烷)得到4-溴甲基-哌啶-1-甲酸叔丁酯，其在放置时形成结晶状固体。Mp 48-50℃; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (bm, 2H), 3.29 (d, 2H), 2.70 (dd, 2H), 1.85-1.73 (m, 3H), 1.46 (s, 9H), 1.28-1.13 (m, 2H); MS (EI) 277 $(M)^+$。

C: 4-(1-叔丁氧羰基-哌啶-4-基甲基)-3-氧代-哌嗪-1-甲酸苄酯

将氢化钠(60%, 0.27g, 6.7mmol)加入到4-苄氧羰基-2-氧代-哌嗪(1.58g, 6.7mmol)的无水DMF(40mL)溶液中。30分钟后加入4-溴甲基-哌啶-1-甲酸叔丁酯(1.87g, 6.7mmol)并将该反应液搅拌16小时。真空除去溶剂，将残余物溶于乙醚并用NH_4Cl洗涤。将水相用乙醚反萃取，将合并的乙醚部分用水和盐水洗涤得到不经进一步的纯化即可使用的4-(1-叔丁氧羰基-哌啶-4-基甲基)-3-氧代-哌嗪-1-甲酸苄酯。^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.16 (d, 2H), 4.16 (s, 2H), 4.13 (br, 2H), 3.73-3.69 (m, 2H), 3.44-3.30 (m, 6H), 2.68 (bt, 2H), 1.85-1.73 (m, 1H), 1.58 (bd, 2H), 1.46 (s, 9H), 1.25-1.10 (m, 2H); MS（离子喷雾）432 $(M+H)^+$。

D: 4-(2-氧代-哌嗪-1-基甲基)-哌啶-1-甲酸叔丁酯

将4-(1-叔丁氧羰基-哌啶-4-基甲基)-3-氧代-哌嗪-1-甲酸苄酯(2.3g, 5.4mmol)的甲醇(75mL)溶液用氮气净化并向其中加入10% Pd/C (0.3g)，然后将反应液再次用氮气净化。将此反应液于氢气氛下置于Parr震动器上摇动16小时。该体系经除去氢气后，滤除催化剂并

用甲醇洗涤。将滤液浓缩得到不经进一步纯化即可使用的4-(2-氧代-哌嗪-1-基甲基)-哌啶-1-甲酸叔丁酯。MS (EI) 298 $(M+H)^+$。

E: 4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-哌啶-1-甲酸叔丁酯

向4-(2-氧代-哌嗪-1-基甲基)-哌啶-1-甲酸叔丁酯(1.44g, 4.8mmol)的CH_2Cl_2 (75mL)和MeCN (10mL)溶液中依次加入二异丙基乙基胺(1.3mL, 4.8mmol)和6-氯-苯并[b]噻吩-2-磺酰氯(1.29g, 4.8mmol), 然后将反应液搅拌16小时。将反应液用CH_2Cl_2稀释、用1N盐酸和碳酸氢钠洗涤、干燥然后浓缩。残余物经柱色谱(硅胶, 40% EtOAc/CH_2Cl_2)纯化得到4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-哌啶-1-甲酸叔丁酯。^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.83 (m, 3H), 7.47 (dd, 1H), 4.1 (br, 2H), 3.86 (s, 2H), 3.46 (bs, 4H), 3.25 (br, 2H), 2.61 (t, 2H), 1.87-1.75 (m, 1H), 1.51 (d, 2H), 1.41 (s, 9H), 1.10 (ddd, 2H); MS (离子喷雾) 528 $(M+H)^+$。

F: 4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-哌啶-4-基甲基-哌嗪-2-酮

将三氟乙酸(4mL)加入到4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-哌嗪-1-基甲基]-哌啶-1-甲酸叔丁酯(1.1g, 2.0mmol)的CH_2Cl_2 (15mL)溶液中。1小时后, 将反应液浓缩, 将残余物溶于CH_2Cl_2并用碳酸钠洗涤, 用硫酸镁干燥然后浓缩得到4-(6-氯苯并[b]噻吩-2-磺酰基)-1-哌啶-4-基甲基-哌嗪-2-酮。^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.83 (m, 3H), 7.46 (dd, 1H), 3.86 (dd, 2H), 3.45 (s, 2H), 3.23 (d, 2H), 3.07 (d, 2H), 2.54 (dt, 2H), 2.39 (s, 1H), 1.83-1.75 (m, 1H), 1.56 (d, 2H), 1.24-1.11 (m, 2H); MS (离子喷雾) 428 $(M+H)^+$。

实施例1245

实施例1277

4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(6'-甲氧基-3,4,5,6-四氢-2H-[1,2']联吡啶-4-基甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.84 (m, 3H), 7.47 (dd, 1H), 7.37 (t, 1H), 6.12 (dd, 1H), 6.03 (dd, 1H), 4.24 (d, 2H), 3.88 (s, 2H), 3.84 (s, 3H), 3.48 (s, 4H), 3.27 (d, 2H), 2.71 (dt, 2H), 1.95-1.84 (m, 1H), 1.61 (d, 2H), 1.32-1.22 (m, 2H); MS (离子喷雾) 535 $(M+H)^+$。

中间体的制备

4-溴甲基-6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶

A: 6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶-4-甲酸乙酯

向圆底烧瓶中加入20ml无水甲苯并通过真空/氮气进行脱气数次。加入2-甲氧基-5-溴吡啶(752mg, 4.0mmol)、六氢异烟酸乙酯(740mg, 4.8mmol)、叔丁醇钠(537mg, 5.6mmol)、$Pd_2(DBA)_3$ (73mg, 2mol%)和BINAP(100mg, 0.16mmol)然后在氮气氛下于70℃加热16小时。将反应液冷却至室温, 加入100ml乙醚中并用盐水(2x50ml)洗涤。将乙醚层用硫酸镁干燥, 过滤然后真空浓缩得到油状物。将该化合物通过快速硅胶色谱纯化, 用20%乙酸乙酯/己烷洗脱得到6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶-4-甲酸乙酯。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H), 7.28 (dd, 1H), 6.66 (d, 1H), 4.15 (q, 2H), 3.87 (s, 3H), 3.42 (dt, 2H), 2.71 (dt, 2H), 2.39 (m, 1H), 2.03 (m, 2H), 1.90 (m, 2H), 1.26 (t, 3H); MS (EI) 264 $(M)^+$。

B: (6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶-4-基)-甲醇

向盛有无水THF(8mL)的圆底烧瓶中加入LAH(122mg, 3.17mmol)。将反应液置于氮气氛下并冷却至0℃。在5分钟内, 向其中加入6'-甲氧

基-3,4,5,6-四氢-2H-[1,3']联吡啶-4-甲酸乙酯(400mg, 1.51mmol)的THF (2ml)溶液。将反应液升温至室温，继续搅拌1小时。加入4滴水，然后加入4滴15%氢氧化钠水溶液并在室温下搅拌20分钟。加入0.5mL水，用硅藻土垫过滤并用THF洗涤。将该溶液真空浓缩成油状物，经快速硅胶色谱纯化，用3%甲醇/二氯甲烷洗脱得到(6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶-4-基)-甲醇。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 1H), 7.29 (dd, 1H), 6.66 (d, 1H), 3.88 (s, 3H), 3.53 (m, 4H), 2.65 (dt, 2H), 1.85 (m, 2H), 1.65 (m, 1H), 1.42 (m, 2H); MS (EI) 222 $(M)^+$。

C: 4-溴甲基-6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶

将(6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶-4-基)-甲醇(300mg, 1.35mmol)溶于二氯甲烷(10mL)，向其中加入四溴化碳(561mg, 1.69mmol)使其溶解。将溶液冷却至0℃并向其中滴加三苯膦(529mg, 2.02mmol)。将反应液升温至室温并搅拌30分钟。真空浓缩至约2ml，经快速硅胶色谱纯化，用2%甲醇/二氯甲烷洗脱得到4-溴甲基-6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶。^{1}H NMR (300 MHz, CD_3OD) δ 7.74 (d, 1H), 7.43 (dd, 1H), 6.72 (d, 1H), 3.83 (s, 3H), 3.54 (m, 2H), 3.38 (d, 2H), 2.65 (dt, 2H), 1.94 (m, 2H), 1.75 (m, 1H), 1.44 (m, 2H); MS (EI) 284 $(M)^+$。

可以用上述烷基化试剂4-溴甲基-6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶制得:

实施例1278

4-(6-氯-苯并[b]噻吩-磺酰基)-1-(6'-甲氧基-3,4,5,6-四氢-2H-[1,3']联吡啶-4-基甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.50-7.43 (m, 2H), 6.88 (dd, 1H), 3.85 (s, 5H), 3.48-3.15 (m, 7H), 3.29-3.17 (m,

2H)，2.89-2.81 (m，1H)，2.25-2.12 (m，1H)，1.65-1.56 (m，4H)；MS (离子喷雾) 535 $(M+H)^+$。

实施例1279

O-苯基-1-氰基-3-{4-[(氯苯并[b]噻吩-2-磺酰基)-2-(酮基)哌嗪-1-基]甲基哌啶基}异脲

向4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-哌啶-4-基甲基-哌嗪-2-酮(0.90g，2.1mmol)的2-丙醇(20ml)悬浮液中加入氰基亚氨基碳酸二苯酯(0.50g，2.1mmol)。搅拌18小时后，TLC (4%甲醇的二氯甲烷溶液)显示原料和主要是一种迁移较快的产物的混合物。补加氰基亚氨基碳酸二苯酯(0.50g)并将反应混合物于80℃加热2小时。冷却至室温后，收集形成的沉淀，用2-丙醇洗涤然后晾干得到黄白色固体状标题化合物；收率0.48g。将样品进一步通过色谱纯化，依次用1%、2%和4%甲醇的二氯甲烷溶液洗脱得到色谱纯的白色固体：MS (ESI)：m/z 572 (M^+H)。

实施例1280

N,N-二甲基-2-{4-[6-(氯苯并[b]噻吩-2-磺酰基)-2-(酮基)哌嗪-1-基]甲基哌啶-1-基}氰基甲脒

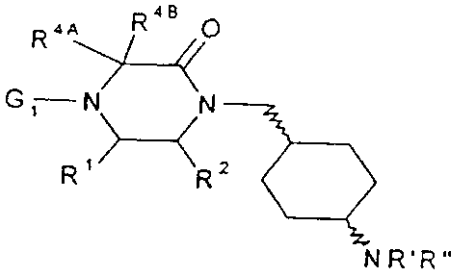
向O-苯基-1-氰基-3-{4-[(氯苯并[b]噻吩-2-磺酰基)-2-(酮基)哌嗪-1-基]甲基哌啶基}异脲(0.10g，0.18mmol)的甲醇(10ml)溶液中加入40%二甲胺水溶液(10ml)并将反应液室温搅拌72小时。蒸除溶剂并将残余物进行色谱分离，依次用1%和2%甲醇的二氯甲烷溶液洗脱。将仅含一种产物的馏份浓缩并将残余物用乙醚研磨得到白色固体状标题化合物；收率17mg：MS (ESI)：m/z 523 (M^+H)。

实施例1281

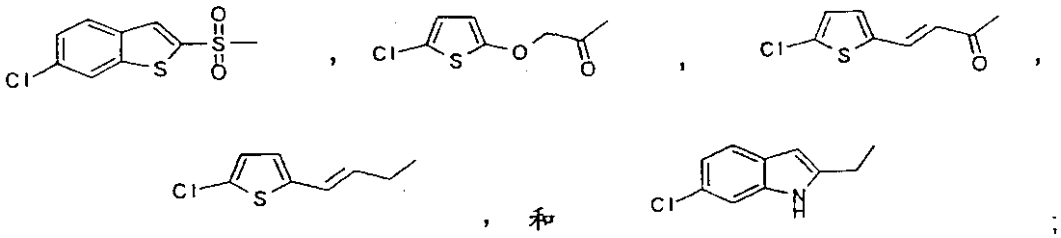
N-甲基-2-{4-[6-(氯苯并[b]噻吩-2-磺酰基)-2-(酮)哌嗪-1-基]甲基哌啶-1-基]}氰基甲脒

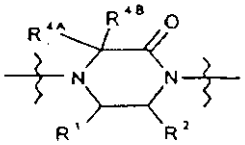
用实施例3的方法制得白色固体状的标题化合物，所不同的是用甲胺代替二甲胺：MS (ESI)：m/z 509 (M^+ + H)。

另外，4-(甲基哌啶-1-基)氰基甲脒化合物可由包括但不限于如下分子式结构的中间体来制备：

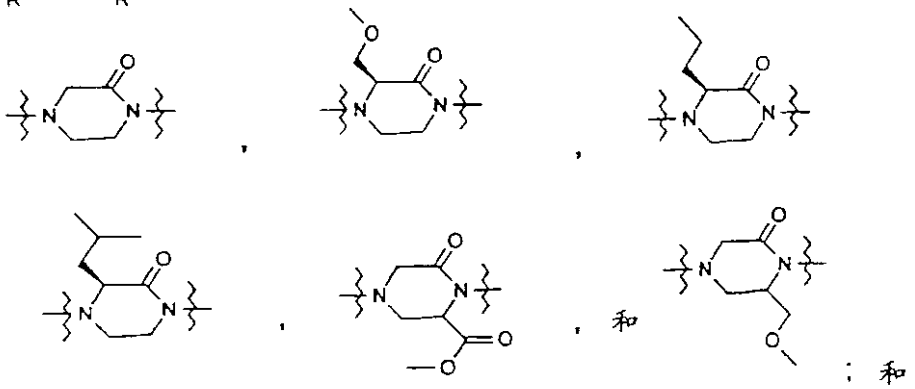


其中G-1包括但不限于

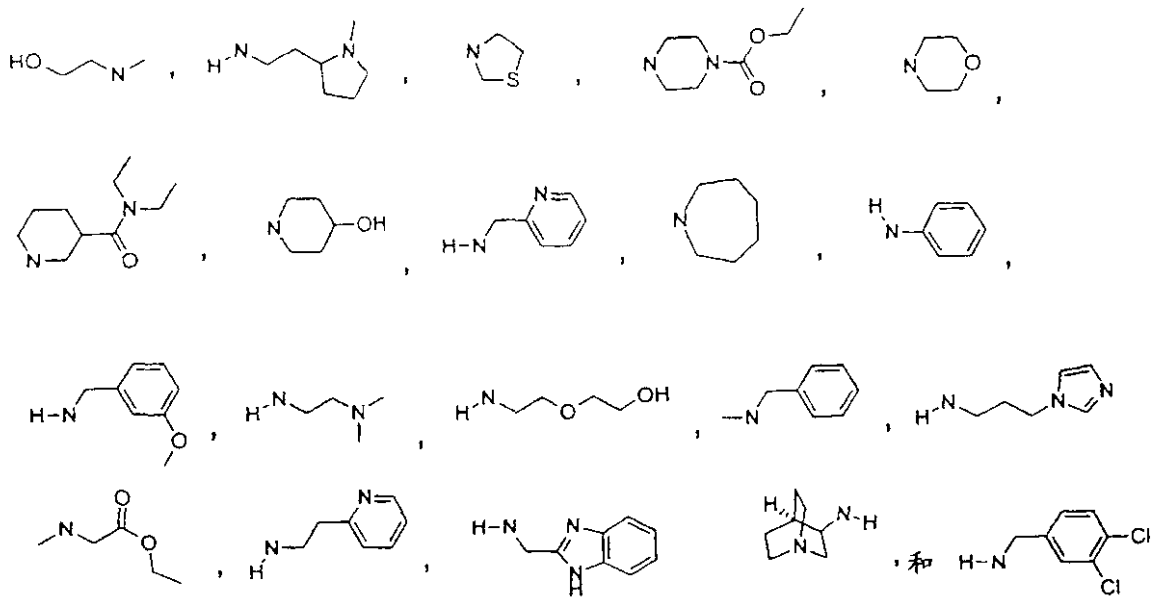




包括但不限于



NRR'包括但不限于



实施例1282

N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-氨基脲的制备

a. 二甲氧基甲基-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-胺

将按照Pearson等人的方法(J. Org. Chem. 62, 1997, 5284)制备的8-甲醛-1,4-二氧杂-螺[4.5]癸烷(4.4g, 26mmol)、氨基乙醛二甲基乙缩醛(3.3g, 0.31mmol)、乙酸(1.6g, 0.26mmol)和氰基硼氢化钠(2.0g, 0.31mmol)在甲醇(140mL)中搅拌6小时。蒸除甲醇，将残余物在乙酸乙酯(200mL)和1N氢氧化钠(100mL)之间进行分配。将有机相用硫酸钠干燥然后蒸发得到黄色油状的中间体标题化合物(7.2g)，其不经纯化直接使用。MS (EI), 259 $[M]^+$。

b. {1-[2,2-二甲氧基-乙基-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-氨基甲酰基]-2-(S)-甲氧基乙基}-氨基甲酸苄基酯

将二甲氧基甲基-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-胺(6.6g, 26mmol)、(S)-(2-苄氧羰基氨基-3-甲氧基)-丙酸(7.2g, 28mmol)、[O-(7-氮杂苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐(12g, 31mmol)和N,N-二异丙基乙胺(7.7g, 60mmol)在DMF(200mL)中搅拌18

小时。蒸除DMF并将残余物用乙酸乙酯(200mL)稀释。将有机相用水(50mL)、2N盐酸(50mL)、1N氢氧化钠(50mL)洗涤并用硫酸镁干燥，蒸除溶剂得到黄色油状中间体标题化合物(13g)，其不经进一步纯化直接使用。MS (ES)，495 $[M+H]^+$。

c. 4-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-3-氧代-3,4-二氢-2H-吡嗪-1-甲酸苄酯

将{1-[2,2-二甲氧基-乙基-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-氨基甲酰基]-2-(S)-甲氧基乙基}-氨基甲酸苄酯(12.8g，26mmol)和对甲苯磺酸一水合物(0.74g，3.9mmol)加入甲苯(150mL)中并于60-70℃搅拌7小时。将混合物蒸发并将残余物通过快速色谱纯化(硅胶，2:1己烷/乙酸乙酯)得到无色透明的油状中间体标题化合物(5.0g，45%)。MS (ES)，431 $[M+H]^+$。

d. 1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-哌嗪-2-酮

4-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-3-氧代-3,4-二氢-2H-吡嗪-1-甲酸苄酯(4.7g，11mmol)、10% Pd/C (1.0g)在氢气氛下在甲醇(150mL)中搅拌18小时。将混合物用硅藻土®过滤然后蒸发得到无色透明的油状中间体标题化合物(3.3g，11mmol)。MS (EI)，298 $[M]^+$。

e. 4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮

将1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-哌嗪-2-酮(3.3g，11mmol)、(5-氯-噻吩-2-基氧基)-乙酸(2.1g，11mmol)、2-(1H-苯并三唑-1-基)-1,1,3,3-四甲基脲四氟硼酸盐(3.9g，12mmol)和三乙胺(3.3g，33mmol)在DMF(100mL)中搅拌8小时。将混合物蒸发并用乙酸乙酯(200mL)稀释。将有机相用水、2N盐酸、

1N氢氧化钠和盐水洗涤，用硫酸镁干燥然后蒸发。将残余物通过快速色谱纯化(硅胶，4:1乙酸乙酯/己烷)得到无色透明的油状中间体标题化合物(2.8g，54%)。MS (ES)，473 $[M+H]^+$。

f. 4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-(4-氧代环己基甲基)-哌嗪-2-酮

将4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮(2.8g，5.9mmol)加入80:20乙酸/水中并于65℃加热0.2小时。将混合物蒸发并用乙酸乙酯(200mL)稀释。将有机相用1N氢氧化钠洗涤，用硫酸镁干燥然后蒸发得到无色透明的油状中间体标题化合物(2.4g，95%)。MS (ES)，429 $[M+H]^+$。

g. 1-顺式-[4-(氨基)-环己基甲基]-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮和1-反式-[4-(氨基)-环己基甲基]-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮

向4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-(4-氧代环己基甲基)-哌嗪-2-酮(0.5g，1.2mmol)和乙酸铵(0.9g，12mmol)的无水甲醇(20mL)混合物中加入氰基硼氢化钠(0.075g，1.2mmol)。将混合物搅拌18小时然后真空浓缩。将残余物用EtOAc(20mL)稀释然后用1N氢氧化钠洗涤。将有机相用硫酸钠干燥然后蒸发，得到顺式和反式异构体混合物形式的中间体标题化合物(0.49g，98%)，其不经纯化直接使用。MS (ES)，430 $[M+H]^+$。

h. N-反式-({[4-(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-环己基)-N'-氰基-O-苯基异脲

将N-(顺式/反式)-({[4-(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-环己基)-N'-氰基-O-苯基异脲

(0.49g, 1.14mmol)和氰基亚氨基碳酸二苯酯(0.28g, 1.17mmol)在异丙基醇(5mL)中搅拌18小时。将混合物真空浓缩并用EtOAc (20mL)稀释。将有机相用2N盐酸、1N氢氧化钠和盐水洗涤，用硫酸镁干燥然后蒸发。将残余物通过快速色谱纯化(硅胶, EtOAc)得到白色固体状中间体标题化合物(0.33g, 50%)。MS (ES), 574 $[M+H]^+$。

还分离出了顺式异构体(0.1g, 15%)。MS (ES), 574 $[M+H]^+$。

i. N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-氰基胍

将N-反式-({[4-(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-环己基)-N'-氰基-O-苯基异脲(0.025g, 0.04mmol)在7N氨的甲醇溶液(2mL)中搅拌18小时。将混合物用EtOAc(20mL)稀释并用1N氢氧化钠和盐水洗涤。将有机相用硫酸镁干燥然后蒸发得到无色树脂状标题化合物(0.014g, 70%)。MS (ES), 497 $[M+H]^+$。

按照实施例1282所描述的方法还可以类似地制得如下化合物:

实施例1283

N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-N',N'-二甲基-氰基胍: MS (ES), 510 $[M+H]^+$。

实施例1284

N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-N'-甲基-氰基胍: MS (ES), 524 $[M+H]^+$。

实施例1285

N-反式-[{4-(5-氯-噻吩-2-基氧基)-乙酰基-2-酮基-3-(S)-甲氧基甲基}-哌嗪-1-基]甲基环己基-N'-(2-羟基乙基)-N'-甲基-氨基脲: MS (ES), 554 [M+H]'。

实施例1286

4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-(4-吗啉-4-基-环己基甲基)-哌嗪-2-酮和4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-(4-吗啉-4-基-环己基甲基)-哌嗪-2-酮的制备

A. 二甲氧基甲基-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-胺

将按照Pearson等人的方法(J. Org. Chem. 62, 1997, 5284)制备的8-甲醛-1,4-二氧杂-螺[4.5]癸烷(4.4g, 26mmol)、氨基乙醛二甲基乙缩醛(3.3g, 0.31mmol)、乙酸(1.6g, 0.26mmol)和氰基硼氢化钠(2.0g, 0.31mmol)在甲醇(140mL)中搅拌6小时。将甲醇蒸发并将残余物在乙酸乙酯(200mL)和1N氢氧化钠(100mL)之间进行分配。将有机相用硫酸钠干燥然后蒸发得到黄色油状中间体标题化合物(7.2g), 其不经纯化直接使用。MS (EI), 259 [M]'。

B. {1-[2,2-二甲氧基-乙基)-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-氨基甲酰基]-2-(S)-甲氧基乙基}-氨基甲酸苄酯

将二甲氧基甲基-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-胺(6.6g, 26mmol)、(S)-(2-苄氧羰基氨基-3-甲氧基)-丙酸(7.2g, 28mmol)、[O-(7-氮杂苯并三唑-1-基)-1,1,3,3-四甲基脲六氟磷酸盐(12g, 31mmol), N,N-二异丙基乙胺(7.7g, 60mmol)在DMF (200mL)中搅拌18小时。蒸除DMF, 将残余物用乙酸乙酯(200mL)稀释。将有机相用水(50mL)、2N盐酸(50mL)和1N氢氧化钠(50mL)洗涤, 用硫酸镁干燥然后蒸发得到黄色油状中间体标题化合物(13g), 其不经纯化直接使用。MS

(ES), 495 $[M+H]^+$。

C. 4-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-3-氧代-3,4-二氢-2H-吡嗪-1-甲酸苄酯

将{1-[2,2-二甲氧基-乙基)-(2,3-二氧杂-螺[4.5]癸-8-基甲基)-氨基甲酰基]-2-(S)-甲氧基乙基}-氨基甲酸苄酯(12.8g, 26mmol)和对甲苯磺酸一水合物(0.74g, 3.9mmol)加入甲苯(150mL)中并于60-70℃搅拌7小时。将混合物蒸发并将残余物通过快速色谱纯化(硅胶, 2:1己烷/乙酸乙酯)得到无色透明的油状中间体标题化合物(5.0g, 45%)。MS (ES), 431 $[M+H]^+$。

D. 1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-哌嗪-2-酮

将4-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-3-氧代-3,4-二氢-2H-吡嗪-1-甲酸苄酯(4.7g, 11mmol)和10% Pd/C (1.0g)在甲醇(150mL)中于氢气压下搅拌18小时。将混合物用硅藻土®过滤然后蒸发得到无色透明的油状中间体标题化合物(3.3g, 11mmol)。MS (EI), 298 $[M]^+$。

E. 4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮

将1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-2-(S)-甲氧基甲基-哌嗪-2-酮(3.3g, 11mmol)、(5-氯-噻吩-2-基氧基)-乙酸(2.1g, 11mmol)、2-(1H-苯并三唑-1-基)-1,1,3,3-四甲基脲四氟硼酸盐(3.9g, 12mmol)和三乙胺(3.3g, 33mmol)在DMF (100mL)中搅拌8小时。将混合物蒸发然后用乙酸乙酯(200mL)稀释。将有机相用水、2N盐酸、1N氢氧化钠和盐水洗涤, 用硫酸镁干燥然后蒸发。将残余物通过快速色谱纯化(硅胶, 4:1乙酸乙酯/己烷)得到无色透明的油状中间体标题化合物(2.8g, 54%)。MS (ES), 473 $[M+H]^+$。

F. 4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-(4-氧代环己基甲基)-哌嗪-2-酮

将4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-(1,4-二氧杂-螺[4.5]癸-8-基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮(2.8g, 5.9mmol)加入80:20乙酸/水中并于65℃加热0.2小时。将混合物蒸发并用乙酸乙酯(200mL)稀释。将有机相用1N氢氧化钠洗涤，用硫酸镁干燥然后蒸发得到无色透明的油状中间体标题化合物(2.4g, 95%)。MS (ES), 429 $[M+H]^+$。

G. 4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-(4-吗啉-4-基-环己基甲基)-哌嗪-2-酮

和

4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-(4-吗啉-4-基-环己基甲基)-哌嗪-2-酮

将4-[(5-氯噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-(4-氧代环己基甲基)-哌嗪-2-酮(0.07g, 0.14mmol)、吗啉(0.025g, 0.28mmol)、乙酸(0.008g, 0.14mmol)和氰基硼氢化钠(0.01g, 0.17mmol)在甲醇(1mL)中搅拌48小时。真空蒸除溶剂，将残余物通过快速柱色谱进行纯化(硅胶, 98:2二氯甲烷/甲醇)得到无色树脂状顺式异构体化合物(0.01g, 15%)。MS (ES), 500 $[M+H]^+$。

也分离出了反式异构体(0.02g, 29%)。MS (ES), 500 $[M+H]^+$。

按照实施例1286描述的方法还可以类似地制得如下化合物。

实施例1287

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-顺式-{4-[(2-羟基-乙基)-甲基-1-氨基]-环己基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES),

488 $[M+H]^+$。

实施例1288

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-{4-[(2-羟基-乙基)-甲基-1-氨基]-环己基甲基)-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 488 $[M+H]^+$。

实施例1289

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-{4-[2-(R,S)-(1-甲基-吡咯烷-2-基)-乙基氨基]-环己基甲基}-哌嗪-2-酮: MS (ES), 541 $[M+H]^+$。

实施例1290

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-{4-[2-(R,S)-(1-甲基-吡咯烷-2-基)-乙基氨基]-环己基甲基}-哌嗪-2-酮: MS (ES), 541 $[M+H]^+$。

实施例1291

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-[4-(2-吡啶-2-基-乙基氨基)-环己基甲基]-哌嗪-2-酮: MS (ES), 535 $[M+H]^+$。

实施例1292

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-[4-(2-吡啶-2-基-乙基氨基)-环己基甲基]-哌嗪-2-酮: MS (ES), 535 $[M+H]^+$。

实施例1293

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-顺式-[4-(2-二甲基氨基-乙

基氨基)-环己基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 501 $[M+H]^+$。

实施例1294

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-[4-(2-二甲基氨基-乙基氨基)-环己基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 501 $[M+H]^+$。

实施例1295

4-(4-顺式-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-哌嗪-1-甲酸乙酯: MS (ES), 571 $[M+H]^+$。

实施例1296

4-(4-反式-{4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-2-氧代-哌嗪-1-基甲基}-哌嗪-1-甲酸乙酯: MS (ES), 571 $[M+H]^+$。

实施例1297

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-顺式-([4-(4-羟基-哌啶-1-基)-环己基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 514 $[M+H]^+$。

实施例1298

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-([4-(4-羟基-哌啶-1-基)-环己基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 514 $[M+H]^+$。

实施例1299

1-顺式-(4-氮杂环庚烷-1-基-环己基甲基)-4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 512 $[M+H]^+$。

实施例1300

1-反式-(4-氮杂环庚烷-1-基-环己基甲基)-4-[(5-氯-嘧吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 512 $[M+H]^+$。

实施例1301

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-{4-[(吡啶-2-基甲基)-氨基]-环己基甲基}-哌嗪-2-酮: MS (ES), 521 $[M+H]^+$。

实施例1302

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-{4-[(吡啶-2-基甲基)-氨基]-环己基甲基}-哌嗪-2-酮: MS (ES), 521 $[M+H]^+$。

实施例1303

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-顺式-(4-苯基氨基-环己基甲基)-哌嗪-2-酮: MS (ES), 506 $[M+H]^+$。

实施例1304

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-3-(S)-甲氧基甲基-1-反式-(4-苯基氨基-环己基甲基)-哌嗪-2-酮: MS (ES), 506 $[M+H]^+$。

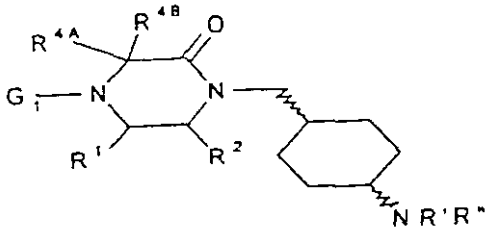
实施例1305

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-顺式-{4-[2-(2-羟基-乙氧基)-乙基氨基]-环己基甲基}-3-(S)-甲氧基甲基-哌嗪-2-酮: MS (ES), 518 $[M+H]^+$。和

实施例1306

4-[(5-氯-噻吩-2-基氧基)-乙酰基]-1-反式-{4-[2-(2-羟基-乙氧基)-乙基氨基]-环己基甲基}-3-(S)-甲氧基甲基-哌嗪-2-酮：MS (ES)，518 [M+H]$^+$。

类似地，可以从具有如下结构的中间体制得其它1-(烷基，芳基)氨基-4-甲基环己基化合物



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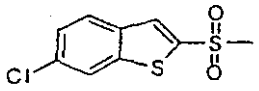
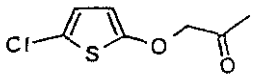
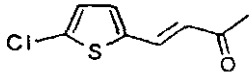
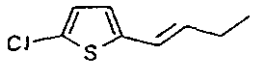
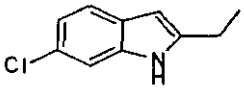
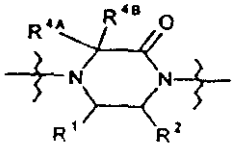
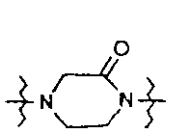
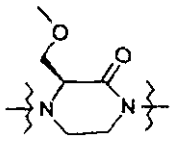
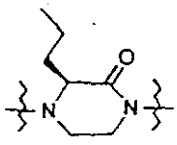
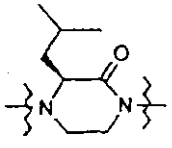
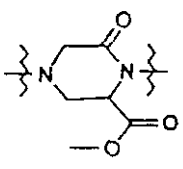
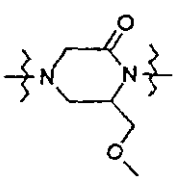
 ，  ，  ，

 ，和  ；

 包括但不限于

 ，  ，  ，

 ，  ，和  ；和

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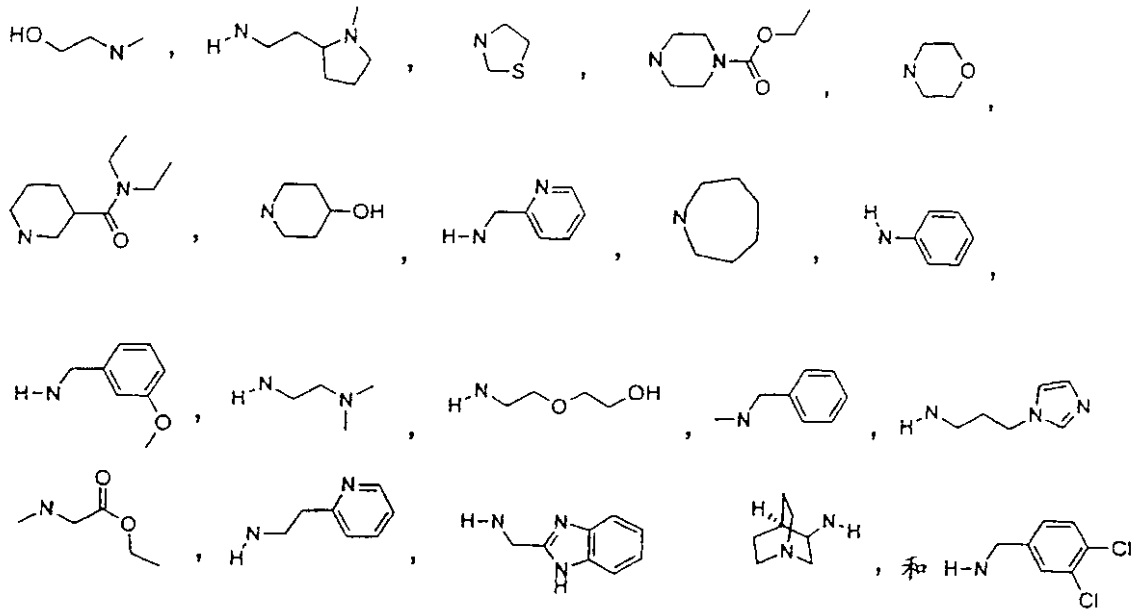


实施例1307

4-[(5-氯噻吩-2-基氧基)-乙酰基]-1-[(2-{[N,N-二甲基氨基乙基]-氨基}-嘧啶-5-基)-甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮

A. 5-羟基甲基-2-甲硫基嘧啶

向按照Gupton等人的方法(J. Het. Chem. 28, 1991, 1281)制备的2-甲硫基嘧啶-5-甲醛(1.35g, 8.7mmol)的甲醇(1mL)溶液中于0℃下加入硼氢化钠(0.3g, 7.9mmol)。将混合物搅拌0.5小时然后真空浓缩。将残余物在乙酸乙酯和1N氢氧化钠之间进行分配。将有机相用硫酸镁干燥然后蒸发得到黄色固体状中间体标题化合物(1.18g, 87%)。MS (ES), 157 $[M+H]^+$。

B. 5-溴甲基-2-甲硫基嘧啶

将5-羟基甲基-2-甲硫基嘧啶(0.1g, 0.61mmol)、三苯膦(0.45g, 1.7mmol)和四溴化碳(0.28g, 0.85mmol)在苯(5mL)中搅拌24小时。将混合物蒸发，将残余物通过快速色谱纯化(硅胶, 4:1己烷/乙酸乙酯)得到白色固体状中间体标题化合物(0.08g, 61%)。MS (ES), 219/221 $[M+H]^+$ (Br)。

C. 4-苄氧羰基-3-(S)-甲氧基甲基-1-[(2-甲硫基嘧啶-5-基)-甲基]-哌嗪-2-酮

将4-苄氧羰基-3-(S)-甲氧基甲基-哌嗪-2-酮(0.1g, 0.37mmol)、5-溴甲基-2-甲硫基嘧啶(0.08g, 0.37mmol)和四正丁基溴化铵(0.06g, 0.19mmol)置于二氯甲烷(1mL)和50%氢氧化钠水溶液(0.03mL)中并搅拌4小时。将混合物用水稀释并用二氯甲烷(2x20mL)萃取。将合并的有机萃取液用硫酸镁干燥然后蒸发。将残余物通过快速色谱纯化(硅胶, 98:2二氯甲烷/甲醇)得到无色油状中间体标题化合物(0.05g, 33%)。MS (ES), 417 $[M+H]^+$。

D. 4-苄氧羰基-1-[(2-{[N,N-二甲基氨基乙基]-氨基}-嘧啶-5-基)-甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮

将4-苄氧羰基-3-(S)-甲氧基甲基-1-[(2-甲硫基嘧啶-5-基)-甲基]-哌嗪-2-酮(0.045g, 0.11mmol)溶于二氯甲烷(3mL)并冷却至-78℃。向其中加入57-86%的3-氯过苯甲酸(0.095g, 0.33mmol)并将混合物升温至室温。将混合物用二氯甲烷(20mL)稀释并用稀碳酸钠水溶液洗涤。将有机相用硫酸钠干燥然后蒸发。粗品残余物不经进一步纯化直接使用。MS (ES), 449 $[M+H]^+$。将残余物加入DMF (1mL)并向其中加入N,N-二甲基乙胺(0.05g, 0.6mmol)。将混合物搅拌4小时然后真空浓缩。经快速色谱纯化(硅胶, 9:1二氯甲烷/甲醇)得到无色树脂状中间体标题化合物(0.01g, 20%)。MS (ES), 457 $[M+H]^+$。

E. 1-[(2-{[N,N-二甲基氨基乙基]-氨基}-嘧啶-5-基)-甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮

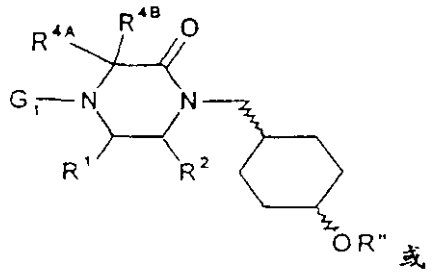
将4-苄氧羰基-1-[(2-{[N,N-二甲基氨基乙基]-氨基}-嘧啶-5-基)-甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮(0.01g, 0.02mmol)和10% Pd/C (0.01g)在乙酸(3mL)中于氢气压下搅拌18小时。将混合物用硅藻土®过滤然后蒸发得到无色透明的油状中间体标题化合物(0.002g)。MS

(ES), 323 $[M+H]^+$。

F. 4-[(5-氯噻吩-2-基氧基)-乙酰基]-1-[(2-{[N,N-二甲基氨基乙基]-氨基}-嘧啶-5-基)-甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮

将1-[(2-{[N,N-二甲基氨基乙基]-氨基}-嘧啶-5-基)-甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮、(5-氯-噻吩-2-基氧基)-乙酸、2-(1H-苯并三唑-1-基)-1,1,3,3-四甲基脲四氟硼酸盐和三乙胺加入DMF中并搅拌8-16小时制得标题化合物。将混合物蒸发并用乙酸乙酯稀释。将有机相用水、2N盐酸、1N氢氧化钠和盐水洗涤，用硫酸镁干燥然后蒸发。将残余物通过快速色谱纯化(硅胶，4:1乙酸乙酯/己烷)得到标题化合物。

类似的，用具有如下结构的中间体可以制得2-氨基&烷氧基-4&5-取代的-甲基嘧啶基化合物



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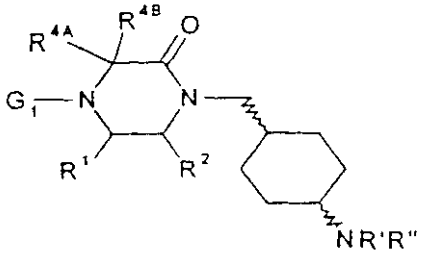

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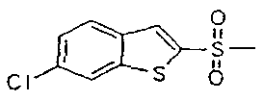

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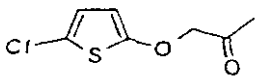

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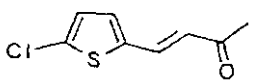

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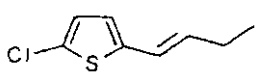

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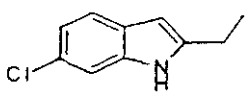

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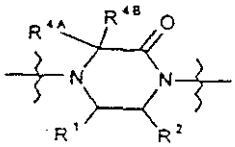

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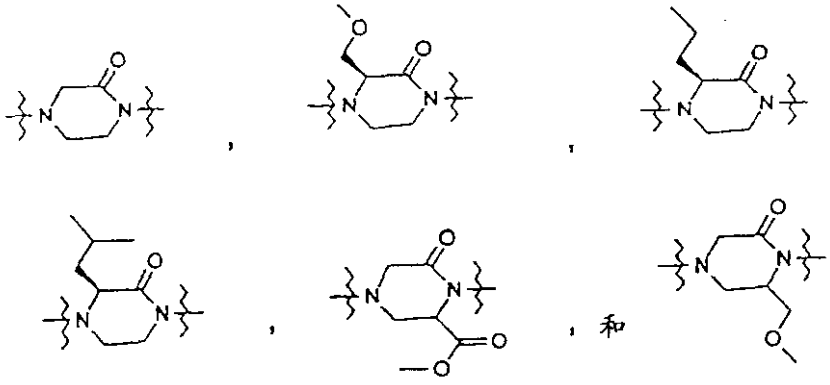

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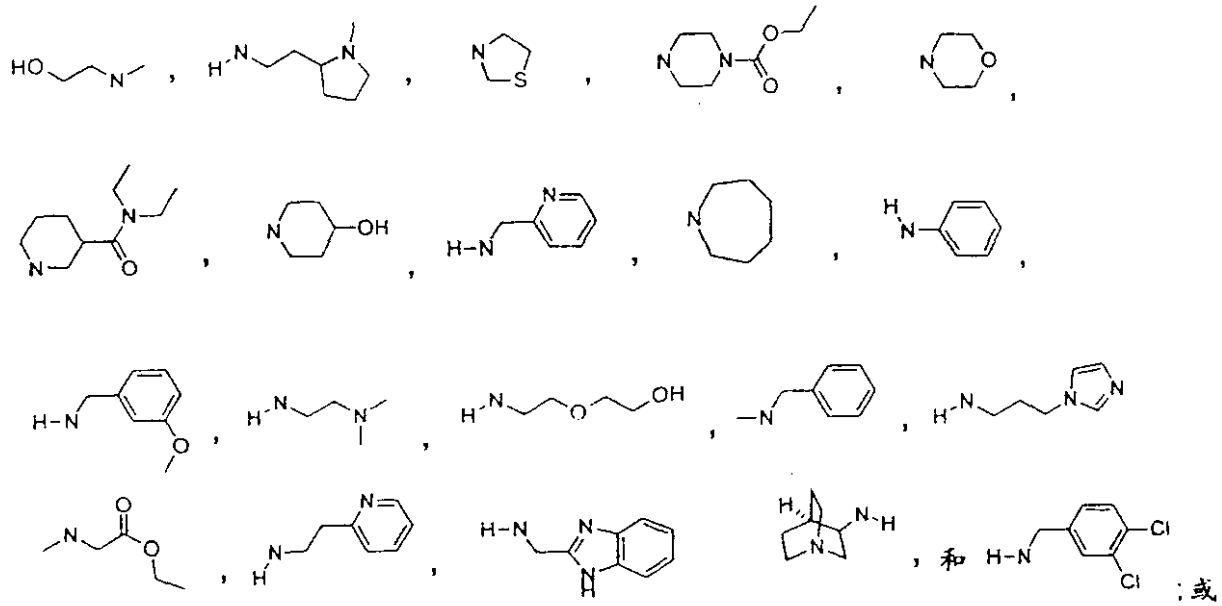

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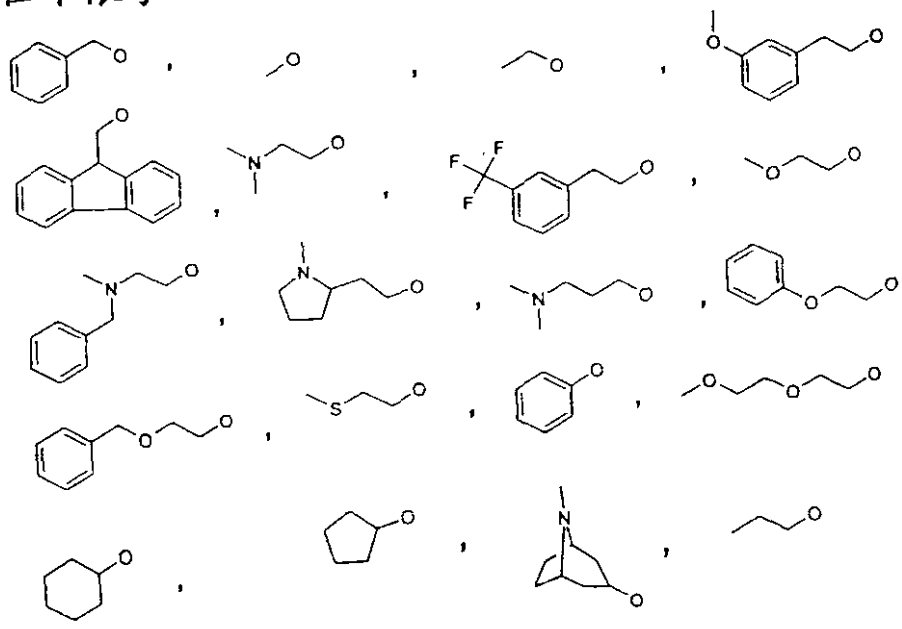


实施例1308

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-烯丙基]-哌嗪基-2,3-二酮

A. 2-氨基-4-羟基甲基苯甲酸甲酯

向冷却至-78℃的16.0g (76.6mmol)氨基对苯二酸二甲酯的200ml无水THF溶液中于1小时内滴加250ml (250mmol) 1M Super Hydride。将混合物继续搅拌1.5小时然后升温至0℃(在TLC上观察到少量原料)。将混合物倒入300ml冷水中并用乙酸乙酯萃取。将有机层用水洗涤并将两层静置30分钟。将有机层用硫酸镁干燥然后过滤。将滤液蒸发。将残余物溶于乙酸乙酯并将该溶液通过含硅胶的布氏漏斗，用150ml乙酸乙酯洗涤漏斗。将滤液蒸发。将残余物溶于最小量的乙酸乙酯中并将该溶液用己烷稀释到浊点。在产物沉淀的过程中补加己烷。总共加入100ml己烷，收集固体并真空干燥得到8.4g标题中间体物质，mp 98-100℃，收率61%。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (d, 1H), 6.67 (s, 1H), 6.60 (d, 1H), 5.75 (bs, 2H), 4.62 (s, 2H), 3.86 (s, 3H), 1.83 (bs, 1H)。EI MS, $[M]^+$=181。

B. 7-羟基甲基喹唑啉-4-酮

将2.0g (19.1mmol) 2-氨基-4-羟基甲基苯甲酸甲酯在4ml甲酰胺中的混合物在180℃的油浴中加热3小时。将混合物冷却并用70ml沸腾的乙酸乙酯研磨。从深色的油中浅析出乙酸乙酯然后在冰箱中冷却过夜得到0.7g沉淀，mp 205-12℃；收率40%。^{1}H NMR (d_6-DMSO, 300MHz) δ 8.08 (s, 1H), 8.06 (d, 1H), 7.60 (s, 1H), 7.45 (d, 1H), 5.48 (bs, 1H), 4.65 (s, 2H), 3.35 (bs, 1H)。EI MS, $[M]^+$=176。

C. 4-氯-7-氯甲基喹唑啉

将2.0g (11.3mmol) 7-羟基甲基喹唑啉-4-酮在25ml三氯氧磷中的

混合物加热回流30分钟。形成很稠的混合物，继续加热1.5小时得到溶液。在旋转蒸发仪中蒸除三氯氧磷并将残余物倒入冰水中。将混合物用乙醚萃取。将乙醚用硫酸镁干燥、过滤然后将滤液蒸发。将残余物用10ml乙醚处理然后过滤。将滤液蒸发得到0.8g中间体产物，其不经进一步纯化直接用于随后的步骤；收率33%。^{1}H NMR ($CDCl_3$, 300MHz) δ 9.07 (s, 1H), 8.30 (d, 1H), 8.06 (s, 1H), 7.78 (d, 1H), 4.78 (s, 2H)。EI MS, $[M]^+$=212, 214, 216 (Cl_2花样)。

D. 4-氨基-7-氯甲基喹唑啉

向15ml饱和乙醇氨溶液中加入1.0g (4.7mmol) 4-氯-7-氯甲基喹唑啉。将混合物于室温搅拌过夜。收集形成的沉淀物得到0.7g标题中间体产物。mp>300℃；收率77%。^{1}H NMR (d_6-DMSO, 300MHz) δ 8.38 (s, 1H), 8.20 (d, 1H), 7.78 (bs, 2H), 7.70 (s, 1H), 7.51 (d, 1H), 4.92 (s, 2H)。EI MS, $[M]^+$=193, 195 (Cl花样)。

E. 3-(4-氯-苯基)-(E)-丙烯醛

在 3 小时内，向 3-(4-氯-苯基)-丙-2-(E)-烯-1-醇 (2.33g, 13.8mmol, 按照 J. Med. Chem. 1997, 1827 中描述的方法制备)的 50ml CH_2Cl_2 溶液中分 3 次加入活性氧化锰(IV) (4.80g, 55.3mmol)并将形成的悬浮液在室温下搅拌过夜。用硅藻土垫过滤后，真空浓缩，将粗品残余物用柱色谱纯化，用 10% EtOAc/己烷洗脱得到浅黄色油状标题中间体化合物(0.80g, 4.80mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 9.71 (d, 1H), 7.48 (m, 3H), 7.41 (dd, 2H), 6.68 (dd, 1H)。

F. {2-[3-(4-氯-苯基)-烯丙基氨基]-乙基}-氨基甲酸叔丁酯

向 N-Boc-乙二胺(0.63g, 4.80mmol)的 20mL 甲醇溶液中加入 3-(4-氯-苯基)-(E)-丙烯醛(0.80g, 4.80mmol)。和 4Å 分子筛一起室温搅拌 3 小时后，加入 $NaBH_4$ (0.19g, 5.00mmol)。将反应混合物搅拌 16 小时，用 EtOAc 稀释并通过硅藻土垫过滤。将溶液减压浓缩。将残余物在 EtOAc 和 H_2O 之间进行分配然后分液。水层用 EtOAc 萃取。合并

的有机层用水和盐水洗涤然后用硫酸镁干燥，过滤然后浓缩。将粗品标题产物用柱色谱纯化，用 25% EtOAc/CH_2Cl_2 至 50% EtOAc/ CH_2Cl_2 梯度洗脱得到标题中间体化合物(0.80g, 2.57mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.26 (s, 4H), 6.49 (d, 1H), 6.23 (dt, 1H), 4.96 (bs, 1H), 3.40 (m, 2H), 3.25 (m, 2H), 2.76 (m, 2H), 1.60 (bs, 1H), 1.45 (s, 9H)。

G. N-(2-叔丁氧羰基氨基-乙基)-N-[3-(4-氯-苯基)-烯丙基]-oxalamic acid 甲酯

向{2-[3-(4-氯-苯基)-烯丙基氨基]-乙基}-氨基甲酸叔丁酯(0.80g, 2.57mmol)的 15ml CH_2Cl_2 溶液中于 0℃加入三乙胺(0.54mL, 3.85mmol)和氯代乙醛酸甲酯(methyl chlorooxoacatate) (0.25mL, 2.70mmol)。将所得混合物于 0℃搅拌 1 小时，然后室温搅拌 1 小时。将该溶液在 EtOAc 和水之间进行分配然后分层。将有机层用 1N 盐酸溶液、水、饱和碳酸氢钠溶液和盐水洗涤，然后用硫酸镁干燥，过滤然后浓缩。将粗产物用柱色谱纯化，用 25% EtOAc/CH_2Cl_2 洗脱得到标题中间体化合物(0.98g, 2.47mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.31 (m, 4H), 6.55 (dd, 1H), 6.14 (m, 1H), 4.88 (bs, 1H), 4.21, 4.10 (d, 2H, 旋转异构体), 3.91, 3.86 (s, 3H, 旋转异构体), 3.55, 3.44 (m, 2H, 旋转异构体), 3.36 (m, 2H), 1.43 (s, 9H)。

H. 1-[3-(4-氯-苯基)-烯丙基]-哌嗪-2,3-二酮

将 N-(2-叔丁氧羰基氨基-乙基)-N-[3-(4-氯-苯基)-烯丙基]-oxalamic acid 甲酯(0.49g, 1.23mmol)的 6mL EtOAc 溶液于 0℃下用 HCl 气体饱和。移走冰浴，将该溶液在室温下搅拌 30 分钟，约 5-10 分钟后形成白色沉淀。此后，将溶液浓缩成白色固体(0.41g)。将粗品胺盐悬浮于 6mL 二氯甲烷和 1.5mL 甲醇中。向该溶液中加入三乙胺(0.5mL, 3.53mmol)，将所得溶液在室温下搅拌过夜。将溶液减压浓缩并在二氯甲烷和水之间进行分配。水层用 0.5N 氢氧化钠碱化。有机层

用水和盐水洗涤，然后用硫酸镁干燥，过滤然后浓缩。得到白色固体状标题中间体化合物(0.32g, 1.21mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (bs, 1H), 7.30 (s, 4H), 6.56 (d, 1H), 6.14 (dt, 1H), 4.27 (d, 2H), 3.58 (m, 4H)。

I. 1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(4-氯-苯基)-烯丙基]-哌嗪-2,3-二酮

向1-[3-(4-氯-苯基)-烯丙基]-哌嗪-2,3-二酮(60mg, 0.23mmol)的1.5mL DMF溶液中加入氢化钠(10mg 60%的矿物油分散液, 0.24mmol)。将混合物于55℃加热20分钟。向该溶液中加入4-氨基-7-氯甲基-喹唑啉(49mg, 0.25mmol)，并将所得混合物于55℃加热20分钟形成白色沉淀。此后，将反应混合物用几滴水和甲醇处理然后浓缩。将粗产物用RP-HPLC纯化，在30分钟内，用10%乙腈/水(0.1%TFA)至70%乙腈/水(0.1%TFA)进行梯度洗脱，合并适当的产物馏分并冷冻干燥得到白色固体状标题化合物(56mg, 0.10mmol)。^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.78 (bs, 2H), 8.83 (s, 1H), 8.40 (s, 1H), 7.72 (d, 1H), 7.65 (s, 1H), 7.49 (d, 2H), 7.38 (d, 2H), 6.61 (d, 1H), 6.30 (dt, 1H), 4.80 (s, 2H), 4.18 (d, 2H), 3.59 (m, 4H)。ISP MS, $[M+H]^+$=422。

实施例1328

1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-4-基-苄基)-哌嗪-2,3-二酮

A. {2-[3-(5-氯-噻吩-2-基)-烯丙基氨基]-乙基}-氨基甲酸叔丁酯

标题化合物按照实施例1306, F部分的描述从3-(5-氯-噻吩-2-基)-(E)-丙烯醛制备。^{1}H NMR ($CDCl_3$, 300MHz) δ 6.77 (d, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 5.99 (dt, 1H), 4.95 (bs, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 2.76 (m, 2H), 1.48 (bs, 1H), 1.45 (s, 9H)。

B. N-1-[3-(5-氯-噻吩-2-基)-烯丙基氨基]-乙烷-1,2-二胺盐酸盐

将{2-[3-(5-氯-噻吩-2-基)-烯丙基氨基]-乙基}-氨基甲酸叔丁酯(0.11g, 0.35mmol)的 20mL EtOAc 溶液在 0℃下用 HCl 气体饱和。移走冰浴并将该溶液在室温下搅拌 1 小时。然后，将溶液浓缩成白色固体(0.41 g)。得到白色固体状的标题化合物(0.07g, 0.27mmol)并将其直接用于随后的步骤。^{1}H NMR ($CDCl_3$, 300MHz) δ 6.76 (d, 1H), 6.68 (d, 1H), 6.54 (d, 1H), 6.01 (dt, 1H), 3.38 (m, 2H), 2.82 (m, 2H), 2.71 (m, 2H), 1.40 (bs, 3H)。

C. N-[3-(5-氯-噻吩-2-基)-烯丙基]-N'-(4-吡啶-4-基-苄基)-乙烷-1,2-二胺

向 N-1-[3-(5-氯-噻吩-2-基)-烯丙基氨基]-乙烷-1,2-二胺盐酸盐(0.07g, 0.27mmol)的 10mL 甲醇溶液中加入 4-吡啶-4-基-苯甲醛(0.05g, 0.27mmol)。与 4Å 分子筛一起在室温下搅拌 16 小时后，加入 $NaBH_4$ (0.01g, 0.27mmol)。将反应混合物搅拌 5 小时，用硅藻土垫过滤然后浓缩。将残余物在乙酸乙酯和水之间进行分配然后分层。水层用 EtOAc 萃取。合并的有机层用水(3 次)和盐水洗涤，然后用硫酸镁干燥，过滤然后浓缩。将粗产物用柱色谱纯化，用 5%甲醇/二氯甲烷至含有 2%氢氧化铵的 10%甲醇/二氯甲烷进行梯度洗脱得到标题化合物(0.042g, 0.11mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 8.65 (d, 2H), 7.61, (d, 2H), 7.50 (d, 2H), 7.45 (d, 2H), 6.76 (d, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 6.00 (dt, 1H), 3.38 (s, 2H), 3.35 (d, 2H), 2.78 (s, 4H), 1.78 (bs, 2H)。

D. 1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-4-基-苄基)-哌嗪-2,3-二酮

向 N-[3-(5-氯-噻吩-2-基)-烯丙基]-N'-(4-吡啶-4-基-苄基)-乙烷-1,2-二胺(0.037g, 0.10mmol)的 1.5ml 乙醇溶液中加入草酸二甲酯(0.012g, 0.10mmol)。将所得混合物室温搅拌 16 小时，然后于

50℃加热16小时。将溶液浓缩。将粗产物用柱色谱纯化，用5%甲醇/二氯甲烷至10%甲醇/二氯甲烷进行梯度洗脱，得到白色固体状标题化合物(0.024g, 0.04mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 8.68 (d, 2H), 7.63, (d, 2H), 7.50 (m, 2H), 7.43 (d, 2H), 6.79 (d, 1H), 6.672 (d, 1H), 6.59 (d, 1H), 5.87 (dt, 1H), 4.76 (s, 2H), 4.20 (d, 2H), 3.48 (s, 4H)。ISP MS, $[M+H]^+$=438, 440, Cl花样。

如下2,3-二酮哌嗪化合物用上述方法以类似的方式制备。

实施例	名称	m/z[M+H]
1309	1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基-甲基)-哌嗪-2,3-二酮	ISP-452, Cl
1310	1-(4-氨基-喹啉-7-基甲基)-4-[3-(4-氯-苯基)-烯丙基]-哌嗪-2,3-二酮	ISP-421, Cl
1311	1-(4-氨基-喹唑啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩-5-基甲基)-哌嗪-2,3-二酮	ISP-484
1312	1-(3-亚氨基甲酰基-苄基)-4-(4-亚氨基甲酰基-苄基)-2,3-二氧代哌嗪	ISP-379
1313	双-1,4-(3-亚氨基甲酰基-苄基)-2,3-二氧代哌嗪	ISP-379
1314	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(3-氯-苯基)-烯丙基]-哌嗪-2,3-二酮	
1315	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮	ISP-428, Cl
1316	1-(4-氨基-喹啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基-甲基)-哌嗪-2,3-二酮	
1317	1-(4-氨基-喹啉-7-基甲基)-4-(5'-氯-[2,2']联噻吩-5-基甲基)-哌嗪-2,3-二酮	

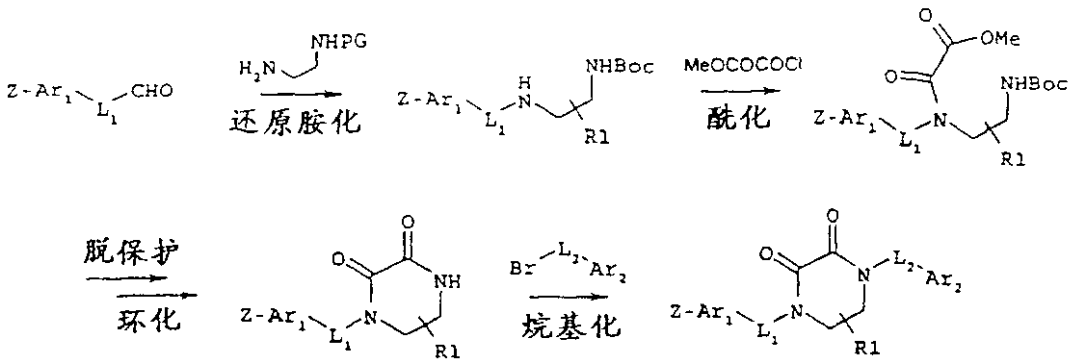
1318	1-(4-氨基-喹啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮	ISP-427, Cl
1319	1-[3-(3-氯-苯基)-烯丙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮	
1320	1-[3-(4-氯-苯基)-烯丙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮	ISP-395, Cl
1321	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮	ISP-401, Cl
1322	1-(6-氯-苯并[b]噻吩-2-基-甲基)-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮	
1323	1-(5'-氯-[2,2']联噻吩-5-基甲基)-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮	
1324	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(1H-吡咯并[2,3-c]吡啶-2-基甲基)-哌嗪-2,3-二酮	
1325	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(噻吩并[3,2-b]吡啶-2-基甲基)哌嗪-2,3-二酮	
1326	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-2-基-苄基)-哌嗪-2,3-二酮	ISP-438, Cl
1327	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(1-羟基-吡啶-2-基)-苄基]-哌嗪-2,3-二酮	ISP-454, Cl
1328	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-4-基-苄基)-哌嗪-2,3-二酮	ISP-438, Cl
1329	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(1-羟基-吡啶-4-基)-苄基]-哌嗪-2,3-二酮	
1330	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(6-甲氧基-吡啶-3-基)-苄基]-哌嗪-2,3-二酮	ISP-468
1331	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(6-氧代-1,6-二氢-吡啶-3-基)-苄基]-哌嗪-2,3-二酮	ISP-454

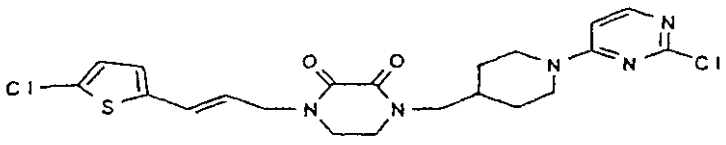
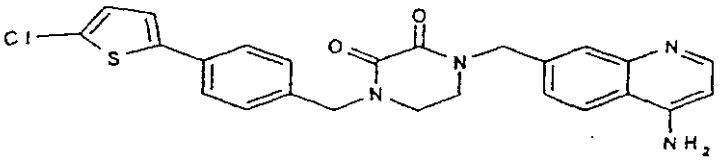
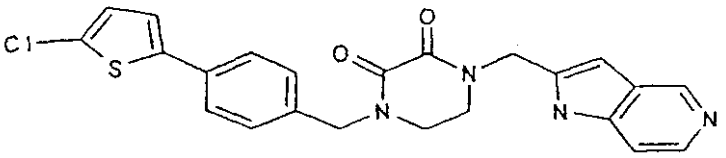
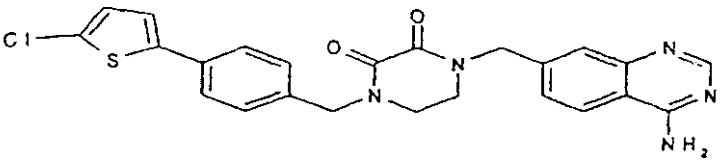
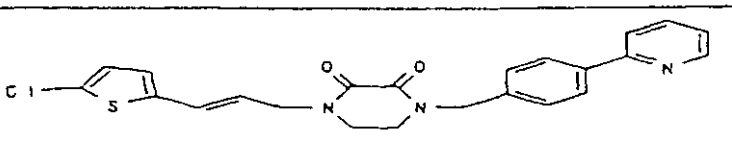
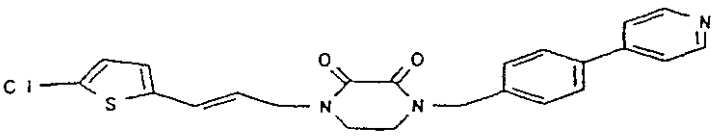
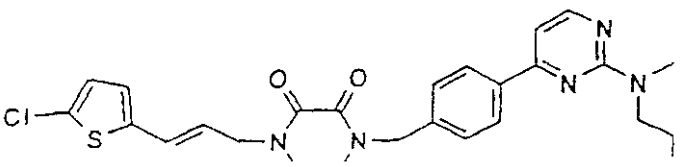
1332	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(2-二甲基氨基-嘧啶-4-基)-苄基]-哌嗪-2,3-二酮	ISP-482, Cl
1333	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-{2-[(2-二甲基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-苄基)-哌嗪-2,3-二酮	ISP-539, Cl
1334	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(2-二甲基氨基-嘧啶-4-基)-环己基甲基]-哌嗪-2,3-二酮	
1335	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-{2-[(2-二甲基氨基-乙基)-甲基-氨基]-嘧啶-4-基}-环己基甲基)-哌嗪-2,3-二酮	
1336	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-甲基-哌嗪-2,3-二酮	
1337	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-乙基-哌嗪-2,3-二酮	
1338	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-丙基-哌嗪-2,3-二酮	
1339	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基) -烯丙基]-5-丁基-哌嗪-2,3-二酮	
1340	4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5-(S)-异丙基-哌嗪-2,3-二酮	ISP-470, Cl
1341	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-异丁基-哌嗪-2,3-二酮	
1342	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-烯丙基]-5-甲氧基甲基-哌嗪-2,3-二酮	
1343	4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2-甲酸	

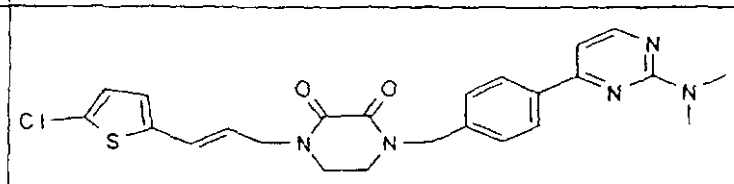
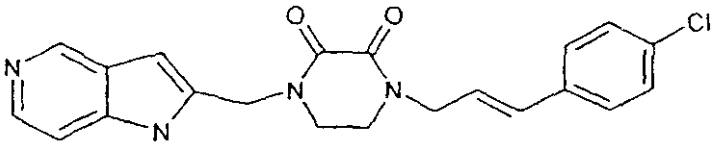
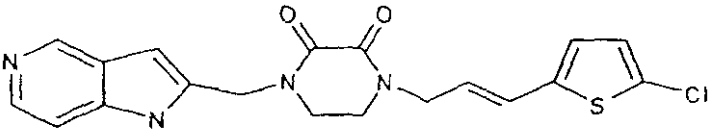
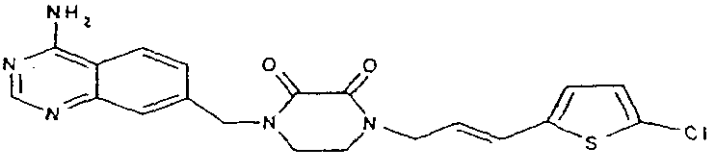
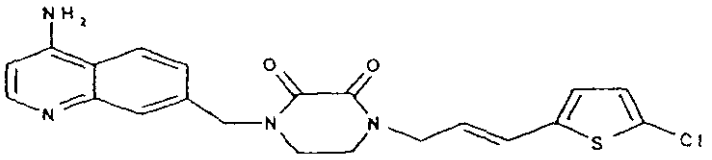
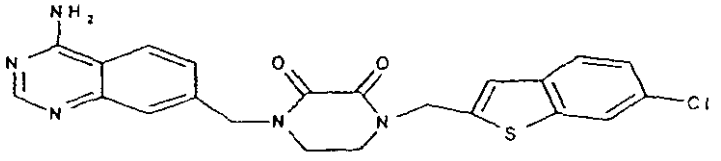
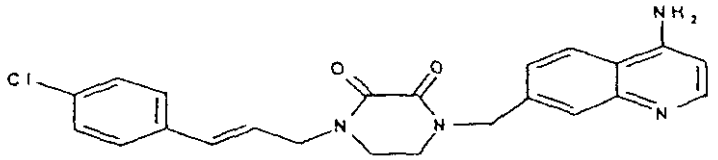
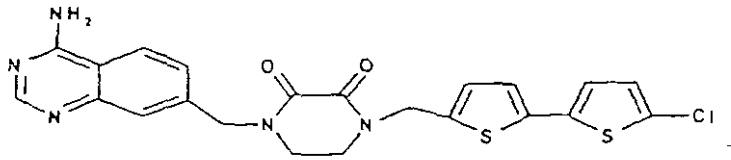
1344	4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2-甲酸甲酯	
1345	4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2-甲酸酰胺	
1346	4-(4-氨基-喹唑啉-7-基甲基)-1-[3-(5-氯-噻吩-2-基)-烯丙基]-5,6-二氧代哌嗪-2-甲酸甲基酰胺	
1347	1-[4-(2-氯-嘧啶-4-基)-苄基]-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮	ISP-473, Cl
1348	1-(4-氨基-喹唑啉-7-基甲基)-4-[4-(5-氯-噻吩-2-基)-苄基]-哌嗪-2,3-二酮	ISP-478, Cl
1349	1-[4-(5-氯-噻吩-2-基)-苄基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2,3-二酮	ISP-451, Cl
1350	1-(4-氨基-喹啉-7-基甲基)-4-[4-(5-氯-噻吩-2-基)-苄基]-哌嗪-2,3-二酮	ISP-477, Cl
1351	1-[1-(2-氯-嘧啶-4-基)-哌啶-4-基甲基]-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮	ISP-480, Cl
1352	1-[3-(5-氯-噻吩-2-基)-烯丙基]-5-(S)-异丙基-4-(3,4,5,6-四氢-2H-[1,4']联吡啶-4-基甲基)-哌嗪-2,3-二酮	ISP-487, Cl
1353	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(3,4,5,6-四氢-2H-[1,4']联吡啶-4-基甲基)-哌嗪-2,3-二酮	ISP-445, Cl
1354	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-吡啶-3-基-苄基)-哌嗪-2,3-二酮	ISP-438, Cl
1355	1-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-4-(4-吡啶-4-基-苄基)-哌嗪-2,3-二酮	ISP-479, Cl

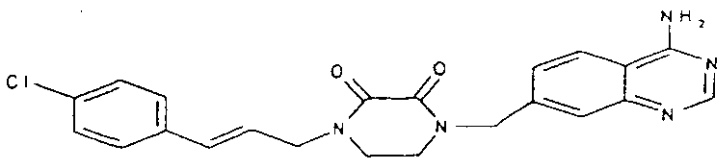
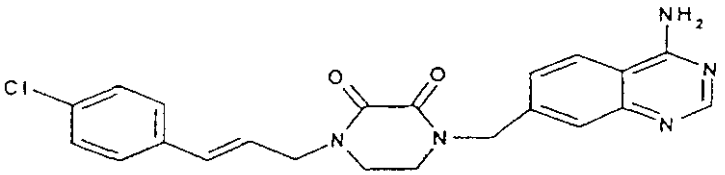
1356	1-[4-(6-氨基-吡啶-3-基)-苄基]-4-[3-(5-氯-噻吩-2-基)-烯丙基]-哌嗪-2,3-二酮	ISP-453, Cl
1357	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-[4-(1-氧基-吡啶-3-基)-苄基]-哌嗪-2,3-二酮	ISP-454, Cl
1358	1-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-5-(S)-异丙基-4-(3,4,5,6-四氢-2H-[1,4']联吡啶-4-基甲基)-哌嗪-2,3-二酮	ISP-528, Cl
1359	1-[3-(5-氯-噻吩-2-基)-烯丙基]-5-(S)-异丙基-4-(4-嘧啶-4-基-苄基)-哌嗪-2,3-二酮	ISP-481, Cl
1360	1-[3-(5-氯-噻吩-2-基)-烯丙基]-4-(4-嘧啶-4-基-苄基)-哌嗪-2,3-二酮	ISP-439, Cl
1361	1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-哌嗪-2,3-二酮	ISP-469, Cl

如下 2,3-二酮基哌嗪化合物按照实施例 1308 中描述的方法以类似的方式制备，在下面的反应方案中进行了简要描述。

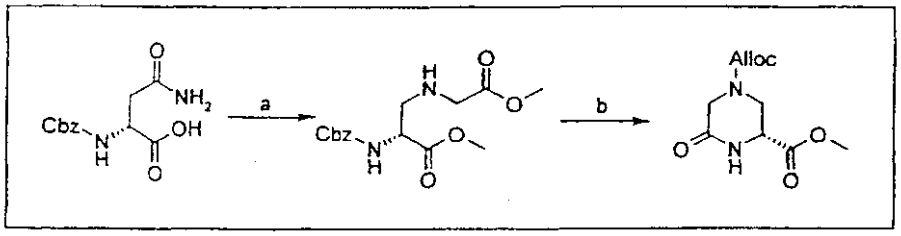


实施例	结构式	分子式	分子量
1362		$C_{21}H_{23}Cl_2N_5O_2S$	480.42
1363		$C_{25}H_{21}ClN_4O_2S$	476.99
1364		$C_{23}H_{19}ClN_4O_2S$	450.95
1365		$C_{24}H_{20}ClN_5O_2S$	477.98
1366		$C_{23}H_{20}ClN_3O_2S$	437.95
1367		$C_{23}H_{20}ClN_3O_2S$	437.95
1368		$C_{27}H_{31}ClN_6O_2S$	539.1

1369		$C_{24}H_{24}ClN_5O_2S$	482,01
1370		$C_{21}H_{19}ClN_4O_2$	394,86
1371		$C_{19}H_{17}ClN_4O_2S$	400,88
1372		$C_{20}H_{18}ClN_5O_2S$	427,91
1373		$C_{21}H_{19}ClN_4O_2S$	426,92
1374		$C_{22}H_{18}ClN_5O_2S$	451,93
1375		$C_{23}H_{21}ClN_4O_2$	420,89
1376		$C_{22}H_{18}ClN_5O_2S_2$	484,00

1377		$C_{22}H_{20}ClN_5O2$	421.88
1378		$C_{22}H_{20}ClN_5O_2$	421.88

方案 1 C(6)-酯模板的合成方案



试剂：(a) 1. PIFA, Py; 2. $SOCl_2$, 甲醇; 3. $BrCH_2CO_2Me$。(b) 1. Pd/C, H_2; 2. Alloc-Cl, Et_3N。

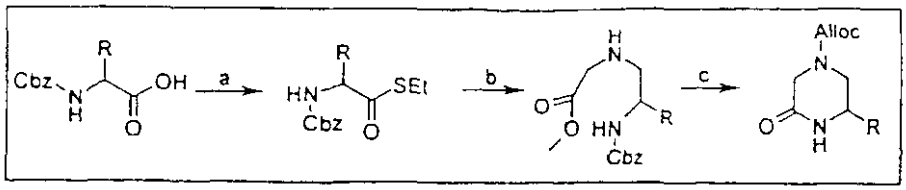
实施例 1379

(R)-5-氧代-哌嗪-1,3-二甲酸 1-烯丙酯 3-甲酯

向含有(R)-6-氧代哌嗪-2-甲酸甲酯(1.32g, 8.35mmol)(按照 Aebischer 的方法制备)的无水二氯甲烷(30mL)溶液中于 0℃下加入三乙胺 (1.26g, 12.5mmol), 随后加入氯甲酸烯丙酯 (1.20g, 10.0mmol)。1 小时后, 将此反应混合物倒入二氯甲烷/水(1:1, 200mL)的混合物中, 用 1N 盐酸酸化然后分层。有机相用盐水洗涤, 用无水硫酸钠干燥, 过滤然后浓缩。将粗品残余物进行硅胶色谱(二氯甲烷至 1%甲醇/二氯甲烷)得到 1.22g (60%)粘稠油状(R)-5-氧代-哌嗪-1,3-二甲酸 1-烯丙酯 3-甲酯。^{1}H NMR (300MHz, $CDCl_3$) δ 6.43 (bs, 1H), 5.90

(m, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 4.05-4.26 (m, 3H), 3.80 (s, 3H), 3.72 (m, 2H) ppm。质谱: (ISP 周线) m/z 243(M+H)。

反应方案 2 C(6)-烷基模板的合成方案



试剂: (a) DCC, EtSH, CH_2Cl_2。(b) 1. TES, Pd/C, 丙酮。2. H_2N-Gly-OMe*HCl, $NaBH_3(CN)$, 甲醇。(c) 1. Pd/C, 甲醇, H_2。2. Alloc-Cl, Et_3N, CH_2Cl_2。

实施例 890:

(R)-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯

A. (R)-2-苄氧羰基氨基-3-甲基-硫代丁酸 S-乙酯。

向含有(R)-2-苄氧羰基氨基-3-甲基-丁酸(5.0g, 20.0mmol)的无水 CH_2Cl_2 (20mL)溶液中加入 DMAP (258mg, 2.0mmol), 随后加入冷的 EtSH (1.6mL, 22.0mmol)。一次性加入二环己基碳二亚胺(4.5g, 22.0mmol), 30 分钟后反应完成。真空过滤除去固体物质并将滤液浓缩。将粗产物用快速硅胶色谱纯化(己烷至 8:1 己烷/EtOAc)得到无色油状的(R)-2-苄氧羰基氨基-3-甲基-硫代丁酸 S-乙酯(5.21g, 88%)。^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.8Hz, 3H), 0.98 (d, J=6.8Hz, 3H), 1.23 (t, J=7.5Hz, 3H), 2.27 (m, 1H), 2.88 (q, J=7.5Hz, 2H), 4.35 (dd, J=9.5, 4.6Hz, 1 H), 5.13 (s, 2H), 5.25 (br d, J=9.5Hz, 1H), 7.30-7.36 (m, 5H) ppm。

用适当的氨基酸制备如下化合物:

实施例	名称	m/z(M+H)+
1380	(S)-2-苄氧羰基氨基-3-甲基-硫代丁酸 S-乙酯	296

1381	(R)-2-苄氧羰基氨基-4-甲基-硫代戊酸 S-乙酯	310
1382	(S)-2-苄氧羰基氨基-4-甲基-硫代戊酸 S-乙酯	310
1383	(S)-2-苄氧羰基氨基-硫代丙酸 S-乙酯	268
1384	(R)-2-苄氧羰基氨基-3-甲氧基-硫代丙酸 S-乙酯	298
1385	(S)-2-苄氧羰基氨基-3-甲氧基-硫代丙酸 S-乙酯	298
1386	(S)-3-苄氧羰基氨基-3-乙硫基羰基-丙酸叔丁酯	368

B. (R)-(1-甲酰基-2-甲基-丙基)-氨基甲酸苄酯。

向含有(R)-2-苄氧羰基氨基-3-甲基-硫代丁酸 S-乙酯(5.2g, 17.6mmol)的丙酮(100mL)溶液中加入 Pd/C (10%, 233mg)。将该多相混合物冷却至0℃并向其中快速加入 Et_3SiH (8.4mL, 53mmol)。30分钟后，将反应混合物用硅藻土垫过滤，将滤液浓缩并在己烷(200mL)和乙腈(300mL)之间进行分配。分液，将 ACN 相用己烷(100mL)洗涤一次，然后浓缩得到粗品(R)-(1-甲酰基-2-甲基-丙基)-氨基甲酸苄酯(4.13g)，其不经进一步纯化直接使用。^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (m, 1H), 4.31 (m, 1H), 5.09 (s, 2H), 5.45 (br, 1H), 7.30-7.45 (m, 5H), 9.65 (s, 1H) ppm。

C. (R)-(2-苄氧羰基氨基-3-甲基-丁基氨基)-乙酸乙酯。

向含有粗品(R)-(1-甲酰基-2-甲基-丙基)-氨基甲酸苄酯(4.13g, 17.6mmol)的无水甲醇(100mL)溶液中于 0℃下加入甘氨酸乙酯盐酸盐(9.5g, 70.4mmol)。10分钟，向其中加入 1.0M $NaCNBH_3$ 的 THF 溶液(27mL, 27mmol)并将该多相反应混合物升温至室温过夜。将反应混合物浓缩，将残余物在乙醚和(200mL)和饱和碳酸氢钠水溶液(200mL)之间进行分配。分层，将水层用乙醚(2x200mL)萃取两次。将合并的有机萃取液用盐水洗涤，用无水硫酸钠干燥，过滤然后浓缩得到粗产物，将粗产物

通过快速硅胶色谱纯化(己烷/EtOAc, 2:1 至 1:1)得到无色油状的(R)-(2-苄氧羰基氨基-3-甲基-丁基氨基)-乙酸乙酯(4.2g, 74%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J=7.0Hz, 3H), 0.92 (d, J=7.0Hz, 3H), 1.25 (t, J=8.4Hz, 3H), 1.62 (br s, 1H), 1.80 (m, 1H), 2.65-2.70 (m, 2H), 3.37 (ABq, Δ_{AB} =32.3Hz, J_{AB}=17.4 Hz, 2H), 4.16 (q, J=8.4Hz, 2H), 5.14 (s, 2H), 7.28-7.36 (m, 5H) ppm。质谱:(离子喷雾): m/z 323 (M+H)。

以下实施例按照上述方法制备:

实施例	名称	m/z $(M+H)^+$
1387	(S)-(2-苄氧羰基氨基-3-甲基-丁基氨基)-乙酸乙酯	323
1388	(S)-(2-苄氧羰基氨基-4-甲基-戊基氨基)-乙酸甲酯	323
1389	(R)-(2-苄氧羰基氨基-4-甲基-戊基氨基)-乙酸甲酯	323
1390	(S)-(2-苄氧羰基氨基-丙基氨基)-乙酸甲酯	295
1391	(R)-(2-苄氧羰基氨基-3-甲氧基-丙基氨基)-乙酸乙酯	325
1392	(S)-(2-苄氧羰基氨基-3-甲氧基-丙基氨基)-乙酸乙酯	325
1393	(S)-3-苄氧羰基氨基-4-(甲氧基羰基甲基-氨基)-丁酸叔丁酯	395

D. (R)-6-异丙基-哌嗪-2-酮。

向盛有(R)-(2-苄氧羰基氨基-3-甲基-丁基氨基)-乙酸乙酯(4.2g, 13.0mmol)的甲醇(130mL)溶液的 Parr 管中加入 Pd/C(10%, 396mmol)。将反应管用 40 PSI 氢气压力加压并在室温下震动 4 小时。然后将反应混合物用硅藻土过滤, 将滤液浓缩得到米黄色固体状的

(R)-6-异丙基-哌嗪-2-酮(1.77g, 95%), 其不经进一步纯化直接使用。^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J=6.8Hz, 3H), 0.97 (d, J=6.8Hz, 3H), 1.68 (sept, J=6.7Hz, 1H), 2.67 (dd, J=12.8, 8.9Hz, 1H), 3.09-3.22 (m, 2H), 3.46 (ABq, Δ_{AB}=34.3Hz, J_{AB}=17.5Hz, 2H), 5.97 (br s, 1H) ppm。

以下实施例按照上述方法制备:

实施例	名称	m/z $(M+H)^+$
1394	(S)-6-异丙基-哌嗪-2-酮	142
1395	(S)-6-异丁基-哌嗪-2-酮	157
1396	(R)-6-异丁基-哌嗪-2-酮	157
1397	(S)-6-甲基-哌嗪-2-酮	
1398	(R)-6-甲氧基甲基-哌嗪-2-酮	144
1399	(S)-6-甲氧基甲基-哌嗪-2-酮	144

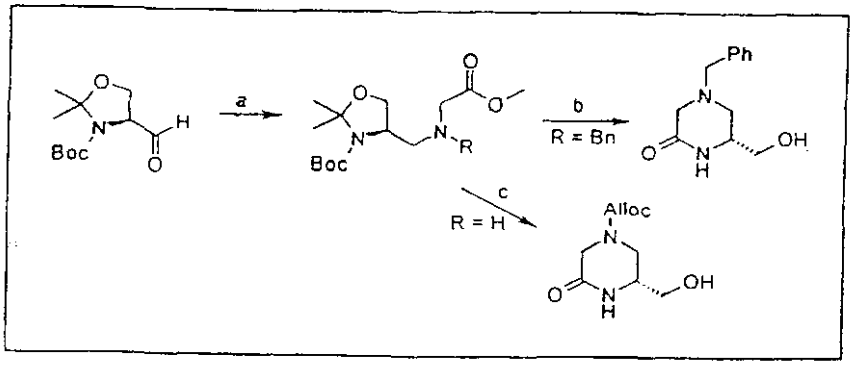
E. (R)-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯。

向(R)-6-异丙基-哌嗪-2-酮(1.77g, 12.5mmol)的无水 CH_2Cl_2 (45mL)溶液中于0℃下加入三乙胺(2.6mL, 18.7mmol), 随后加入氯甲酸烯丙酯(1.6mL, 15.0mmol)。将该混合物在0℃下搅拌30分钟然后室温搅拌30分钟, 然后将其在 CH_2Cl_2 (30mL)和水(75mL)之间进行分配。将水层用 CH_2Cl_2 (3x75mL)萃取, 将合并的有机相用盐水(50mL)洗涤, 用硫酸钠干燥, 过滤然后浓缩到硅胶上。将混合物通过快速硅胶色谱纯化(二氯甲烷→1%甲醇/二氯甲烷→2%→4%)得到无色油状(R)-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯(2.62g, 93%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85-7.08 (m, 1H), 5.82-5.99 (m, 1H), 5.19-5.33 (m, 2H), 4.60 (d, J=5.6Hz, 2H), 4.21 (d, J=18.4 Hz, 1H), 3.97 (d, J=18.4 Hz, 1H), 3.71-3.90 (m, 1H), 3.16-3.37 (m, 2H), 1.69-1.81 (m, 1H), 0.94-1.01 (m, 6H) ppm。质谱: (ESI) m/z 226 $(M+H)^+$。

以下实施例按照上述方法制备：

实施例	名称	m/z (M+H)$^+$
1400	(S)-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯	226
1401	(S)-3-异丁基-5-氧代-哌嗪-1-甲酸烯丙酯	241
1402	(R)-3-异丁基-5-氧代-哌嗪-1-甲酸烯丙酯	241
1403	(S)-3-甲基-5-氧代-哌嗪-1-甲酸烯丙酯	199
1404	(R)-3-甲氧基甲基-5-氧代-哌嗪-1-甲酸烯丙酯	229
1405	(S)-3-甲氧基甲基-5-氧代-哌嗪-1-甲酸烯丙酯	229
1406	(S)-3-叔丁氧羰基甲基-5-氧代-哌嗪-1-甲酸烯丙酯	298

反应方案 3 C(6)-羟基甲基酮基哌嗪的合成方案



试剂：(a) 1. $RNHCH_2CO_2Me$, $NaB(OAc)_3H$, 4A MS。(b) 饱和的 HCl/甲醇; K_2CO_3。(c) 1. Alloc-Cl, Et_3N, CH_2Cl_2。2. 饱和的 HCl/甲醇; K_2CO_3。

实施例 1407

(R)-4-苄基-6-羟基甲基-哌嗪-2-酮

A: (R)-4-[(苄基-乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯。

向 Garner's 醛 1 (Garner, P., Park, J. M. Org. Synthesis 1991, 70, 18) (31g, 135mmol)、N-苄基甘氨酸乙酯(28.7g, 149mmol)和粉状 4Å 分子筛(40g)的 1,2-二氯乙烷(300mL)混合物中于 0℃下加入三

乙酰氧基硼氢化钠(43g, 203mmol)。在室温下 12 小时后，将反应混合物用饱和碳酸氢钠溶液处理，用硅藻土过滤并用二氯甲烷萃取。萃取液用盐水洗涤，用硫酸镁干燥，过滤然后浓缩。用硅胶色谱处理(己烷/EtOAc, 10:1 至 3:1)得到油状的(R)-4-[(苄基-乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(42.6g, 78%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 4.14 (q, J=6.9Hz, 2H), 4.1-3.9 (m, 3H), 3.85-3.7 (m, 2H), 3.41-3.24 (m, 2H), 3.0 (d, J=12.5Hz, 1H), 2.68-2.55 (m, 1H), 1.57 (m, 3H), 1.47 (s, 9H), 1.45 (m, 3H), 1.26 (t, J=7.1Hz, 3H) ppm。质谱：(ESI) m/z 407 $(M+H)^+$。

B: (R)-4-苄基-6-羟基甲基-哌嗪-2-酮。

向(R)-4-[(苄基-乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(42.6g, 105mmol)的甲醇(500mL)溶液中于 0℃下通入无水 HCl 气体 30 分钟。在室温下 15 小时后，将混合物减压浓缩并用碳酸钾(100g, 0.72mol)的甲醇(500mL)溶液处理。继续搅拌直至等分试样的 pH 呈碱性(约 24 小时)，此时的悬浮液变成无色。将混合物过滤，将滤液浓缩并进行硅胶色谱(5%至 15%甲醇的二氯甲烷溶液)得到固体状的(R)-4-苄基-6-羟基甲基-哌嗪-2-酮(23g, 100%)。^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 6.95 (s, 1H), 3.68-3.6 (m, 2H), 3.58-3.45 (m, 4H), 3.17 (d, J=14Hz, 1H), 3.11 (d, J=14Hz, 1H), 2.71 (dd, J=10.0, 3.5 Hz, 1H), 2.56 (dd, J=9.5, 4.5 Hz, 1H) ppm。质谱：(ESI) m/z 221 $(M+H)^+$。

实施例 1408

(R)-3-羟基甲基-5-氧代-哌嗪-1-甲酸烯丙酯

A: (R)-4-[(乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯

将甘氨酸甲酯盐酸盐(26g, 208mmol)和三乙胺(28mL, 203mmol)

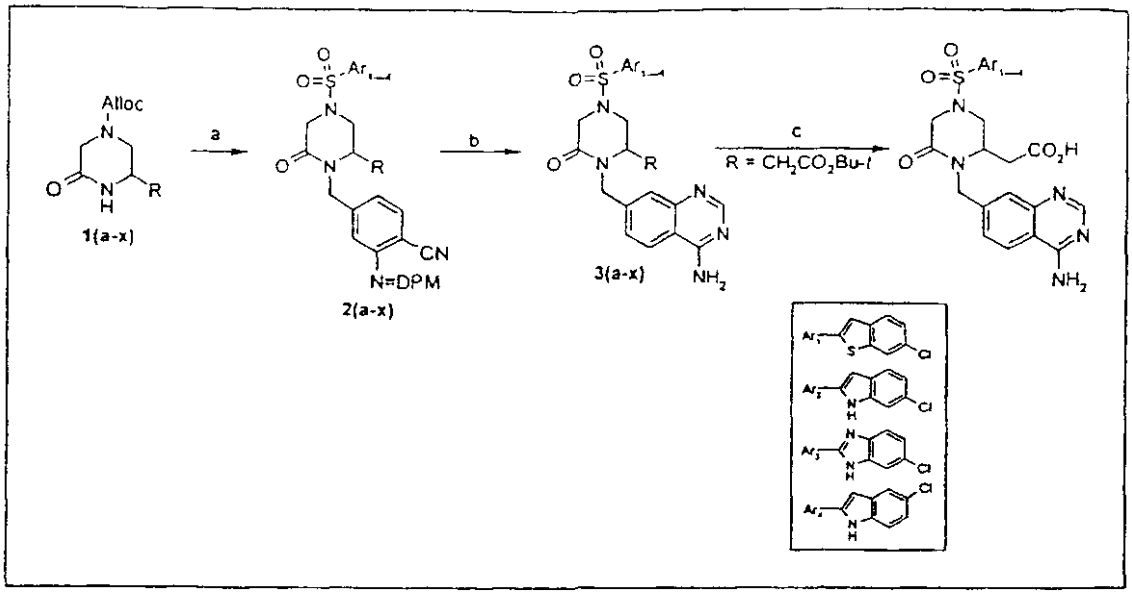
的甲醇(200mL)溶液于 0℃下用 Garner's 醛 1 (12g, 52mmol)处理，然后向其中加入 1.0M $NaBH_3CN$ 的 THF 溶液(60ml, 60mmol)。室温下 3 小时后，将反应混合物浓缩并用 EtOAc 和饱和碳酸氢钠溶液稀释。将有机相分离，用硫酸镁干燥，过滤然后浓缩。经硅胶色谱(己烷/EtOAc, 2:1 至 1:2)得到油状的(R)-4-[(乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(14.5g, 92%)。^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 2H), 3.75 (m, 1H), 3.7 (s, 3H), 3.45 (s, 2H), 2.7 (m, 2H), 1.5 (m, 15H) ppm。质谱：(ESI) m/z 303 $(M+H)^+$。

B. (R)-3-羟基甲基-5-氧代-哌嗪-1-甲酸烯丙酯。

向(R)-4-[(乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(14.5g, 48mmol)的 CH_2Cl_2 (200mL)溶液中在 0℃下依次加入三乙胺(12mL, 86mmol)和氯甲酸烯丙酯(6.6mL, 63mmol)。室温下 1 小时后，将反应混合物用饱和氯化铵稀释然后用二氯甲烷萃取。萃取液用盐水洗涤，用硫酸镁干燥，过滤然后浓缩。将粗品残余物进行硅胶色谱(己烷/EtOAc, 4:1)得到粘稠油状的(R)-4-[(烯丙氧基羰基-乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(15.4g, 83%)。质谱：(ESI) m/z 387 $(M+H)^+$。

将(R)-4-[(烯丙氧基羰基-乙氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(15.4g, 40mmol)的二氯甲烷(20mL)和 TFA (150mL)溶液在室温下搅拌 12 小时。将混合物减压浓缩(与甲苯共沸蒸发)，用过量碳酸钾的甲醇(300mL)溶液处理。继续搅拌直至等分试样的 pH 呈碱性(约 24 小时)。将混合物过滤，将滤液浓缩然后进行硅胶色谱(5%至 20%甲醇的二氯甲烷溶液)得到固体状的(R)-3-羟基甲基-5-氧代-哌嗪-1-甲酸烯丙酯(6g, 70%)。^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.97-5.88 (m, 1H), 5.35-5.24 (m, 2H), 4.62 (d, J=5.7Hz, 2H), 4.2-4.1 (m, 2H), 3.8-3.4 (m, 5H), 2.65 (s, 1H) ppm。质谱：(ESI) m/z 214 $(M+H)^+$。

反应方案 4 C(6)-取代的磺胺抑制剂的合成方案



试剂：(a). 1. NaH，4-溴甲基-2-二苯基亚甲基氨基苯甲腈，THF。2. $Pd(PPh_3)_4$，吗啉，二氯甲烷。3. 磺酰氯，Et_3N，二氯甲烷。(b). 1. c-HCl，甲醇；2. 三嗪，AcOH，乙醇，回流。(c). TFA，二氯甲烷。

实施例 1409

(R)-1-(4-氨基-喹唑啉-7-基-甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基-哌嗪-2-酮

A. (R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯。

向(R)-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯(2.60g，11.5mmol)的无水 THF (30mL)和无水 DMF (2mL)溶液中于 0℃下加入氢化钠(600mg，60%矿物油分散液，14.95mmol)。将混合物在 0℃下搅拌 15 分钟直至不再有气体溢出，然后加入 2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(4.41g，12.1mmol)。将该反应混合物在 3 小时内缓慢升温至室温，然后将黑色溶液用饱和氯化铵水溶液(100mL)处理并在水(250mL)和乙醚(250mL)之间进行分配。将水层用乙醚(2x250mL)萃取，合并后的有机相用盐水(200mL)洗涤，用硫酸钠干燥，过滤然后浓

缩。将粗产物用快速硅胶色谱纯化(二氯甲烷→1%甲醇/二氯甲烷→1.8%→2%)得到粘稠的棕色固体状(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯(4.98g, 83%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J=7.2Hz, 2H), 7.17-7.52 (m, 10H), 6.86 (dd, J=7.9, 1.4Hz, 1H), 6.58 (s, 1H), 5.83-5.98 (m, 1H), 5.18-5.42 (m, 3H), 4.61 (d, J=5.5Hz, 2H), 4.20-4.31 (m, 1H), 3.92-4.16 (m, 2H), 3.71 (d, J=15.1Hz, 1H), 2.70-2.78 (m, 2H), 1.87-2.02 (m, 1H), 0.94 (d, J=6.8Hz, 3H), 0.84 (d, J=6.8Hz, 3H) ppm。质谱: (ESI) m/z 521 $(M+H)^+$。

B (R)-2-(二苯亚甲基-氨基)-4-(2-异丙基-6-氧代-哌嗪-1-基甲基)-苯甲腈。

向(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丙基-5-氧代-哌嗪-1-甲酸烯丙酯(2.0g, 3.85mmol)的无水 CH_2Cl_2 (40mL)溶液中于室温加入吗啉(1.6mL, 19.2mmol), 随后加入四(三苯基膦)钯(444mg, 0.385mmol)。将黄色的溶液搅拌 1 小时然后浓缩到硅胶上并进行快速柱色谱(二氯甲烷→1%甲醇/二氯甲烷→2%)得到黄色油状的(R)-2-(二苯亚甲基-氨基)-4-(2-异丙基-6-氧代-哌嗪-1-基甲基)-苯甲腈(1.4g, 83%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J=7.2Hz, 2H), 7.19-7.69 (m, 9H), 6.86 (dd, J=7.9, 1.4Hz, 1H), 6.60 (d, J=1.0Hz, 1H), 5.31 (d, J=15.4Hz, 1H), 3.85 (d, J=15.5Hz, 1H), 3.72 (t, J =4.6Hz, 1H), 3.43-3.59 (m, 1H), 2.82-2.91 (m, 2H), 2.42-2.48 (m, 1H), 1.96-2.05 (m, 1H), 0.86 (d, J=7.0Hz, 3H), 0.82 (d, J=7.0Hz, 3H) ppm。质谱: (ESI) m/z 437 $(M+H)^+$。

C (R)-2-(二苯亚甲基-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-(2-异丙基-6-氧代-哌嗪-1-基甲基)-苯甲腈(0.61g, 1.4mmol)的无水二氯甲烷(15mL)溶液中于 0℃

下加入二异丙基乙基胺(320μL, 1.82mmol), 随后加入6-氯-苯并[b]噻吩-2-磺酰氯(375mg, 1.4mmol)。将反应液室温搅拌1小时, 然后浓缩到硅胶上并进行快速柱色谱(己烷:EtOAc, 4:1→2:1)得到黄色胶状的(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]-苯甲腈(681mg, 73%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.86 (m, 3H), 7.72 (d, J=7.0Hz, 2H), 7.32-7.52 (m, 5H), 7.09-7.27 (m, 5H), 6.77 (dd, J=7.9, 1.4Hz, 1H), 6.53 (d, J=1.1Hz, 1H), 5.30 (d, J=15.2Hz, 1H), 4.03-4.16 (m, 1H), 3.75 (d, J=15.2Hz, 1H), 3.57 (d, J=16.7Hz, 1H), 2.82-2.90 (m, 1H), 2.63 (dd, J=12.3, 3.7Hz, 1H), 2.07-2.17 (m, 1H), 0.93-1.04 (m, 6H) ppm。质谱: (ESI) m/z 667 $(M+H)^+$。

实施例:

实施例	名称	m/z $(M+H)^+$
1410	(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]-苯甲腈	651
1411	(R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丙基-5-氧代-哌嗪-1-磺酰基}-5-氯-吲哚-1-甲酸叔丁酯	750
1412	(R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丙基-5-氧代-哌嗪-1-磺酰基}-6-氯-吲哚-1-甲酸叔丁酯	750
1413	(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]-苯甲腈	667
1414	(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]-苯甲腈	651

1415	(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丙基-5-氧代-哌嗪-1-磺酰基}-5-氯-吲哚-1-甲酸叔丁酯	750
1416	(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丙基-5-氧代-哌嗪-1-磺酰基}-6-氯-吲哚-1-甲酸叔丁酯	750
1417	(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈	681
1418	(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈	665
1419	(R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丁基-5-氧代-哌嗪-1-磺酰基}-5-氯-吲哚-1-甲酸叔丁酯	764
1420	(R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丁基-5-氧代-哌嗪-1-磺酰基}-6-氯-吲哚-1-甲酸叔丁酯	764
1421	(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈	681
1422	(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-异丁基-6-氧代-哌嗪-1-基甲基]-苯甲腈	665
1423	(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丁基-5-氧代-哌嗪-1-磺酰基}-5-氯-吲哚-1-甲酸叔丁酯	764

1424	(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-异丁基-5-氧代-哌嗪-1-磺酰基}-6-氯-吲哚-1-甲酸叔丁酯	764
1425	(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈	
1426	(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈	
1427	(S)-2-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲基-5-氧代-哌嗪-1-磺酰基}-5-氯-吲哚-1-甲酸叔丁酯	
1428	(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲基-5-氧代-哌嗪-1-磺酰基}-6-氯-吲哚-1-甲酸叔丁酯	
1429	(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈	653
1430	(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-1H-苯并咪唑-2-磺酰基)-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈	653
1431	(R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲氧基甲基-5-氧代-哌嗪-1-磺酰基}-6-氯-吲哚-1-甲酸叔丁酯	752
1432	(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲氧基甲基-5-氧代-哌嗪-1-磺酰基}-6-氯-吲哚-1-甲酸叔丁酯	752

1433	(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲氧基甲基-5-氧代-哌嗪-1-磺酰基}-5-氯-吲哚-1-甲酸叔丁酯	752
1434	(S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基]-乙酸叔丁酯	739

实施例 1435

(R)-2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]苯甲腈

向(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]-苯甲腈(681mg, 1.02mmol)的甲醇(15mL)和 THF (3mL)溶液中于 0℃下加入浓盐酸(10 滴)。将溶液于 0℃搅拌 15 分钟然后浓缩至干，将残余物用快速硅胶色谱进行纯化(二氯甲烷→1%甲醇/二氯甲烷→2%)得到易碎的白色固体状(R)-2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]苯甲腈(481mg, 94%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.88 (m, 3H), 7.46 (dd, J=8.6, 1.8Hz, 1H), 7.23-7.30 (m, 1H), 6.55 (s, 1H), 6.49 (dd, J=7.9, 1.4Hz, 1 H), 5.30 (d, J=15.3Hz, 1H), 4.37 (s, 2H), 4.08-4.22 (m, 1H), 3.78-3.90 (m, 2H), 3.57-3.69 (m, 1H), 3.10-3.18 (m, 1H), 2.78 (dd, J=12.5, 4.0Hz, 1H), 2.18-2.29 (m, 1H), 1.08 (d, J=6.9Hz, 3H), 1.04 (d, J=6.9Hz, 3H) ppm。质谱: (ESI) m/z 503 $(M+H)^+$。

实施例 1436:

(R)-1-(4-氨基-喹唑啉-7-基-甲基)-4-(6-氯-苯并[b]噻吩-2 磺酰基)-6-异丙基-哌嗪-2-酮

向(R)-2-氨基-4-[4-(6-氯苯并[b]噻吩-2-磺酰基)-2-异丙基-6-氧代-哌嗪-1-基甲基]苯甲腈(468mg, 0.93mmol)的无水乙醇(12mL)

溶液中加入冰乙酸(540μL, 9.31mmol)和三嗪(775mg, 9.31mmol)。将混合物加热至回流(成为均相)并搅拌16小时,然后冷却然后浓缩至干。将粗产物通过反相HPLC在2″ Dynamax C18柱上纯化(10→100% ACN的水溶液/0.1%TFA)得到白色冻干固体状的(R)-1-(4-氨基-喹唑啉-7-基-甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基-哌嗪-2-酮(365mg, 61%)。^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (br s, 2H), 8.75 (s, 1H), 8.24-8.34 (m, 2H), 8.19 (s, 1H), 8.06 (d, J=8.7Hz, 1H), 7.53-7.62 (m, 3H), 5.07 (d, J=16.4Hz, 1H), 4.45 (d, J=16.3Hz, 1H), 4.06 (d, J=16.4Hz, 1H), 3.83 (d, J=16.2Hz, 1H), 3.63 (d, J=16.2Hz, 1H), 3.34-3.45 (m, 1H), 3.02 (AB q, J=12.6, 3.6Hz, 1H), 2.11-2.22 (m, 1H), 0.99 (d, J=6.8Hz, 3H), 0.93 (d, J=6.8Hz, 3H) ppm。质谱: (ESI): m/z 530 $(M+H)^+$。

以下实施例按照上述方法制备:

实施例1437

(R)-1-(4-氨基喹唑啉-7-基-甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (bs, 2H); 8.76 (s, 1H); 8.29 (d, J=8.6Hz, 1H); 7.65-7.73 (m, 2H); 7.55-7.62 (m, 2H); 7.40 (d, J=8.7Hz, 1H); 5.05 (d, J=16.2Hz, 1H); 4.47 (d, J=16.2Hz, 1H); 4.13 (d, J=16.6Hz, 1H); 3.80-3.93 (m, 2H); 3.35-3.65 (m, 1H); 3.18 (AB q, J=12.9, 3.6Hz, 1H), 2.09-2.19 (m, 1H); 0.99 (d, J=6.8Hz, 3H); 0.93 (d, J=6.9Hz, 3H) ppm。质谱: (ESI) m/z 514 $(M+H)^+$。

实施例1438

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基-哌嗪-2-酮

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.96 (dd, J=15.9, 6.85Hz, 6H), 2.19 (m, 1H), 3.02 (dd, J=12.4, 3.6Hz, 1H), 3.40 (m, 2H), 3.82 (d, J=12.4Hz, 1H), 4.03 (d, J=16.3Hz, 1H), 4.47 (d, J=16.3Hz, 1H), 5.06 (d, J=16.3Hz, 1H), 7.55 (m, 3H), 8.06 (d, J=8.6Hz, 1H), 8.20 (s, 1H), 8.28 (d, J=8.6Hz, 1H), 8.33 (d, J=1.9Hz, 1H), 8.76 (s, 1H), 9.71 (br·s, 2H) ppm。质谱：(ESI) m/z 530 $(M+H)^+$。

实施例 1439

(S)-1-(4-氨基喹唑啉-7-基-甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丙基-哌嗪-2-酮

^{1}H NMR (300 MHz, d_6-DMSO) δ 0.96 (dd, J=17.84, 6.86Hz, 6H), 2.15 (m, 1H), 3.18 (dd, J=12.8, 3.5Hz, 2H), 3.88 (m, 3H), 4.13 (d, J=16.5Hz, 1H), 4.47 (d, J=16.3Hz, 1H), 5.06 (d, J=16.3Hz, 1H), 7.40 (dd, J=8.7, 1.8Hz, 1H), 7.57 (s, 1H), 7.60 (d, J=8.65Hz, 1H), 7.74 (m, 2H), 8.29 (d, J=8.54Hz, 1H), 8.76 (s, 1H), 9.71 (br s, 2H) ppm。质谱：(ESI) m/z 514 $(M+H)^+$。

实施例 1440

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯苯并[b]噻吩-2-磺酰基)-6-异丁基-哌嗪-2-酮

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.82 (dd, J=17.6, 6.4Hz, 6H), 1.41 (m, 1H), 1.60 (m, 1H), 1.74 (m, 1H), 3.06 (d, J=10.0Hz, 1H), 3.42 (d, J=8.8Hz, 1H), 3.65 (d, J=16.2Hz, 1H), 3.73 (s, 1H), 4.05 (d, J=16.2Hz, 1H), 4.41 (d, J=16.6Hz, 1H), 5.02 (d, J=16.6Hz, 1H), 7.53 (s, 1H), 7.58 (dd, J=8.6, 2.0Hz, 2H), 8.06 (d, J=8.6Hz, 1H), 8.22 (s, 1H), 8.29 (d, J=8.6Hz, 1H), 8.33 (d, J=1.8Hz, 1H), 8.77 (s, 1H), 9.74 (s, 2H) ppm。质谱：(ESI) m/z 544 $(M+H)^+$。

实施例 1441

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮

^{1}H NMR (500 MHz, d_6-DMSO)↗ 0.82 (dd, J=24.0, 6.6Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, J=10.2Hz, 1H), 3.43 (m, 1H), 3.80 (d, J=12.7Hz, 1H), 3.89 (s, 1H), 3.93 (d, J=9.8Hz, 1H), 4.18 (d, J=16.1Hz, 1H), 4.42 (d, J=16.6Hz, 1H), 5.04 (d, J=16.6Hz, 1H), 7.41 (dd, J=8.8, 2.0Hz, 1H), 7.56 (s, 1H), 7.61 (d, J=8.8Hz, 1H), 7.73 (d, J=8.8Hz, 1H), 7.79 (d, J=2.0Hz, 1H), 8.33 (d, J=8.3Hz, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm。质谱: (ESI) m/z 544 $(M+H)^+$。

实施例 1442

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丁基-哌嗪-2-酮

^{1}H NMR (300 MHz, d_6-DMSO)↗ 0.82 (dd, J=17.6, 6.4Hz, 6H), 1.41 (m, 1H), 1.74 (m, 1H), 3.06 (d, J=10.0Hz, 1H), 3.42 (d, J=8.8Hz, 1H), 3.65 (d, J=16.2Hz, 1H), 3.73 (s, 1H), 4.05 (d, J=16.2Hz, 1H), 4.41 (d, J=16.6Hz, 1H), 5.02 (d, J=16.6Hz, 1H), 7.53 (s, 1H), 7.58 (dd, J =8.6, 2.0Hz, 2H), 8.06 (d, J=8.6Hz, 1H), 8.22 (s, 1H), 8.29 (d, J=8.6Hz, 1H), 8.33 (d, J=1.8Hz, 1 H), 8.77 (s, 1H), 9.74 (s, 2H) ppm。质谱: (ESI) m/z 544 $(M+H)^+$。

实施例 1443

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮

^{1}H NMR (500 MHz, d_6-DMSO)↗ 0.82 (dd, J =24.0, 16.6Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, J=10.2Hz, 1H), 3.43 (m, 1H), 3.80 (d, J=12.7Hz, 1H), 3.89 (s, 1H), 3.93

(d, J=9.8Hz, 1H), 4.18 (d, J=16.1Hz, 1H), 4.42 (d, J=16.6Hz, 1H), 5.04 (d, J=16.6Hz, 1H), 7.41 (dd, J=8.8, 2.0Hz, 1H), 7.56 (s, 1H), 7.61 (d, J=8.8Hz, 1H), 7.73 (d, J=8.8Hz, 1H), 7.79 (d, J =2.0Hz, 1H), 8.33 (d, J=8.3Hz, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm。质谱: (ESI) m/z 528 $(M+H)^+$。

实施例 1444

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-异丁基-哌嗪-2-酮

^1H NMR (500 MHz, d_6-DMSO) ↗ 0.82 (dd, J=24.0, 6.6Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, J=10.2Hz, 1H), 3.43 (m, 1H), 3.80 (d, J=12.7Hz, 1H), 3.89 (s, 1H), 3.93 (d, J=9.8Hz, 1H), 4.18 (d, J=16.1Hz, 1H), 4.42 (d, J=16.6Hz, 1H), 5.04 (d, J=16.6Hz, 1H), 7.41 (dd, J=8.8, 2.0Hz, 1H), 7.56 (s, 1H), 7.73 (d, J=8.8Hz, 1H), 7.79 (d, J=2.0Hz, 1H), 8.62 (s, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm。质谱: (ESI) m/z 562 $(M+H)^+$。

实施例 1445

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↑ 8.37 (d, J=10.2Hz, 2H), 8.19 (s, 1H), 8.10 (d, J=8.7Hz, 1H), 7.73 (br·s, 2H), 7.60 (d, J=8.6Hz, 1H), 7.50 (s, 1H), 7.31 (d, J=8.6Hz, 1H), 5.06 (d, J=15.8Hz, 1H), 4.35 (d, J=15.8Hz, 1H), 3.98 (d, J=16.0Hz, 1H), 3.77 (d, J=16.0Hz, 1H), 3.62-3.48 (m, 2H), 3.21 (d, J=9.2Hz, 1H), 1.25 (d, J=6.1Hz, 3H) ppm。质谱: (ESI) m/z 502 $(M+H)^+$。

实施例 1446

(S)-1-(4-氨基喹唑啉-7-基-甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰

基)-6-甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 9.80 (d, J=6.2Hz, 2H), 8.82 (s, 1H), 8.35 (d, J=8.6Hz, 1H), 7.84 (s, 1H), 7.78 (d, J=8.7Hz, 1H), 7.64 (d, J=8.7Hz, 1H), 7.60 (s, 1H), 7.47 (d, J=8.7Hz, 1H), 4.98 (d, J=16.5Hz, 1H), 4.60 (d, J=16.5Hz, 1H), 4.19 (d, J=16.4Hz, 1H), 3.96 (d, J=16.4Hz, 1H), 3.60 (m, 3H), 1.26 (d, J=6.1Hz, 3H) ppm。质谱: (ESI) m/z 486 $(M+H)^+$。

实施例 1447

(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基]-乙酸叔丁酯

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.86-7.88 (m, 1H), 7.84 (d, J=8.7Hz, 1H), 7.80 (d, J=0.55Hz, 1H), 7.66 (d, J=8.5Hz, 1H), 7.59 (d, J=1.2Hz, 1H), 7.46 (dd, J=8.6, 1.8Hz, 1H), 7.33 (dd, J=8.5, 1.6Hz, 1H), 5.36 (d, J=15.7Hz, 1H), 4.24 (d, J=17.1Hz, 1H), 4.11 (d, J=15.7Hz, 1H), 3.95 (d, J=12.4Hz, 1H), 3.80-3.88 (m, 1H), 3.59 (d, J=16.7Hz, 1H), 2.86-2.98 (m, 2H), 2.65 (dd, J=16.8, 2.5Hz, 1H) 1.43 (s, 9H) ppm。质谱: (ESI) m/z 602 $(M+H)^+$。

实施例 1448

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 2H), 8.77 (s, 1H), 8.34 (d, J=8.6Hz, 1H), 8.28 (d, J=8.6Hz, 1H), 8.21 (s, 1H), 8.07 (d, J=8.6Hz, 1H), 7.54-7.62 (m, 2H), 7.50 (s, 1H), 4.95 (d, J=16.5Hz, 1H), 4.59 (d, J=16.6Hz, 1H), 4.02 (d, J=16.5Hz, 1H), 3.45-3.80 (m, 3H), 3.09-3.19 (m, 4H) ppm。质谱: (ESI) m/z 532 $(M+H)^+$。

实施例 1449

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 8.44 (s, 1H), 8.36 (s, 1H), 8.21-8.09 (m, 5H), 7.58 (dd, J=11.0, 1.3Hz, 1H), 7.49 (s, 1H), 7.36 (d, J=8.5Hz, 1H), 5.06 (d, J=16.0Hz, 1H), 4.49 (d, J=16.0Hz, 1H), 4.04 (d, J=16.1Hz, 1H), 3.79-3.72 (m, 2H), 3.58-3.49 (m, 3H), 3.21 (s, 3H), 3.14 (d, J=10.3Hz, 1 H) ppm。质谱: (ESI) m/z 532 $(M+H)^+$。

实施例 1450

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (d, J=5.8Hz, 2H), 8.78 (s, 1H), 8.31 (d, J=8.6Hz, 1H), 7.68-7.79 (m, 2H), 7.52-7.61 (m, 2H), 7.40 (dd, J=8.7, 1.9Hz, 1H), 4.94 (d, J=16.6Hz, 1H), 4.59 (d, J=16.6Hz, 1H), 4.14 (d, J=16.4Hz, 1H), 3.82-3.94 (m, 2H), 3.63-3.68 (m, 1H), 3.43-3.52 (m, 2H), 3.32 (dd, J=12.6, 3.4Hz, 1H), 3.14 (s, 3H) ppm。质谱: (ESI) m/z 516 $(M+H)^+$。

实施例 1451

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (bs, 2H); 8.78 (s, 1H); 8.30 (d, J=8.6Hz, 1H); 7.73 (bs, 2H); 7.51-7.62 (m, 2H); 7.37-7.44 (m, 2H); 4.94 (d, J=16.5Hz, 1H); 4.59 (d, J=16.5Hz, 1H); 4.15 (d, J=16.5Hz, 1H); 3.90 (d, J=16.5Hz, 1H); 3.83 (s, 1H); 3.62-3.68 (m, 1H); 3.41-3.52 (m, 2H); 3.32 (AB q, J=12.7,

3.5Hz, 1H); 3.14 (s, 3H) ppm。质谱: (ESI) m/z 516 $(M+H)^+$。

实施例 1452

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮。(RPR 252864A)

对于芳基磺酰胺含有吲哚部分的实施例，化合物用以上顺序构建，但在最后的步骤中采用 Boc-脱保护步骤:

将(R)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-异丙基-5-氧代-哌嗪-1-磺酰基]-6-氯-吲哚-1-甲酸叔丁酯(102mg, 0.17mmol)的二氯甲烷(5mL)溶液于 0℃下用三氟乙酸(1mL)处理，将此溶液升温至室温并搅拌16小时。将混合物浓缩至干，然后通过反相HPLC在1″ Dynamax, C18 柱上纯化(5→100% ACN 的水溶液/0.1%TFA)得到白色冻干固体状的(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮(27mg, 25%)。^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.48 (s, 1H), 9.61 (br s, 2H), 8.74 (s, 1H), 8.26 (d, J=8.5Hz, 1H), 7.73 (d, J=8.6Hz, 1H), 7.58 (d, J=8.5Hz, 1H), 7.45-7.52 (m, 2H), 7.12-7.20 (m, 2H), 5.03 (d, J=16.4Hz, 1H), 4.45 (d, J=16.8Hz, 1H), 4.00 (d, J=16.3Hz, 1H), 3.79 (d, J=12.2Hz, 1H), 3.54 (d, J=16.3Hz, 1H), 3.30-3.37 (m, 1H), 2.88 (ABq, J =12.4, 3.9 Hz, 1H), 2.10-2.18 (m, 1H), 1.00 (d, J=6.9Hz, 3H), 0.91 (d, J=6.9Hz, 3H) ppm。质谱: (ESI) m/z 513 $(M+H)^+$。

以下实施例按照上述方法制备:

实施例 1453

(R)-1-(4-氨基喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.54 (s, 1H), 9.62 (br.s, 2H), 8.74 (s, 1H), 8.26 (d, J=8.6Hz, 1H), 7.77 (d, J=2.0Hz, 1H),

7.45-7.61 (m, 3H), 7.34 (dd, J=8.8, 2.0Hz, 1H), 7.11 (d, J=1.4Hz, 1H), 5.05 (d, J=16.3Hz, 1H) 4.45 (d, J=16.3Hz, 1H), 4.02 (d, J=16.4Hz, 1H), 3.79 (d, J=16.4Hz, 1H), 3.55 (d, J=16.4Hz, 1H), 3.31-3.33 (m, 1H), 2.39 (AB q, J =12.5, 3.6Hz, 1H), 2.08-2.20 (m, 1H), 0.98 (d, J=6.8Hz, 3H), 0.92 (d, J=6.9Hz, 3H) ppm。质谱: (ESI) m/z 513 $(M+H)^+$。

实施例 1454

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↗ 0.95 (dd, J=18.8, 6.8Hz, 6H), 2.15 (m, 1H), 2.89 (dd, J=12.6, 3.7Hz, 1H), 3.35 (m, 1H), 3.54 (d, J=16.3Hz, 1H), 3.80 (d, J=12.3Hz, 1H), 4.00 (d, J=16.3Hz, 1H), 4.44 (d, J=16.3Hz, 1H), 5.03 (d, J=16.3Hz, 1H), 7.11 (d, J=1.5Hz, 1H), 7.31 (dd, J=8.9, 2.1Hz, 1H), 7.51 (m, 2H), 7.57 (d, J=8.6Hz, 1H), 7.77 (d, J=2.1Hz, 1H), 8.26 (d, J=8.6Hz, 1H), 8.73 (s, 1H), 9.59 (br. s, 2H), 12.53 (s, 1H) ppm。质谱: (ESI) m/z 513 $(M+H)^+$。

实施例 1455

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↗ 0.95 (dd, J=18.7, 6.8Hz, 6H), 2.15 (m, 1H), 2.89 (dd, J=12.7, 3.7Hz, 1H), 3.32 (m, 1H), 3.54 (d, J=16.3Hz, 1H), 3.83 (d, J=12.3Hz, 1H), 4.00 (d, J=16.3 Hz, 1H), 4.45 (d, J=16.3Hz, 1H), 5.04 (d, J=16.3Hz, 1H), 7.15 (m, 2H), 7.48 (d, J=0.84Hz, 1H), 7.49 (s, 1H), 7.60 (d, J=7.3Hz, 1H), 7.72 (d, J=8.6Hz, 1H), 8.27 (d, J=8.6Hz, 1H), 8.76 (s, 1H), 9.71 (s, 2H), 12.49 (s, 1H) ppm。质谱: (ESI) m/z 513

$(M+H)^+$。

实施例 1456

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, J=13.4, 6.4Hz, 6H), 1.40 (m, 1H), 1.55 (m, 1H), 1.70 (m, 1H), 2.93 (d, J=10.4Hz, 1H), 3.19 (m, 1H), 3.57 (d, J=16.3Hz, 1H), 3.69 (d, J=12.4Hz, 1H), 4.05 (d, J=16.3Hz, 1H), 5.00 (d, J=16.6Hz, 1H), 7.13 (d, J=1.4Hz, 1H), 7.32 (dd, J=8.8, 2.1Hz, 1H), 7.48 (d, J=4.6Hz, 1H), 7.50 (s, 1H), 7.57 (d, J=8.6Hz, 1H), 7.78 (d, J=1.8Hz, 1H), 8.28 (d, J=8.6Hz, 1H), 8.74 (s, 1H), 9.63 (s, 2H) ppm。质谱: (ESI) m/z 527 $(M+H)^+$。

实施例 1457

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, J=13.8, 6.4Hz, 6H), 1.40 (m, 1H), 1.58 (m, 1H), 1.70 (m, 1H), 2.92 (d, J=10.2Hz, 1H), 3.20 (m, 1H), 3.57 (d, J=16.3Hz, 1H), 3.69 (d, J=12.2Hz, 1H), 4.04 (d, J=16.3Hz, 1H), 4.38 (d, J=16.5Hz, 1H), 5.01 (d, J=16.5Hz, 1H), 7.15 (d, J=1.8Hz, 1H), 7.73 (d, J=8.6Hz, 1H), 8.27 (d, J=8.6Hz, 1H), 8.73 (s, 1H), 9.52 (s, 2H) ppm。质谱: (ESI) m/z 527 $(M+H)^+$。

实施例 1458

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, J=13.4, 6.4Hz, 6H), 1.40

(m, 1H), 1.55 (m, 1H), 1.70 (m, 1H), 2.93 (d, J=10.4Hz, 1H), 3.19 (m, 1H), 3.57 (d, J=16.3Hz, 1H), 3.69 (d, J=12.4Hz, 1H), 4.05 (d, J=16.3Hz, 1H), 4.38 (d, J=16.6Hz, 1H), 5.00 (d, J=16.6Hz, 1H), 7.13 (d, J=1.4Hz, 1H), 7.32 (dd, J=8.8, 2.1Hz, 1H), 7.48 (d, J=4.6Hz, 1H), 7.50 (s, 1H), 7.57 (d, J=8.6Hz, 1H), 7.78 (d, J=1.8Hz, 1H), 8.28 (d, J=8.6Hz, 1H), 8.74 (s, 1H), 9.63 (s, 2H) ppm。质谱: (ESI) m/z 527 $(M+H)^+$。

实施例 1459

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丁基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, J=13.8, 6.4Hz, 6H), 1.40 (m, 1H), 1.58 (m, 1H), 1.70 (m, 1H), 2.92 (d, J=10.2Hz, 1H), 3.20 (m, 1H), 3.57 (d, J=16.3Hz, 1H), 3.69 (d, J=12.2Hz, 1H), 4.04 (d, J=16.3Hz, 1H), 4.38 (d, J=16.5Hz, 1H), 5.01 (d, J=16.5Hz, 1H), 7.15 (d, J=1.8Hz, 1H), 7.18 (d, J=1.8Hz, 1H), 7.49 (s, 1H), 7.56 (d, J=8.7Hz, 1H), 7.73 (d, J=8.6Hz, 1H), 8.27 (d, J=8.6Hz, 1H), 8.27 (d, J=8.6Hz, 1H), 8.73 (s, 1H), 9.57 (s, 2H) ppm。质谱: (ESI) m/z 527 $(M+H)^+$。

实施例 1460

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) ↗ 12.60(s, 1H), 9.56 (br.s, 2H), 8.75 (s, 1H), 8.28 (d, J=8.6Hz, 1H), 7.82 (s, 1H), 7.57 (d, J=8.5Hz, 1H), 7.52 (br.s, 2H), 7.35 (d, J=8.8Hz, 1H), 7.13 (s, 1H), 4.95 (d, J=16.7Hz, 1H), 4.53 (d, J=16.7Hz, 1H), 3.99 (d, J=16.2Hz, 1H), 3.64 (d, J=16.3Hz, 2H), 3.16 (d, J=9.5Hz, 2H), 1.21 (d, J=6.2Hz, 3H) ppm。质谱: (ESI) m/z 485 $(M+H)^+$。

实施例 1461

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.5 (s, 1H), 9.54 (br.s, 2H), 8.75 (s, 1H), 8.29 (d, J=8.5Hz, 1H), 7.75 (d, J=8.6Hz, 1H), 7.58 (d, J=8.5Hz, 1H), 7.52 (s, 2H), 7.19 (br.s, 2H), 4.95 (d, J=16.5Hz, 1H), 4.52 (d, J=16.5Hz, 1H), 4.00 (d, J=16.4Hz, 1H), 3.64 (d, J=16.2Hz, 2H), 3.14 (d, J=9. 5Hz, 2H), 1.21 (d, J=6.1Hz, 3H)ppm。质谱: (ESI) m/z 485 $(M+H)^+$。

实施例 1462

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

实施例 1463

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.55 (s, 1H), 9.67 (bs, 2H), 8.75 (s, 1H), 8.29 (d, J=8.6Hz, 1H), 7.77 (d, J=1.7Hz, 1H), 7.45-7.59 (m, 3H), 7.31 (dd, J=8.8, 1.9Hz, 1H), 7.11 (d, J=1.4Hz, 1H), 4.94 (d, J=16.5Hz, 1H), 4.56 (d, J=16.6Hz, 1H), 4.03 (d, J=16.3Hz, 1H), 3.76 (d, J=12.0Hz, 1H), 3.42-3.66 (m, 4H), 3.15 (s, 3H), 3.02 (AB q, J=12.3, 3.1Hz, 1H) ppm。质谱: (ESI) m/z 515 $(M+H)^+$。

实施例 1464

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.53 (d, J=1.7Hz, 1H), 9.74 (d,

J=14.3Hz, 2H), 8.73 (s, 1H), 8.30 (d, J=8.6Hz, 1H), 7.72 (d, J=8.6Hz, 1H), 7.47-7.59 (m, 3H), 7.11-7.18 (m, 2H), 4.94 (d, J=16.7Hz, 1H), 4.55 (d, J=16.4Hz, 1H), 3.76 (d, J=12.0Hz, 1H), 3.43-3.64 (m, 4H), 3.14 (s, 3H), 3.02 (AB q, J=12.3, 3.29Hz, 1H) ppm。质谱: (ESI) m/z 515 $(M+H)^+$。

实施例 1465

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-哌嗪-2-酮

^1H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H); 9.63 (bs, 2H); 8.75 (s, 1H); 8.27 (d, J=8.5Hz, 1H) ; 7.73 (d, J=8.6Hz, 1H) ; 7.56 (d, J=8.8Hz, 1H) ; 7.48 (s, 2H); 7.13-7.20 (m, 2H); 4.95 (d, J=16.5Hz, 1H); 4.56 (d, J=16.7Hz, 1H); 4.03 (d, J=15.9Hz, 1H) ; 3.76 (d, J=12.7Hz, 1H); 3.44-3.65 (m, 4H); 3.16 (s, 3H); 3.00 (AB q, J=11.7, 2.6Hz, 1H) ppm。质谱: (ESI) m/z 515 $(M+H)^+$。

实施例 1466

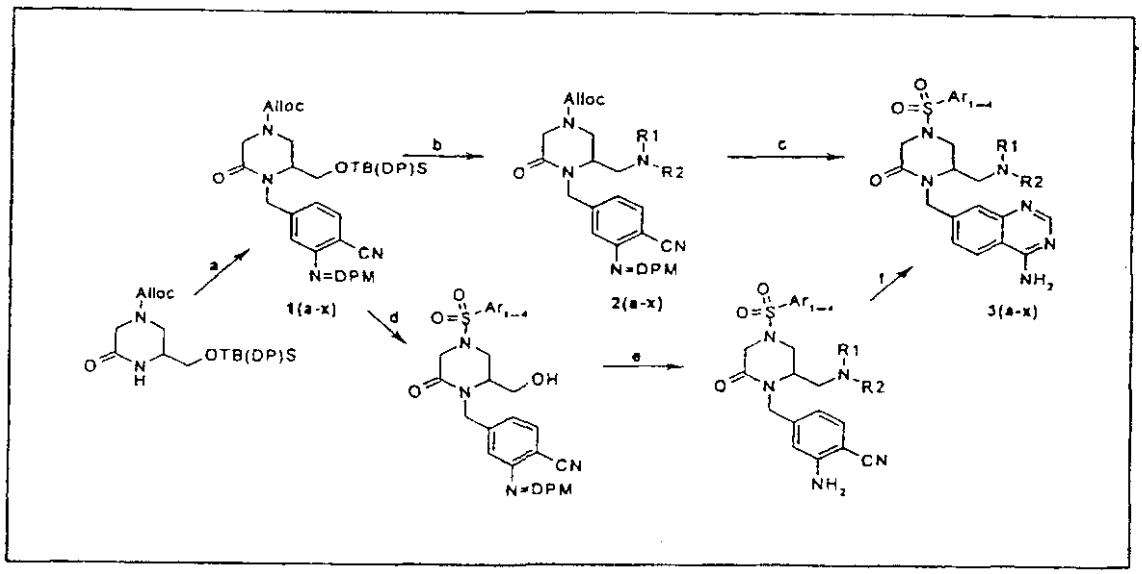
(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基]-乙酸

A: (S)-[2-(4-氨基-喹唑啉-7-基甲基)-5-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基]-乙酸。

将(S)-[2-(4-氨基-喹唑啉-7-基甲基)-5-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基]-乙酸叔丁酯(58mg, 0.096mmol)的二氯甲烷溶液冷却至0℃并向其中加入TFA (1mL)。在0℃下搅拌30分钟后, 将反应液升温至室温。搅拌2小时后, 将溶剂浓缩并将残余物溶于水。经冷冻干燥得到白色固体状的(S)-[2-(4-氨基-喹唑啉-7-基甲基)-5-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基]-乙酸(53mg, 82%)。^1H NMR (300 MHz, DMSO-d_6) δ 9.52 (bs, 2H), 8.74 (s, 1H), 8.34 (d, J=1.8Hz, 1H), 8.27 (d, J=8.5Hz, 1H), 8.21

(s, 1H), 8.07 (d, J=8.7Hz, 1H), 7.50-7.60 (m, 3H), 5.02 (d, J=16.4Hz, 1H), 4.50 (d, J=16.4Hz, 1H), 3.72-3.81 (m, 2H), 3.63 (d, J=16.2Hz, 1H), 3.14-3.21 (m, 1H), 2.70-2.80 (m, 2H) ppm。质谱: (ESI) m/z 546 $(M+H)^+$。

反应方案 5 C(6)-烷基氨基甲基取代的磺胺抑制剂的合成方案



试剂: (a). NaH, 4-溴甲基-2-二苯基亚甲基氨基苯甲腈, THF。(b). 1. TBAF, THF。2. SO_3-Py, DMSO。3. 胺, $NaB(OAc)_3H$, 4A MS。(c). 1. $Pd(PPh_3)_4$, 吗啉, 二氯甲烷。2. "磺酰氯", Et_3N, 二氯甲烷。3. c-HCl, 甲醇。4. 1,3,5-三嗪, AcOH, 乙醇, 回流。(d). 1. 见(c. 1-2, b. 1)。(e). 1. Dess-Martin。2. 见(b3, c. 3)。(f) 见(c. 4)。

实施例 1467

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-甲基-哌嗪-1-基甲基)-哌嗪-2-酮(RPR257023A)

A: (R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二苯基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯。

向(R)-3-(叔丁基-二苯基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸

烯丙酯(5.2g, 11.5mmol)在 THF: DMF (5:1, 120mL)混合物中的溶液中于 0℃下加入氢化钠(60%矿物油分散液, 0.6g, 15mmol), 15 分钟后加入 2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(4.7g, 12.7mmol)。在室温下 2 小时后, 将反应混合物用饱和氯化铵稀释, 用 EtOAc 萃取。将萃取液用水洗涤两次, 用硫酸镁干燥, 过滤然后浓缩。粗品残余物不经进一步纯化直接用于随后的反应。质谱: (ESI) m/z 747 $(M+H)^+$。

B: (S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(4-甲基-哌嗪-1-基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯。

将(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二苯基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯的 THF (100mL)溶液用 1.0M TBAF 的 THF 溶液(17mL, 17mmol)处理。室温下 0.5 小时后, 将反应混合物用饱和氯化铵稀释并用 EtOAc 萃取。将萃取液用硫酸镁干燥, 过滤然后浓缩。将粗品残余物进行硅胶色谱(己烷/EtOAc, 1:1 至 1:5)得到(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-羟基甲基-5-氧代-哌嗪-1-甲酸烯丙酯(4.3g, 50%)。质谱: (ESI) m/z 509 $(M+H)^+$。

将(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-羟基甲基-5-氧代-哌嗪-1-甲酸烯丙酯(2.4g, 4.7mmol)的 DMSO (8mL)和三乙胺(4mL)溶液在 0℃下用 SO_3.Py (3.76g, 24mmol)处理。在室温下 20 小时后, 将混合物用水稀释, 用 EtOAc 萃取。将萃取液用饱和氯化铵溶液和水洗涤, 用硫酸镁干燥然后浓缩。粗品(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲酰基-5-氧代-哌嗪-1-甲酸烯丙酯(约 2.3g)不经进一步纯化直接用于随后的反应。质谱: (ESI) m/z 507 $(M+H)^+$。

向(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲酰基-5-氧代-哌嗪-1-甲酸烯丙酯(100mg, 0.2mmol)、N-甲基哌嗪(0.066mL, 0.59mmol)和粉状 4Å 分子筛(0.1g)的 1,2-二氯乙烷(2mL)混合物中于 0℃下加入三乙酰氧基硼氢化钠(0.13g, 0.6mmol)。在室温下 20 小时后, 将反应混合物用饱和碳酸氢钠溶液处理, 然后用二氯甲烷溶液萃

取。萃取液用盐水洗涤，用硫酸镁干燥，过滤然后浓缩。经硅胶色谱(2%至 10%甲醇的二氯甲烷溶液)得到(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(4-甲基-哌嗪-1-基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯(50mg, 43%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=7.1Hz, 2H), 7.5-7.1 (m, 9H), 6.85 (d, J=8.0Hz, 1H), 6.59 (s, 1H), 6.0-5.85 (m, 1H), 5.35-5.23 (m, 3H), 4.7-4.55 (m, 2H), 4.5-4.5 (m, 1H), 4.23 (d, J=15Hz, 1H), 4.0-3.8 (m, 2H), 3.0-2.8 (m, 2H), 2.5-2.3 (m, 10H), 2.28 (s, 3H) ppm。质谱：(ESI) m/z 591 $(M+H)^+$。

C：(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-甲基-哌嗪-1-基甲基)-哌嗪-2-酮。

将四(三苯基膦)钯(0) (21mg, 0.02mmol)加入到(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(4-甲基-哌嗪-1-基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯(50mg, 0.085mmol)和吗啉(0.074mL, 0.85mmol)的二氯甲烷(5mL)溶液中。在室温下 1 小时后，将反应混合物浓缩并进行硅胶色谱(5%至 15%甲醇的二氯甲烷溶液)得到(S)-2-(二苯亚甲基-氨基)-4-[2-(4-甲基-哌嗪-1-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(40mg, 93%)。质谱：(ESI) m/z 507 $(M+H)^+$。

向(S)-2-(二苯亚甲基-氨基)-4-[2-(4-甲基-哌嗪-1-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(40mg, 0.08mmol)的二氯甲烷(3mL)溶液中于 0℃下加入三乙胺(0.055mL, 0.4mmol)，随后加入 6-氯-苯并[b]噻吩-2-磺酰氯(30mg, 0.12mmol)。室温下 1 小时后，将反应混合物用饱和碳酸氢钠溶液处理并用二氯甲烷萃取。萃取液用饱和氯化铵溶液和盐水洗涤，用硫酸镁干燥然后浓缩。粗品残余物不经进一步的纯化直接用于随后的反应。质谱：(ESI) m/z 737 $(M+H)^+$。

将浓盐酸(12M, 5 滴)于 0℃加入到(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-(4-甲基-哌嗪-1-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈的甲醇(5mL)溶液中。在室温下 1 小

时后，将反应混合物浓缩并在 EtOAc 和饱和碳酸氢钠溶液之间进行分配。分出的有机相用盐水洗涤，用硫酸镁干燥，过滤然后浓缩。将粗品残余物进行硅胶色谱(10%至 20%甲醇的二氯甲烷溶液)得到(S)-2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-(4-甲基-哌嗪-1-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(20mg, 44%)。质谱：(ESI) m/z 573 $(M+H)^+$。

向(S)-2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-(4-甲基-哌嗪-1-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(20mg, 0.035mmol)的无水乙醇(3mL)溶液中加入 1,3,5-三嗪(28mg, 0.35mmol)和乙酸(0.02mL, 0.35mmol)。将溶液加热至回流。48 小时后，将溶液浓缩，将所得粗产物进行硅胶色谱(10%至 30%甲醇的二氯甲烷溶液)得到 15mg (71%)的(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-甲基-哌嗪-1-基甲基)-哌嗪-2-酮。质谱：(ESI) m/z 600 $(M+H)^+$。

按照上述方法，用适当的胺和磺酰氯可以制得如下化合物。

实施例	化合物名称	m/z (M+H)
1468	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-吡咯烷-1-基甲基-哌嗪-2-酮	555
1469	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-吡咯烷-1-基甲基-哌嗪-2-酮	
1470	(6S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-{[(2-二甲基氨基-乙基)-甲基-氨基]-甲基}-哌嗪-2-酮	602

实施例 1471

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰

基)-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-2-酮(RPR257982A)

A: (R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯。

向(R)-3-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯(2.5g, 7.62mmol)在 THF(40mL)和 DMF(2mL)的混合物中的溶液中于 0℃下加入氢化钠(60%矿物油分散液, 400mg, 9.91mmol)。搅拌 10 分钟后一次性加入 2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(2.81g, 7.62mmol)。1 小时后补加氢化钠(63mg, 1.5mmol)。继续搅拌 1 小时后, 用氯化铵水溶液终止反应并用乙醚萃取。将乙醚用盐水洗涤, 用硫酸钠干燥, 过滤然后浓缩。经硅胶色谱(二氯甲烷至 1%甲醇/二氯甲烷)得到黄色固体状(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯(3.90g, 82%)。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J=7.3Hz, 2H), 7.38-7.50 (m, 4H), 7.25-7.28 (m, 3H), 7.17 (br s, 2H), 6.86 (dd, J=8.0, 0.9Hz, 1H), 6.59 (s, 1H), 5.84-5.98 (m, 1H), 5.20-5.35 (m, 3H), 4.60 (s, 2H), 4.27-4.39 (m, 1H), 4.13 (d, J=13.4Hz, 1H), 3.90 (d, J=15.2Hz, 2H), 3.54 (br s, 2H), 3.00-3.05 (m, 1H), 2.84-2.95 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm。质谱: (ESI) m/z 623 $(M+H)^+$。

B: (R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-羟基甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈。

向(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸烯丙酯(3.90g, 6.27mmol)和吗啉(2.75mL, 31mmol)的二氯甲烷(60mL)溶液中加入$(PPh_3)_4Pd$(728mg, 0.630mmol)。搅拌 20 分钟后将反应液进行硅胶色谱(二氯甲烷至 2%甲醇/二氯甲烷)得到黄色油状的(R)-2-(二苯亚甲基-氨基)-4-[2-(叔丁基-二甲基-硅烷氧基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(3.0g, 89%)。质谱: (ESI) m/z 539 $(M+H)^+$。

向(R)-2-(二苯亚甲基-氨基)-4-[2-(叔丁基-二甲基-硅烷氧基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(3.0g, 5.57mmol)和 DIPEA (1.3mL, 7.24mmol)的二氯甲烷溶液中于 0℃下加入 6-氯-苯并[b]噻吩-2-磺酰氯(1.50g, 5.57mmol)。将反应液升温至室温 16 小时然后浓缩。经硅胶色谱(己烷至 2:1 己烷/EtOAc)得到 3.29g (76%)黄色固体状的(R)-2-(二苯亚甲基-氨基)-4-[2-(叔丁基-二甲基-硅烷氧基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-1-基甲基]-苯甲腈。质谱: (ESI) m/z 769 $(M+H)^+$。

向(R)-2-(二苯亚甲基-氨基)-4-[2-(叔丁基-二甲基-硅烷氧基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(3.16g, 4.11mmol)的 THF (20mL)溶液中于 0℃下加入 TBAF (5.4mL 1M 的 THF 溶液, 5.4mmol)。15 分钟后反应完成, 经硅胶色谱(二氯甲烷至 2%甲醇/二氯甲烷)得到 2.42g (90%)黄色泡沫状(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-羟基甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈。^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.87 (m, 1H), 7.82 (d, J =2.9Hz, 1H), 7.72 (d, J=7.3Hz, 2H), 7.37-7.51 (m, 6H), 7.09-7.23 (m, 5H), 6.81 (dd, J=7.9, 1.5Hz, 1H), 6.55 (d, J=1.3Hz, 1H), 4.98 (d, J=15.1Hz, 1H), 4.20 (d, J=16.6Hz, 1H), 4.03 (d, J=15.1Hz, 1H), 3.94 (d, J=12.3Hz, 1H), 3.59-3.72 (m, 2H), 3.51 (d, J=16.7Hz, 1H), 3.12-3.19 (m, 1H), 2.65 (dd, J =12.4, 3.17Hz, 1H), 2.23 (t, J=5.4Hz, 1H) ppm。质谱: (ESI) m/z 655 $(M+H)^+$。

C: (S)-2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-6-(4-吡咯烷-1-基哌啶-1-基甲基)-哌嗪-1-基甲基]-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-羟基甲基-6-氧代-哌嗪-1-基甲基]-苯甲腈(1.3g, 2.0mmol)的二氯甲烷(20mL)溶液中加入 Dess-Martin Periodinane(1.77g, 4.1mmol)。搅拌 30 分钟后, 将反应液进行硅胶色谱(二氯甲烷至 1%

甲醇/二氯甲烷)得到 975mg(75%)黄色固体状(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲酰基-6-氧代-哌嗪-1-基甲基]-苯甲腈。^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.25 (dd, J=7.6, 1.5Hz, 2H), 7.66-8.01 (m, 8H), 7.11-7.48 (m, 5H), 6.76 (dd, J=7.9, 1.4Hz, 1H), 6.51 (d, J=1.2Hz, 1H), 5.20 (d, J=15.1Hz, 1H), 4.17-4.28 (m, 2H), 3.84 (d, J=15.1Hz, 1H), 3.40-3.52 (m, 2H), 2.82 (dd, J=12.8, 4.0Hz, 1H) ppm。

向(R)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-甲酰基-6-氧代-哌嗪-1-基甲基]-苯甲腈(440mg, 0.674mmol)、4-(1-吡咯烷基)-哌啶(422mg, 2.73mmol)和 4Å 分子筛(725mg)的 1,2-二氯乙烷(10mL)溶液中加入 $NaBH(OAc)_3$ (432mg, 2.04mmol)。搅拌 16 小时后, 滤除分子筛并用二氯甲烷洗涤。然后将滤液依次用氯化铵水溶液和盐水洗涤, 用硫酸钠干燥, 过滤然后浓缩, 得到 289mg(54%)黄色固体状(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-1-基甲基]-苯甲腈。质谱: (ESI) m/z 791 $(M+H)^+$。

向(S)-2-(二苯亚甲基-氨基)-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-1-基甲基]-苯甲腈(289mg, 0.365mmol)在甲醇(4mL)和 THF(2mL)混合物中的溶液中于 0℃下加入浓盐酸(3 滴)。搅拌 20 分钟后, 加入碳酸氢钠并将反应液浓缩至干。将残余物进行硅胶色谱(二氯甲烷至5%甲醇/二氯甲烷)得到 96mg(42%)白色固体状(S)-2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-1-基甲基]-苯甲腈。^{1}H NMR (300MHz, $CDCl_3$) δ 7.79-7.87 (m, 3H), 7.43 (dd, J=8.6, 1.8Hz, 1H), 7.21 (d, J=8.0Hz, 1H), 6.66 (s, 1H), 6.33-6.40 (m, 1H), 5.14 (d, J=15.1Hz, 1H), 4.24 (d, J=16.1Hz, 1H), 3.94-4.09 (m, 2H), 3.73 (br s, 1H), 3.54-3.69 (m, 2H), 3.48 (d, J=16.6Hz, 1H), 3.30-3.38 (m, 2H), 2.72-3.06 (m, 5H), 2.64-2.70 (m, 1H), 2.19-2.32 (m, 2H), 1.97-2.15 (m, 8H) ppm。

质谱：(ESI) m/z 627 $(M+H)^+$。

D：(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-2-酮。

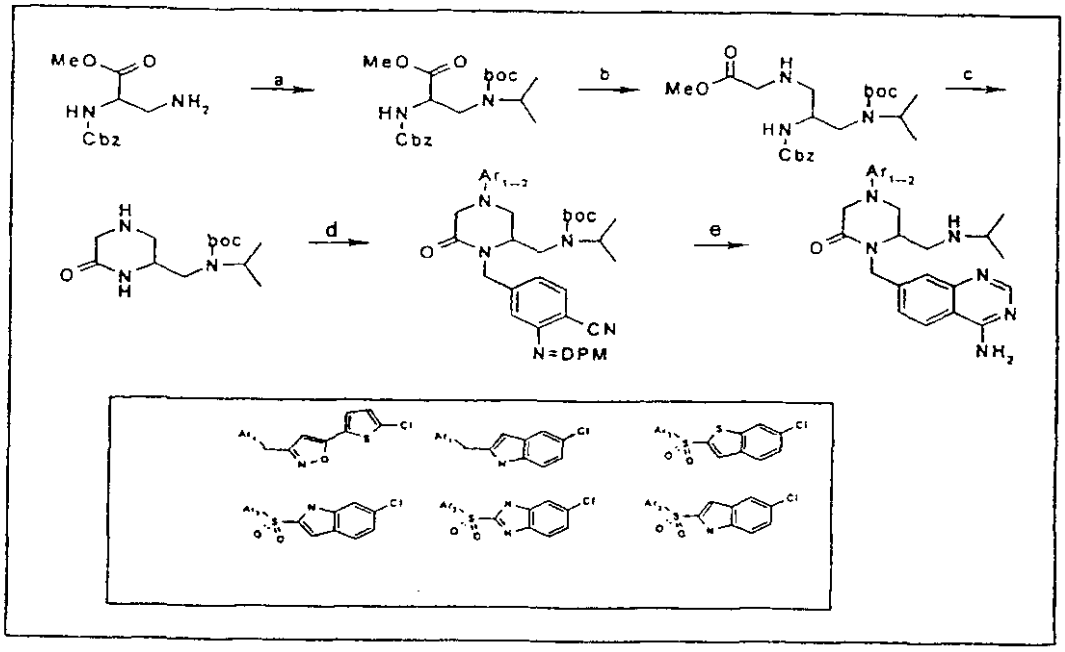
将(S)-2-氨基-4-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-氧代-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-1-基甲基]-苯甲腈(96mg, 0.153mmol)、HOAc (88μL, 1.53mmol)和 1,3,5-三嗪(143mg, 1.76mmol)在无水乙醇(6mL)中的混合物回流过夜。将粗产物通过 RP-HPLC 纯化，用 10%乙腈/水(0.1% TFA)至 80%乙腈/水(0.1% TFA)进行梯度洗脱，合并适当的产物馏分然后冷冻干燥得到 106mg (90%)白色固体状(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-2-酮的 TFA 盐。^1H NMR (300 MHz, CD_3OD) δ 8.61 (s, 1H), 8.24 (d, J=8.6Hz, 1H), 8.09 (d, J=1.9Hz, 1H), 7.97-8.05 (m, 2H), 7.62 (dd, J=8.6, 1.4Hz, 1H), 7.49-7.57 (m, 2H), 5.14 (d, J=16.5Hz, 1H), 4.60 (d, J=16.4Hz, 1H), 4.17-4.32 (m, 2H), 3.70-3.76 (m, 1H), 3.57-3.67 (m, 3H), 3.09-3.18 (m, 5H), 2.94-3.05 (m, 2H), 2.75-2.79 (m, 1H), 2.33-2.48 (m, 2H) ppm。质谱：(ESI) m/z 654 $(M+H)^+$。

按照上述方法，用适当的胺和 6-氯-苯并[b]噻吩-2-磺酰氯可以制得如下化合物

实施例	化合物名称	m/z(M+H)
1472	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[([1,3]二氧戊环-2-基甲基)-甲基-氨基)-甲基]-哌嗪-2-酮	617
1473	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(4-吡咯烷-1-基-哌啶-1-基甲基)-哌嗪-2-酮	654

1474	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[(2-异丙氧基-乙基氨基-甲基)-哌嗪-2-酮	603
1475	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[(环戊基-甲基-氨基)-甲基]-哌嗪-2-酮	599

反应方案 6 C(6)-异丙基取代的抑制剂的合成方案



试剂：(a) 1. 丙酮，$NaBH_3CN$，甲醇；2. Boc_2O，DMAP，THF；(b) 1. "$CaBH_4$"，乙醇；2. $(COCl)_2$，DMSO，Et_3N，CH_2Cl_2，-78℃；3. Gly-OMe.HCl，$NaBH_3CN$，甲醇；(c) H_2，甲醇，10% Pd/C；(d) 1. Alloc-Cl，Et_3N，CH_2Cl_2；2. 氢化钠，2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈，THF；3. $Pd(PPh_3)_4$，吗啉，二氯甲烷；4. 磺酰氯/芳基溴化物，Et_3N，二氯甲烷；(e) 1. 浓盐酸，甲醇；2. 1,3,5-三嗪，AcOH，乙醇，回流。

实施例 1476

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基氨基甲基)哌嗪-2-酮

A: (S)-3-氨基-2-苄氧羰基氨基-丙酸甲酯盐酸盐。

在0℃下，将亚硫酰氯(4.48mL, 61.34mmol)小心地加入到无水甲醇(50mL)中。5分钟后，加入3-氨基-2-苄氧羰基氨基-丙酸(14.6g, 61.34mmol)。将该多相混合物升温至室温(变成均相)，然后加热至回流2.5小时。将冷却的混合物浓缩然后真空干燥得到16g (90%)白色固体状(S)-3-氨基-2-苄氧羰基氨基-丙酸甲酯盐酸盐，其不经纯化直接使用。^{1}H NMR (300MHz, DMSO-d_6) ↗ 3.08 (m, 1H), 3.20 (m, 1H), 3.65 (s, 3H) 4.42 (m, 1H), 5.05 (s, 2H), 7.3 (br. s, 5H), 7.89 (d, J=8.3Hz, 1H), 8.20 (br. s, 2H) ppm。质谱: (ESI) m/z 253 $(M+H)^+$。

B: (S)-2-苄氧羰基氨基-3-异丙基氨基-丙酸甲酯。

向(S)-3-氨基-2-苄氧羰基氨基-丙酸甲酯盐酸盐(5g, 17.33mmol)的无水甲醇(50mL)溶液中于0℃加入丙酮(1.15mL, 15.6mmol)，随后加入氰基硼氢化钠(26mL, 1.0M/THF, 26mmol)。将混合物室温搅拌4小时，然后加入丙酮(0.5mL, 13mmol)并将混合物继续搅拌16小时。将混合物浓缩至干然后在碳酸氢钠(200mL)水溶液和EtOAc(200mL)之间进行分配。水层用EtOAc (2x100mL)萃取，将合并的有机相用盐水(100mL)洗涤，用硫酸钠干燥，过滤然后浓缩得到灰色油状物。

将粗产物通过快速硅胶色谱纯化(二氯甲烷→1%甲醇/二氯甲烷)得到2.96g (58%)无色油状(S)-2-苄氧羰基氨基-3-异丙基氨基-丙酸甲酯。^{1}H NMR (300 MHz, $CDCl_3$) ↗ 0.99 (d, J=6.3Hz, 6H), 1.15 (m, 1H), 2.75 (m, 1H), 2.91 (dd, J=12.5, 4.5Hz, 1H), 3.03 (dd, J=12.5, 4.5Hz, 1H), 3.70 (s, 3H), 4.40 (m, 1H), 5.10 (s, 2H), 5.70 (m, 1H), 7.30 (br, s, 5H) ppm。质谱: (ESI) m/z 294 $(M+H)^+$。

C: (S)-2-苄氧羰基氨基-3-(叔丁氧羰基-异丙基-氨基)-丙酸甲酯。

向(S)-2-苄氧羰基氨基-3-异丙基氨基-丙酸甲酯(2.96g, 10.07mmol)的无水 THF (50mL)溶液中于 0℃下加入 DMAP (100mg), 随后加入 Boc-酐(2.42g, 11.07mmol)。将溶液在室温下搅拌 16 小时然后浓缩至干。将粗产物通过快速硅胶色谱纯化(二氯甲烷→1%甲醇/二氯甲烷→2%→5%)得到 5.0g(65%)无色油状(S)-2-苄氧羰基氨基-3-(叔丁氧羰基-异丙基-氨基)-丙酸甲酯。^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.16 (d, J=3.8Hz, 6H) 1.45 (s, 9H), 3.40 (m, 2H), 3.70 (s, 3H), 4.00 (m, 1H), 4.40 (br. s, 1H), 5.50 (s, 2H), 6.10 (br. s, 1H), 7.30 (br. s, 5H) ppm。质谱: (ESI) m/z 394 M^+。

D: (S)-[2-(叔丁氧羰基-异丙基-氨基)-1-羟基甲基-乙基]-氨基甲酸苄酯。

于-40℃下向搅拌中的新研磨的硼氢化钠(1.92g, 50.76mmol)的无水乙醇(100mL)悬浮液中加入氯化钙(2.82g, 25.38mmol)。将该多相混合物于-20℃搅拌 45 分钟, 然后通过移液管加入(S)-2-苄氧羰基氨基-3-(叔丁氧羰基-异丙基-氨基)-丙酸甲酯(5.0g, 12.69mmol)的无水乙醇(50mL)溶液。将混合物于-20℃搅拌 1 小时, 然后将用水(200mL)终止反应并用 2N 盐酸小心地酸化至大约 PH 3。将混合物用二氯甲烷(3x200mL)萃取, 将合并的有机相用盐水洗涤(200mL), 用硫酸钠干燥, 过滤然后浓缩得到无色油状物。

将粗产物通过快速硅胶色谱纯化(二氯甲烷→1%甲醇/二氯甲烷→2%→5%)得到 4.14g (95%)无色油状(S)-[2-(叔丁氧羰基-异丙基-氨基)-1-羟基甲基-乙基]-氨基甲酸苄酯。^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.19 (dd, J=18.7, 6.7Hz, 6H), 1.45 (s, 9H), 3.10 (m, 1H), 3.50 (m, 2H), 3.61 (m, 2H), 4.00 (m, 1H), 4.20 (m, 1H), 5.10 (s, 2H), 5.50 (m, 1H), 7.30 (br. s, 5H) ppm。质谱: (ESI) m/z 366 M^+。

E: (S)-[2-苄氧羰基氨基-3-(叔丁氧羰基-异丙基-氨基)-丙基氨基]-乙酸甲酯。

向草酰氯(1.18mL, 13.57mmol)的无水二氯甲烷(40mL)溶液中于-78℃滴加 DMSO (1.93mL, 27.14mmol)。将该溶液于-78℃搅拌 10 分钟，然后通过移液管加入(S)-[2-(叔丁氧羰基-异丙基-氨基)-1-羟基甲基-乙基]-氨基甲酸苄酯(4.14g, 11.31mmol)的无水二氯甲烷(80mL)溶液。将反应液于-78℃搅拌 1 小时，然后加入三乙胺(7.88mL, 56.55mmol)并将反应液在 0℃下搅拌 10 分钟。将该混合物在硫酸氢钠(200mL)和二氯甲烷(200mL)之间进行分配，水层用二氯甲烷(2x100mL)萃取。将合并的有机相用盐水(100mL)洗涤，用硫酸钠干燥，过滤然后浓缩得到黄色油状(S)-[2-(叔丁氧羰基-异丙基-氨基)-1-甲酰基-乙基]-氨基甲酸苄酯，其不经纯化直接使用。

向(S)-[2-(叔丁氧羰基-异丙基-氨基)-1-甲酰基-乙基]-氨基甲酸苄酯(11.31mmol)的无水甲醇(80mL)溶液中于 0℃下加入甘氨酸甲酯盐酸盐(5.68g, 45.24mmol)。将溶液在 0℃下搅拌 10 分钟，然后加入氰基硼氢化钠(16.97mL, 1.0M/THF, 16.97mmol)，将该多相混合物升温至室温并搅拌 16 小时。将混合物浓缩至干，然后在碳酸氢钠(100mL)水溶液和 EtOAc (100mL)之间进行分配。将水层用 EtOAc(3x100mL)萃取，合并的有机相用盐水(100mL)洗涤，用硫酸钠干燥，过滤然后浓缩得到 4.75g (96%)无色油状(S)-[2-苄氧羰基氨基-3-(叔丁氧羰基-异丙基-氨基)-丙基氨基]-乙酸甲酯，其不经进一步的纯化直接用于随后的步骤。质谱: (ESI) m/z 438 $(M+H)^+$。

F: (S)-异丙基-(6-氧代-哌嗪-2-基甲基)-氨基甲酸叔丁酯。

将(S)-[2-苄氧羰基氨基-3-(叔丁氧羰基-异丙基-氨基)-丙基氨基]-乙酸甲酯(2.58g, 5.9mmol)的甲醇(150mL)溶液置于大的 Parr 瓶中并用 10%钯/碳(300mg)在氮气氛下进行处理。将混合物于 40 psi 的压力下氢化5小时然后用硅藻土过滤。将滤液浓缩得到 1.60g (100%)灰色油状的(S)-异丙基-(6-氧代-哌嗪-2-基甲基)-氨基甲酸叔丁

酯，其不经进一步纯化直接使用。质谱：(ESI) m/z 272 $(M+H)^+$。

G：(S)-3-[(叔丁氧羰基-异丙基-氨基)-甲基]-5-氧代-哌嗪-1-甲酸烯丙酯。

向(S)-异丙基-(6-氧代-哌嗪-2-基甲基)-氨基甲酸叔丁酯(1.6g, 5.9mmol)的无水二氯甲烷(100mL)溶液中在 0℃下依次加入三乙胺(1.23mL, 8.85mmol)和氯甲酸烯丙酯(0.75mL, 7.08mmol)。将溶液室温搅拌 16 小时，然后在碳酸氢钠(100mL)和二氯甲烷(100mL)之间进行分配。水层用二氯甲烷(2x100mL)萃取，将合并的有机相用盐水(50mL)洗涤，用硫酸钠干燥，过滤然后浓缩。将粗产物用快速硅胶色谱纯化并真空干燥得到 1.51g (72%)无色油状的(S)-3-[(叔丁氧羰基-异丙基-氨基)-甲基]-5-氧代-哌嗪-1-甲酸烯丙酯。^{1}H NMR (300 MHz, $CDCl_3$) →1.12 (dd, J=6.8, 3.7Hz, 6H), 1.45 (s, 9H), 3.10 (m, 1H), 3.20 (m, 2H), 3.70 (m, 2H), 3.85 (m, 2H), 4.11 (ABq, J=47.2, 18.2Hz, 2H), 4.62 (d, J=5.6Hz, 2H), 5.30 (m, 2H), 5.90 (m, 1H) ppm。质谱：(ESI) m/z 356 $(M+H)^+$。

H：(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-[(叔丁氧羰基-异丙基-氨基)-甲基]-5-氧代-哌嗪-1-甲酸烯丙酯。

向(S)-3-[(叔丁氧羰基-异丙基-氨基)-甲基]-5-氧代-哌嗪-1-甲酸烯丙酯(1.51g, 4.25mmol)在无水 THF(100mL)和无水 DMF(10mL)的混合物中的溶液中于 0℃下加入氢化钠(0.2g, 60%油分散液, 5.1mmol)。将混合物在 0℃下搅拌 30 分钟直至停止放出气体，然后加入 2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(1.75g, 4.68mmol)。将棕色的混合物在 0-10℃下搅拌 3 小时，然后在饱和氯化铵水溶液(200mL)和 EtOAc(200mL)之间进行分配。将水层用 EtOAc(2x100mL)萃取，合并后的有机相用盐水(100mL)洗涤，用硫酸钠干燥，过滤然后浓缩得到棕色油状物。将粗产物用快速硅胶色谱纯化得到 2.76g (100%)浅黄色油状的(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-[(叔

丁氧羰基-异丙基-氨基)-甲基]-5-氧代-哌嗪-1-甲酸烯丙酯。^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.15 (m, 6H), 1.45 (s, 9H), 2.65 (m, 1H), 3.00 (m, 1H), 3.35 (m, 2H), 3.50 (m, 1H), 3.90 (m, 9H), 4.32 (d, J=18.5Hz, 1H), 4.63 (d, J=5.5Hz, 2H), 5.30 (m, 2H), 5.95 (m, 1H), 6.80 (br. s, 1H), 7.0 (br. s, 1H), 7.20 (br. s, 5H), 7.40 (br. s, 5H), 7.80 (m, 1H) ppm。质谱: (ESI) m/z 650 $(M+H)^+$。

I: (S)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯。

向(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-[(叔丁氧羰基-异丙基-氨基)-甲基]-5-氧代-哌嗪-1-甲酸烯丙酯(2.76g, 4.28mmol)的无水二氯甲烷(250mL)溶液中加入吗啉(1.87mL, 21.4mmol), 随后加入四(三苯基膦)钯(495mg, 0.43mmol)。将该黄色的溶液室温搅拌1小时, 然后浓缩到硅胶上, 经快速柱色谱处理(二氯甲烷→1%甲醇/二氯甲烷→2%→3%→5%)得到 1.9g (79%)黄色泡沫状(S)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯。^{1}H NMR (300 MHz, $CDCl_3$) ↑ 1.08 (t, J=6.8Hz, 6H), 1.45 (s, 9H), 2.42 (m, 1H), 2.69 (m, 1H), 2.90 (m, 2H), 3.18 (m, 1H), 3.57 (d, J=9.7Hz, 2H), 3.71 (m, 1H), 3.90 (br.s, 1H), 4.04 (d, J=15.2Hz, 1H), 5.07 (d, J=15.2Hz, 1H), 6.75 (br.s, 1H), 6.90 (m, 1H), 7.15-7.45 (m, 10H), 7.75 (m, 1H) ppm。质谱: (ESI) m/z 566 $(M+H)^+$。

J: (S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯。

向(S)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-2-基甲基)-异丙基-氨基甲酸叔丁酯(1g, 1.77mmol)的无水二氯甲烷(50mL)溶液中于0℃下加入三乙胺(0.37mL, 2.66mmol), 随后加入6-

氯-苯并[b]噻吩-2-磺酰氯(0.57g，2.12mmol)。将溶液在0℃下搅拌2小时，室温搅拌1小时，然后在水(100mL)和二氯甲烷(100mL)之间进行分配。将水层用二氯甲烷(2x100mL)萃取，合并后的有机相用盐水(100mL)洗涤，用硫酸钠干燥，过滤然后浓缩得到1.41g (100%)黄色泡沫状(S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯，其不经进一步纯化直接使用。质谱：(ESI) m/z 796 $(M+H)^+$。

按照上述方法，用适当的磺酰氯或芳基溴化物制备如下化合物。

实施例	名称	m/z $(M+H)^+$
1477	(S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(5-氯-1H-吲哚-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯	879
1478	(S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-1H-吲哚-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯	879
1479	(S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯	780
1480	(S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(5-氯-1H-吲哚-2-基-甲基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯	829
1481	(S)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯	763

实施例1482：

(S)-[1-(3-氨基-4-氰基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-

6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯

向(S)-[1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯(1.41g, 1.77mmol)在甲醇(20mL)和 THF(50mL)的混合物中的溶液中于 0℃下加入浓盐酸(10 滴)。将混合物在 0℃下搅拌 1 小时然后浓缩至干, 经快速硅胶柱色谱处理(二氯甲烷→1%甲醇/二氯甲烷→5%)得到 1.11g (100%)黄色胶状的(S)-[1-(3-氨基-4-氰基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯。质谱: (ESI) m/z 632 $(M+H)^+$。

实施例 1483:

(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯

向(S)-[1-(3-氨基-4-氰基-苄基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯(1.11g, 1.77mmol)的无水乙醇(50mL)悬浮液中加入 1,3,5-三嗪(1.43g, 17.7mmol)和冰乙酸(1.01mL, 17.7mmol)。将混合物加热至回流(变为均相)并搅拌 16 小时。将冷却的混合物浓缩至干, 经快速硅胶柱色谱(二氯甲烷→1%甲醇/二氯甲烷→2%→5%)得到 0.8g (68%)黄色泡沫状(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯。^1H NMR (300 MHz, $CDCl_3$) ↗ 1.23 (t, J=6.6Hz, 6H), 1.45 (s, 9H), 2.80 (br s, 1H), 3.30 (m, 1H), 3.85 (m, 3H), 4.28 (d, J=16.7Hz, 1H), 5.39 (d, J=15.4Hz, 1H), 7.45 (dd, J=8.6, 1.9Hz, 2H), 7.62 (d, J=8.4Hz, 2H), 7.84 (m, 3H), 8.40 (s, 1H) ppm。质谱: (ESI) m/z 659 $(M+H)^+$。

实施例 1484

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰

基)-6-异丙基氨基甲基)-哌嗪-2-酮

向(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲基]-异丙基-氨基甲酸叔丁酯(0.8g, 1.22mmol)的无水二氯甲烷溶液中于0℃下加入三氟乙酸(5mL)。将溶液密封搅拌16小时然后浓缩至干，通过反相HPLC在2″ Dynamax C18柱(10→80% ACN/水/0.1% TFA)上纯化。将适当的馏分合并然后冷冻干燥得到0.58g (86%)白色固体状(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-异丙基氨基甲基)-哌嗪-2-酮的TFA盐。^{1}H NMR (300 MHz, DMSO-d_6) ↗1.22 (dd, J=6.5, 2.1Hz, 6H), 3.22 (m, 3H), 3.72 (m, 3H), 4.01 (s, 1H), 4.07 (d, J=15.6Hz, 1H), 4.38 (d, J=16.7Hz, 1H), 5.12 (d, J=16.7Hz, 1H), 7.58 (s, 1H), 7.59 (s, 1H), 7.60 (dd, J=8.6, 1.9Hz, 1H), 8.09 (d, J=8.6Hz, 1H), 8.19 (s, 1H), 8.26 (d, J=8.6Hz, 1H), 8.36 (s, 1H), 8.50 (br.s, 1H), 8.72, (s, 1H), 9.49 (br.s, 2H) ppm。质谱: (ESI) m/z 559 $(M+H)^+$。

以下化合物按照上述方法制备:

实施例1485

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-1H-苯并咪唑-2-磺酰基)-6-(异丙基氨基-甲基)-哌嗪-2-酮

^{1}HNMR (300 MHz, DMSO-d_6) ↗1.20 (d, J=6.41Hz, 6H), 3.45 (m, 5H), 3.76 (m, 1H), 3.93 (d, J=16.5Hz, 1H), 4.15 (m, 1H), 4.39 (d, J=16.6Hz, 1H), 5.12 (d, J=16.6Hz, 1H), 7.43 (d, J=6.6Hz, 1H), 7.56 (s, 2H), 7.79 (m, 2H), 8.28 (d, J=8.59Hz, 1H), 8.45 (m, 1H), 8.70 (s, 2H), 9.52 (br.s, 2H) ppm。质谱: (ESI) m/z 542 (M^+)。

实施例1486

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-磺酰基)-6-

(异丙基氨基-甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) ↗1.20 (m, 6H), 3.15 (m, 1H), 3.32 (m, 1H), 3.50 (m, 3H), 3.75 (m, 1H), 3.92 (d, J=13.1Hz, 1H), 4.10 (d, J=16.3Hz, 1H), 4.36 (d, J=16.8Hz, 1H), 5.12 (d, J==16.8Hz, 1H), 7.09 (s, 1H), 7.35 (dd, J=9.1, 2.1Hz, 1H), 7.54 (m, 3H), 7.80 (s, 1H), 8.26 (d, J=8.6Hz, 1H), 8.47 (m, 1H), 8.64 (m, 1H), 8.72 (br s, 1H), 12.58 (s, 1H) ppm。质谱: (ESI) m/z 542 $(M+H)^+$。

实施例 1487

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-(6-氯-1H-吲哚-2-磺酰基)-6-异丙基氨基-甲基)-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) ↗1.20 (m, 6H), 3.38 (m, 5H), 3.72 (m, 1H), 3.90 (d, J=13.0Hz, 1H), 4.10 (d, J=16.2Hz, 1H), 4.36 (d, J=16.2Hz, 1H), 5.12 (d, J=17.0Hz, 1H), 7.20 (m, 2H), 7.51 (m, 3H), 7.75 (d, J=8.6Hz, 1H), 8.25 (d, J=8.6Hz, 1H), 8.45 (m, 1H), 8.59 (m, 1H), 8.71 (br s, 1H), 12.53 (s, 1H) ppm。质谱: (ESI) m/z 542 $(M+H)^+$。

实施例 1488

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-(异丙基氨基-甲基)-哌嗪-2-酮

^{1}H NMR (500 MHz, DMSO-d_6) ↗1.15 (dd, J=15.93, 6.59Hz, 6H), 2.70 (dd, J=12.63, 3.29Hz, 1H), 3.06 ((m, 2H), 3.20 (d, J=12.09Hz, 1H), 3.28 (m, 1H), 3.47 (d, J=17.20Hz, 1H), 3.57 (m, 1H), 3.59 (m, 2H), 4.37 (d, J=16.48 Hz, 1H), 5.15 (d, J=16.48Hz, 1H), 7.04 (dd, J=8.51, 1.92Hz, 1H), 7.33 (d, J =8.79Hz, 1H), 7.50 (d, J=2.2Hz, 1H), 7.55 (s, 1H), 7.60 (dd, J=8.78, 1.10Hz, 1H), 8.36 (d, J=8.24Hz, 3H), 8.78 (s, 1H),

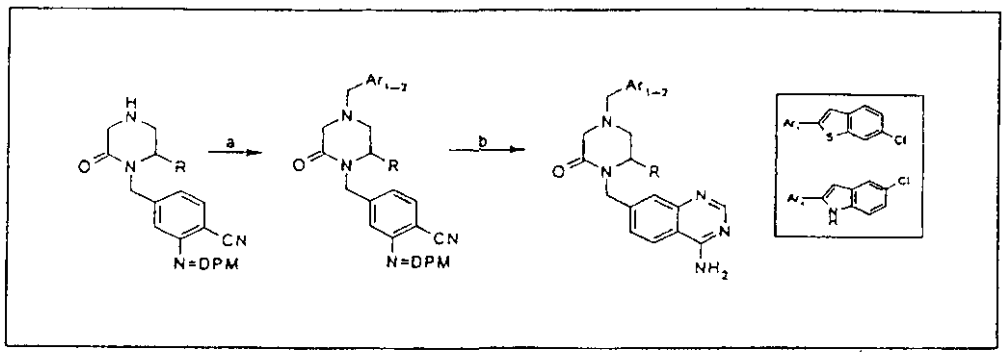
9.70 (m, 2H) ppm。质谱：(ESI) m/z 492 $(M+H)^+$。

实施例 1489

(S)-1-(4-氨基喹唑啉-7-基甲基)-4-[5-(5-氯噻吩-2-基)异噁唑-3-基甲基]-6-(异丙基氨基-甲基)-哌嗪-2-酮

^1H NMR (600 MHz, DMSO-d_6) ↗ 1.23 (dd, J=10.0, 6.50Hz, 6H), 2.70 (d, J=10.4Hz, 1H), 3.20 (m, 3H), 3.40 (m, 1H), 3.60 (m, 3H), 3.84 (dd, J=33.9, 14.5Hz, 2H), 4.41 (d, J=16.7Hz, 1H), 5.21 (d, J=16.7Hz, 1H), 6.95 (s, 1H), 7.31 (d, J=4.0Hz, 1H), 7.62 (m, 3H), 8.40 (m, 3H), 8.85 (s, 1H), 9.81 (br s, 1H) ppm。质谱：(ESI) m/z 526 $(M+H)^+$。

反应方案 7 C(6)-烷基氨基甲基取代的烷基抑制剂的合成方案



试剂：(a) 芳基溴化物，碳酸钾，DMF。(b) 1. 浓盐酸，甲醇。2. 三嗪，乙酸，乙醇，回流。(c)TFA，二氯甲烷。

实施例 1490

(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基]-乙酸(RPR 257329A)

A: (S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-叔丁氧羰基甲基-5-氧代-哌嗪-1-基甲基}-5-氯-吲哚-1-甲酸叔丁酯。

向(S)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-6-氧代-哌嗪-

2-基}-乙酸叔丁酯(265mg, 0.52mmol)和碳酸钾(133mg, 0.96mmol)的乙腈(1mL)悬浮液中于0℃下加入2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯(253mg, 0.73mmol)。将反应液在16小时内升温至室温，然后将反应液在乙酸乙酯和水之间进行分配。将水层用乙酸乙酯萃取，合并的有机层用盐水洗涤，用硫酸钠干燥，过滤然后浓缩。经硅胶色谱(二氯甲烷→1%甲醇/二氯甲烷)得到 300mg (75%)黄色玻璃状的(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基]-3-叔丁氧羰基甲基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J=9.0Hz, 1H), 7.77 (d, J=6.5Hz, 2H), 7.38-7.47 (m, 4H), 7.23-7.29 (m, 4H), 7.17-7.21 (m, 3H), 6.84 (d, J=8.0Hz, 1H), 6.66 (s, 1H), 6.48 (s, 1H) 5.05 (d, J=15.5Hz, 1H), 3.97 (d, J=14.3Hz, 1H), 3.78-3.89 (m, 2H), 3.58 (d, J=16.3Hz, 1H), 3.41-3.49 (m, 2H), 2.99 (d, J=16.7Hz, 1H), 2.71-2.87 (m, 2H), 2.29-2.42 (m, 2H), 1.67 (s, 9H), 1.26 (s, 9H) ppm。质谱：(ESI) m/z 772 $(M+H)^+$。

B: (S)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-叔丁氧羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。

向(S)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-叔丁氧羰基甲基-5-氧代-哌嗪-1-基甲基}-5-氯-吲哚-1-甲酸叔丁酯(300mg, 0.388mmol)在甲醇(10mL)和 THF(2mL)的混合物中的溶液中于 0℃下加入浓盐酸(7 滴)。搅拌 1 小时后，停止反应，经快速硅胶柱色谱处理(二氯甲烷→8%甲醇/二氯甲烷)得到 170mg (72%)黄色胶状(S)-2-[4-(3-氨基-4-氰基-苄基)-3-叔丁氧羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。质谱：(ESI) m/z 608 $(M+H)^+$。

将(S)-2-[4-(3-氨基-4-氰基-苄基)-3-叔丁氧羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(170mg, 0.28mmol)、冰乙酸(160uL, 2.80mmol)和 1,3,5-三嗪(225mg, 2.80mmol)的无水乙醇(4mL)溶液加热至回流 16 小时。将混合物浓缩至干，经快速硅胶柱色

谱处理(二氯甲烷→8%甲醇/二氯甲烷)得到 101mg (58%)米黄色玻璃状(S)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-叔丁氧羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。^{1}H NMR (300 MHz, CD_3OD) δ 8.36 (s, 1H), 8.11 (d, J=8.6 Hz, 1H), 7.97 (d, J=9.0 Hz, 1H), 7.46-7.56 (m, 2H), 7.42 (d, J=7.2 Hz, 1H), 7.22 (dd, J =9.0, 2.2 Hz, 1H), 6.60 (s, 1H), 5.21 (d, J =15.7 Hz, 1H), 4.34 (d, J =15.6 Hz, 1H), 4.18 (d, J =13.6 Hz, 1H), 3.58-3.73 (m, 2H), 3.17 (d, J =16.8 Hz, 1H), 2.73-2.89 (m, 2H), 2.48-2.61 (m, 2H), 1.70 (s, 9H), 1.08 (s, 9H) ppm。质谱: (ESI) m/z 635 $(M+H)^+$。

C: (S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基]-乙酸(RPR 257329A)。

将(S)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-叔丁氧羰基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(101mg, 0.159mmol)的二氯甲烷(5mL)和 TFA(1mL)溶液搅拌 16 小时。将该混合物浓缩至干并将粗产物用 RP-HPLC 纯化, 用 10%乙腈/水(0.1%TFA)至 80%乙腈/水(0.1%TFA)进行梯度洗脱。将适当的产物馏分合并然后冷冻干燥得到 34mg (36%)白色固体状(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪基 2-基]-乙酸的 TFA 盐。^{1}H NMR (300 MHz, CD_3OD) ↗10.68 (s, 1H), 8.64 (s, 1H), 8.27 (d, J=8.5Hz, 1H), 7.66 (dd, J=8.5, 1.5Hz, 1H), 7.57 (s, 1H), 7.43 (d, J=2.0Hz, 1H), 7.29 (d, J=8.6Hz, 1H), 7.02 (dd, J=8.6, 2.0Hz, 1H), 6.34 (s, 1H), 5.18 (d, J=16.3Hz, 1H), 4.51 (d, J=16.3Hz, 1H), 3.71-3.89 (m, 3H), 3.56 (d, J=17.8Hz, 1H), 3.02-3.17 (m, 3H), 2.61-2.75 (m, 2H) ppm。质谱: (ESI) m/z 479 $(M+H)^+$。

以下化合物按照上述方法制备:

实施例 1491

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-异丁基-哌嗪-2-酮

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (s, 1H); 8.33 (s, 1H); 8.12 (d, J=8.5Hz, 1H); 7.72 (bs, 2H); 7.44 (d, J=15.6Hz, 1H); 7.25-7.32 (m, 2H); 7.00 (dd, J=8.6, 2.0Hz, 1H); 6.29 (s, 1H); 5.05 (d, J=15.4Hz, 1H); 4.23 (d, J=15.7Hz, 1H); 3.81 (d, J=13.3Hz, 1H); 3.57 (d, J=13.8Hz, 1H); 3.40 (d, J =16.2Hz, 1H); 3.21-3.34 (m, 1H); 3.10-3.18 (m, 1H); 3.04 (d, J=16.5Hz, 1H); 2.66-2.74 (m, 1H); 2.31-2.39 (m, 1H); 1.22-1.30 (m, 1H); 1.06-1.19 (m, 1H); 0.70 (d, J=6.5Hz, 3H); 0.62 (d, J=6.3Hz, 3H) ppm。质谱: (ESI) m/z 477 $(M+H)^+$。

实施例 1492

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-异丁基-哌嗪-2-酮

^{1}H NMR (DMSO-d_6) ↗ 11.30 (s, 1H), 9.74 (s, 2H), 8.79 (s, 1H), 8.34 (d, J =8.6Hz, 1H), 7.58 (m, 3H), 7.33 (d, J=8.6Hz, 1H), 7.03 (dd, J=8.6, 2.1Hz, 1H), 6.35 (s, 1H), 5.02 (d, J=16.5Hz, 1H), 4.38 (d, J=16.5Hz, 1H), 3.95 (br d, 1H), 3.82 (d, 1H), 3.60 (d, 1H), 3.40 (d, 1H), 3.29 (br d, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 1.90 (m, 1H), 1.29 (m, 2H), 0.71 (dd, J=21.1, 6.0Hz, 6H) ppm。质谱: (ESI) m/z 477 $(M+H)^+$。

实施例 1493

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-6-异丁基-哌嗪-2-酮

^{1}H NMR (300 MHz, CD_3OD) ↑ 8.65 (s, 1H), 8.29 (d, J=8.6Hz, 1H), 7.83 (d, J=1.9Hz, 1H), 7.70 (m, 2H), 7.58 (s, 1H), 7.30 (m,

2H), 5.11 (d, J=16.4Hz, 1H), 4.52 (d, J=16.4Hz, 1H), 4.02 (dd, J=13.9, 0.86Hz, 1H), 3.86 (d, J=14.1 Hz, 1H), 3.63 (d, J=16.7Hz, 1H), 3.40 (m, 1H), 3.19 (d, J=16.8Hz, 1H), 3.0 (m, 1H), 2.60 (m, 1H), 2.08 (m, 1H), 1.32 (m, 2H), 0.80 (dd, J=13.7, 5.9Hz, 6H) ppm。质谱: (ESI) m/z 494 $(M+H)^+$。

实施例 1494

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-6-异丁基-哌嗪-2-酮

^1H NMR (300 MHz, CD_3OD) δ 8.65 (s, 1H), 8.28 (d, J=8.6Hz, 1H), 7.84 (d, J=1.8Hz, 1H), 7.66 (dd, J=8.7, 1.6Hz, 1H), 7.59 (s, 1H), 7.32 (dd, J=8.5, 1.9Hz, 1H), 7.29 (s, 1H), 5.12 (d, J=16.4Hz, 1H), 4.53(d, J=16.4Hz, 1H), 4.04(d, J=14.0Hz, 1H), 3.88(d, J=14.0Hz, 1H), 3.65 (d, J=16.7Hz, 1H), 3.40 (d, J=9.3Hz, 1H), 3.22 (d, J=16.7Hz, 1H), 3.00 (d, J=12.1Hz, 1H), 2.68 (m, 1H), 2.08 (m, 1H), 1.35 (m, 2H), 0.81 (dd, J=23.0, 5.9Hz, 6H) ppm。质谱: (ESI) m/z 494 $(M+H)^+$。

实施例 1494

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-甲氧基甲基-哌嗪-2-酮

^1H NMR (DMSO-d_6) δ 11.31 (s, 1H), 9.75 (d, J=5.5Hz, 2H), 8.79 (s, 1H), 8.34 (d, J=8.6Hz, 1H), 7.55 (m, 3H), 7.06 (d, J=1.9Hz, 1H), 7.03 (d, J=1.7Hz, 1H), 6.38 (s, 1H), 4.96 (d, J=16.6Hz, 1H), 4.61 (d, J=16.6Hz, 1H), 3.88 (q, J=13.9Hz, 2H), 3.40-3.62 (m, 4H), 3.28 (m, 1H), 3.07 (s, 3H), 3.01 (m, 1H), 2.72 (m, 1H) ppm。质谱: (ESI) m/z 465 $(M+H)^+$。

实施例 1495

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (DMSO-d_6) δ 11.31 (s, 1H), 9.75 (d, J=5.7Hz, 1H), 8.79 (s, 1H), 8.34 (d, J=8.6Hz, 1H), 7.55 (m, 3H), 7.35 (d, J=8.6Hz, 1H), 7.04 (dd, J=8.6, 2.1Hz, 1H), 6.38 (s, 1H), 4.95 (d, J=16.6Hz, 1H), 4.60 (d, J=16.6Hz, 1H), 3.88 (q, J=13.9Hz, 2H), 3.40-3.60 (m, 4H), 3.20 (m, 1H), 2.72 (m, 1H) ppm。质谱: (ESI) m/z 465 $(M+H)^+$。

实施例 1496

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-6-甲氧基甲基-哌嗪-2-酮

^{1}H NMR (300 MHz, CD_3OD) δ 11.10 (s, 1H), 8.28 (d, J=8.6Hz, 1H), 7.86 (d, J=1.9Hz, 1H), 7.71 (d, J=8.6Hz, 1H), 7.65 (dd, J=8.6, 1.6Hz, 1H), 7.58 (s, 1H), 7.32 (m, 2H), 5.07 (d, J=16.4Hz, 1H), 4.76 (d, J=16.4Hz, 1H), 3.97 (ABq, J=32.9, 14.6Hz, 2H), 3.55-3.70 (m, 4H), 3.19 (s, 3H), 3.10 (m, 2H), 2.72 (m, 1H) ppm。质谱: (ESI) m/z 481M^+。

实施例 1497

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-基甲基)-6-甲氧基甲基-哌嗪-2-酮

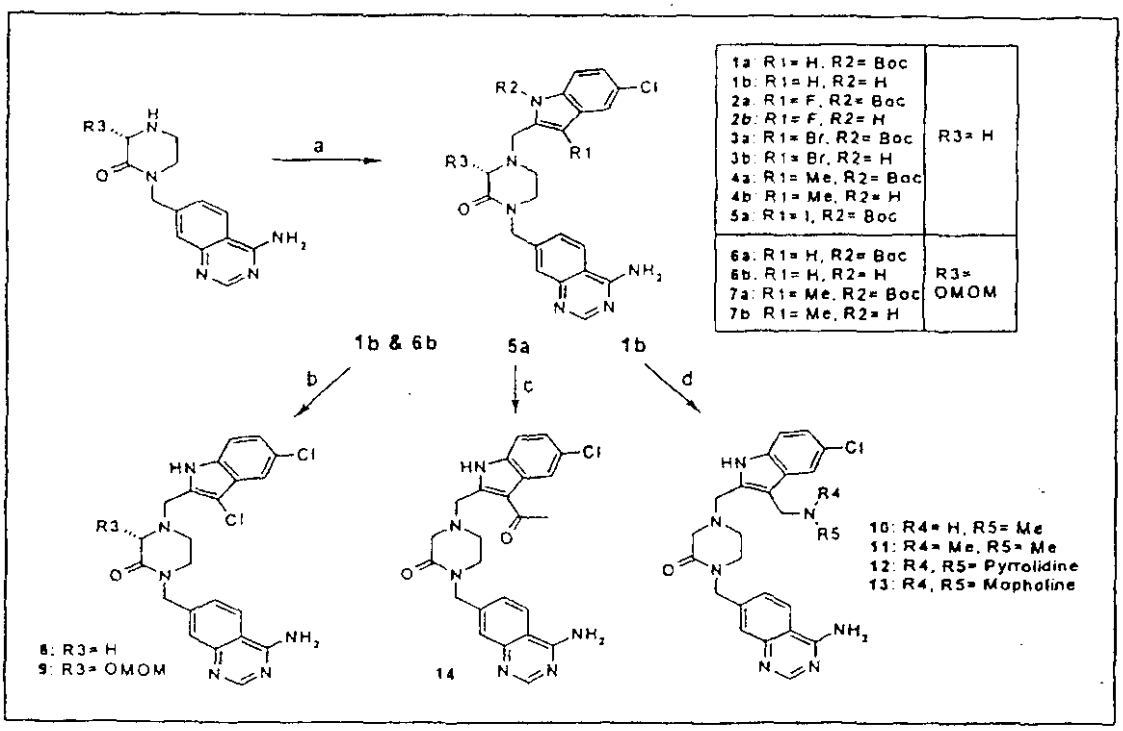
^{1}H NMR (300 MHz, CD_3OD) δ 8.65 (s, 1H), 8.28 (d, J=8.6Hz, 1H), 7.86 (d, J=1.9Hz, 1H), 7.71 (d, J=8.6Hz, 1H), 7.65 (dd, J=8.6, 1.6Hz, 1H), 7.58 (s, 1H), 7.32 (m, 2H), 5.07 (d, J=16.5Hz, 1H), 4.76 (d, J=16.5Hz, 1H), 3.99 (ABq, J=33.0, 14.1Hz, 2H), 3.58-3.70 (m, 4H), 3.19 (s, 3H), 3.15 (m, 2H), 2.76 (m, 1H) ppm。质谱: (ESI) m/z 482 $(M+H)^+$。

实施例 1498

(R/S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-甲酸

^{1}H NMR (300 MHz, CD_3OD) δ 8.63 (s, 1H), 8.25 (d, J=8.6Hz, 1H), 7.64 (dd, J=8.6, 1.5Hz, 1H), 7.57 (s, 1H), 7.43 (d, J=1.9Hz, 1H), 7.26 (d, J=8.6Hz, 1H), 7.01 (dd, J=8.6, 2.0Hz, 1H), 6.32 (s, 1H), 5.38 (d, J=16.4Hz, 1H), 4.28 (d, J=16.4Hz, 1H), 4.17-4.22 (m, 1H), 3.68-3.89 (m, 2H), 3.58 (d, J=16.9Hz, 1H), 3.47 (d, J=12.0Hz, 1H), 3.16 (d, J=16.7Hz, 1H), 2.73-2.80 (m, 1H) ppm。质谱: (ESI) m/z 465 $(M+H)^+$。

反应方案 8 C (3')-取代的吲哚基甲基抑制剂的合成方案



试剂: (a). 1. $ArCH_2Br$, K_2CO_3, DMF。2. (a→b) TFA, CH_2Cl_2。(b). NCS (c). 1. $Pd(PPh_3)_4$, CuI, TEA, TMSCCH, DMF。2. K_2CO_3 (d). 胺, 甲醛, 二氧六环/AcOH。

实施例 1499

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮

A: 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。

向 1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮(500mg, 1.94mmol)的 DMSO(15mL)溶液中加入碳酸钾(423mg, 3.01mmol), 随后加入 2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯(744mg, 2.16mmol)。搅拌 16 小时后, 将反应液在水和乙酸乙酯之间进行分配。将 EtOAc 层依次用水和盐水洗涤, 用硫酸钠干燥, 过滤然后浓缩。经硅胶色谱(二氯甲烷→8%甲醇/二氯甲烷)得到 924mg (92%)浅色易碎固体状的 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。^{1}H NMR (300MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.92 (d, J=8.9Hz, 1H), 7.76 (d, J=8.5Hz, 1H), 7.67 (d, J=1.0Hz, 1H), 7.40-7.47 (m, 2H), 7.19 (dd, J=8.9, 2.1Hz, 1H), 6.50 (s, 1H), 5.87 (br s, 2H), 4.75 (s, 2H), 3.94 (s, 2H), 3.37 (s, 2H), 3.30 (t, J=4.9Hz, 2H), 2.77 (t, J=5.6Hz, 2H), 1.64 (s, 9H) ppm。

B: 1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮(RPR 210312A)。

向 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(400mg, 0.76mmol)的二氯甲烷(10mL)溶液中加入 TFA(2mL)。搅拌 16 小时后, 经硅胶色谱处理(二氯甲烷→20%甲醇/二氯甲烷)得到 393mg (>100%)米黄色固体状 1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮。^{1}H NMR (300 MHz, DMSO-d_6) ↗ 11, 9.64 (br s, 2H), 8.77 (s, 1H), 8.35 (d, J=8.5Hz, 1H), 7.53-7.62 (m, 2H), 7.49 (d, J=2.0Hz, 1H), 7.31 (d, J=8.6Hz, 1H), 7.02 (dd, J=8.6, 2.0 Hz, 1H), 6.33 (s, 1H), 4.70 (s, 2H), 3.78 (s, 2H), 3.26-3.34 (m, 2H), 3.22 (s, 2H),

2.76 (s, 2H) ppm。

实施例 1500

1-(4-氨基-喹唑啉-7-基甲基)-4-(3,5-二氯-1H-吲哚-2-基甲基)-哌嗪-2-酮

将 1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮 (115mg, 0.273mmol) 的甲醇 (3mL) 溶液用 NCS (35mg, 0.262mmol) 处理并搅拌 90 分钟。将粗产物用 RP-HPLC 纯化, 用 10% 乙腈/水 (0.1%TFA) 至 60%乙腈/水 (0.1%TFA) 进行梯度洗脱, 将适当的产物馏分合并然后冷冻干燥得到 55mg (41%) 白色固体状 1-(4-氨基-喹唑啉-7-基甲基)-4-(3,5-二氯-1H-吲哚-2-基甲基)-哌嗪-2-酮的 TFA 盐。^{1}H NMR (300MHz, DMSO-d_6) δ 11 (s, 1H), 9.73 (br s, 2H), 8.79 (s, 1H), 8.35 (d, J=8.4Hz, 1H), 7.59 (d, J=8.7Hz, 1H), 7.55 (s, 1H), 7.45-7.45 (m, 2H), 7.15 (dd, J=8.6, 2.0 Hz, 1H), 4.70 (s, 2H), 4.44 (s, 2H), 3.82 (s, 2H), 3.32 (br s, 4H) ppm。质谱: (ESI) m/z 455 (M+H)$^+$。

实施例 1501

4-(3-乙酰基-5-氯-1H-吲哚-2-基甲基)-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮

A: 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-3-三甲基硅烷基乙炔基-吲哚-1-甲酸叔丁酯。

向 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-3-碘-吲哚-1-甲酸叔丁酯 (190mg, 0.29mmol)、碘化亚铜 (I) (10mg, 0.046mmol) 和二 (三苯基膦)-二氯化钯 (12mg, 0.17mmol) 在三乙胺 (1.5mL) 和 DMF (0.5mL) 中的混合物中加入 (三甲基硅烷基) 乙炔 (100μL, 0.70mmol)。搅拌 16 小时后, 将反应液在水和 EtOAc 之间进行分配。水相用 EtOAc 萃取, 合并后的有机萃取液用盐水洗涤, 用硫酸钠干燥, 过滤然后浓缩。经硅胶色谱 (二氯甲烷→8%甲醇/二氯甲

烷)得到 133mg (74%)棕色固体状 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-3-三甲基硅烷基乙炔基-吲哚-1-甲酸叔丁酯。质谱: (ESI) m/z 617 $(M+H)^+$。

B: 4-(3-乙酰基-5-氯-1H-吲哚-2-基甲基)-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮。

向 2-[4-(4-氨基-喹唑啉-7-基甲基)-3-氧代-哌嗪-1-基甲基]-5-氯-3-三甲基硅烷基乙炔基-吲哚-1-甲酸叔丁酯 (133mg, 0.215mmol)的甲醇(5mL)溶液中加入碳酸钾(513mg, 3.71mmol)。搅拌 6 小时后, 将反应液用水稀释并用 EtOAc 萃取。合并的有机萃取液用盐水洗涤, 用硫酸钠干燥, 过滤然后浓缩。将粗产物用 RP-HPLC 纯化, 用 10%乙腈/水(0.1%TFA)至 50%乙腈/水(0.1%TFA)进行梯度洗脱, 将适当的产物馏分合并然后冷冻干燥得到 22mg (15%)白色固体状 4-(3-乙酰基-5-氯-1H-吲哚-2-基甲基)-1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮的 TFA 盐。^{1}H NMR (300 MHz, CD_3OD) δ 8 s, 1H), 8.31 (d, J=8.5Hz, 1H), 8.01 (d, J=1.9Hz, 1H), 7.69 (dd, J=8.5, 1.5Hz, 1H), 7.65 (s, 1H), 7.43 (d, J=8.0Hz, 1H), 7.21 (dd, J=8.7, 2.0Hz, 1H), 4.27 (s, 2H), 3.47-3.54 (m, 6H), 3.01-3.06 (m, 2H), 2.68 (s, 3H) ppm。质谱: (ESI) m/z 463 $(M+H)^+$。

实施例 1502

1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-吡咯烷-1-基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮

向甲醛(40mg, 0.47mmol)在 HOAc (1mL)和二氧六环(4mL)的混合物中的溶液中于 0℃下加入吡咯烷(36μL, 0.43mmol)。搅拌 5 分钟后, 一次性加入 1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮(107mg, 0.254mmol)。将反应液升温至室温, 搅拌 2.5 小时后, 用饱和碳酸氢钠溶液终止反应并用 EtOAc 萃取。有机萃取液用盐水洗涤, 用硫酸钠干燥, 过滤然后浓缩。将粗产物用 RP-HPLC 纯

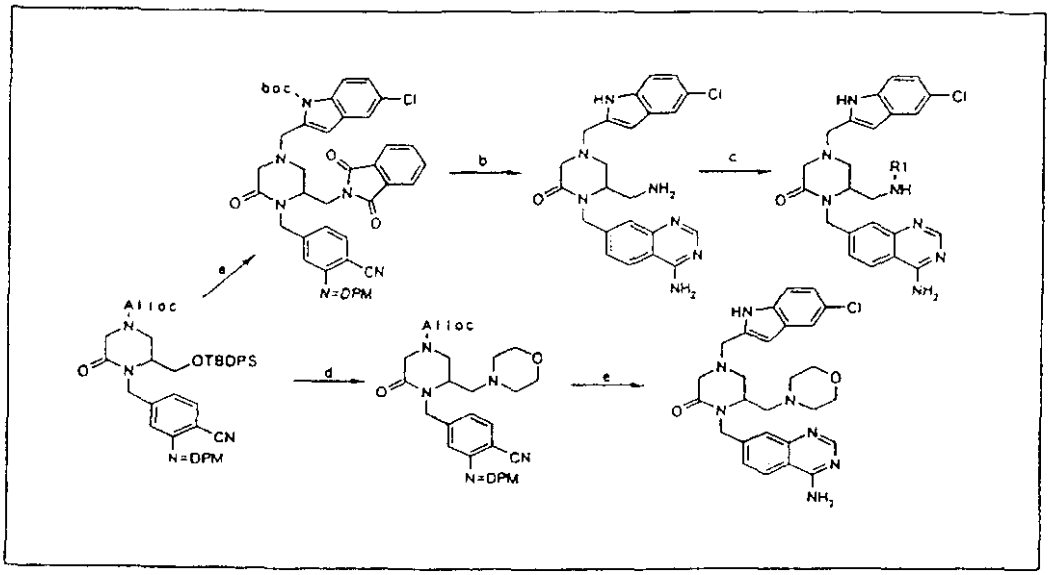
化，用 10%乙腈/水(0.1%TFA)至 60%乙腈/水(0.1%TFA)进行梯度洗脱，将适当的产物馏分合并然后冷冻干燥得到 70 mg (47%)白色固体状 1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-吡咯烷-1-基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮的 TFA 盐。^{1}H NMR (300 MHz, DMSO-d_6) δ 11 (s, 1H), 9.78 (d, J=1.7Hz, 2H), 8.79 (s, 1H), 8.39 (d, J=8.5Hz, 1H), 7.87 (d, J=1.5Hz, 1H), 7.56-7.64 (m, 2H), 7.38 (d, J=8.6Hz, 1H), 7.12 (dd, J=8.6, 1.8Hz, 1H), 4.71 (s, 2H), 4.54 (s, 2H), 3.95 (s, 2H), 3.29 (s, 6H), 3.12 (br s, 2H), 2.82 (s, 2H), 1.95 (br s, 2H), 1.83 (br s, 2H) ppm。质谱：(ESI) m/z 504 $(M+H)^+$。

按照上面实施例中描述的方法，用适当的吲哚前体制备如下化合物：

实施例	化合物名称	m/z (M+H)
1503	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(3-溴-5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮	499
1504	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮	434
1505	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-吗啉-4-基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮	520
1506	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-甲基氨基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮	463
1507	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-二甲基氨基甲基-1H-吲哚-2-基甲基)-哌嗪-2-酮	477
1508	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-甲基-1H-吲哚-2-基甲基)-3-甲氧基甲基-哌嗪-2-酮	478

1509	1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-3-氟-1H-吲哚-2-基甲基)-哌嗪-2-酮	438
1510	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(3,5-二氯-1H-吲哚-2-基甲基)-3-甲氧基甲基-哌嗪-2-酮	499

反应方案 9 C(6)-烷基氨基甲基取代的吲哚基甲基抑制剂的合成方案



试剂：(a) 1. $Pd(PPh_3)_4$，吗啉，CH_2Cl_2。2. K_2CO_3，2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯，DMF。3. TBAF，THF。4. 邻苯二甲酰亚胺，PPh_3，DEAD，THF。(b) 1. 浓盐酸，甲醇。2. 1,3,5-三嗪，AcOH，乙醇，回流。3. TFA，二氯甲烷。4. 肼，乙醇。(c) Et_3N，亲电试剂，二氯甲烷。(d) 1. TBAF，THF。2. SO_3-Py，DMSO。3. 胺，$NaB(OAc)_3H$，4A MS，甲醇。(e) 见(a. 1-2)，(b. 1-2,4)。

实施例 1511

(S)-6-氨基甲基-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮

A：(R)-2-(二苯亚甲基-氨基)-4-[2-(叔丁基-二苯基-硅烷氧基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈。

将四(三苯基膦)钯(470mg, 0.38mmol)加入到(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二苯基-硅烷氧基-甲基)-5-氧代-哌嗪-1-甲酸烯丙酯(2.8g, 3.8mmol)和吗啉(1.7mg, 19mmol)的二氯甲烷(30mL)溶液中。在室温下 30 分钟后，将反应混合物浓缩并进行硅胶色谱(1%二氯甲烷→5%甲醇的二氯甲烷溶液)得到 2.6g (100%)油状的(R)-2-(二苯亚甲基-氨基)-4-[2-(叔丁基-二苯基-硅烷氧基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈。质谱：(ESI) m/z 677 $(M+H)^+$。

B: (R)-2-[4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二苯基-硅烷氧基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。

向(R)-2-(二苯亚甲基-氨基)-4-[2-(叔丁基-二苯基-硅烷氧基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(1.08g, 1.6mmol)和碳酸钾(0.66g, 4.8mmol)的 DMF(3mL)混合物中于 0℃加入 2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯(0.67g, 1.95mmol)。在室温下 1 小时后，将反应混合物用乙酸乙酯和水稀释，然后用乙酸乙酯萃取。将合并的有机萃取液用水和盐水洗涤两次，用硫酸镁干燥，过滤然后浓缩得到粗品(R)-2-[4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二苯基-硅烷氧基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯，其不经进一步的纯化直接用于随后的反应。质谱：(ESI) m/z 940 $(M+H)^+$。

C: (R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-羟基甲基-5-氧代-哌嗪-1-基甲基}-5-氯-吲哚-1-甲酸叔丁酯。

将(R)-2-[4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(叔丁基-二苯基-硅烷氧基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯的 THF(20mL)溶液用 1.0M TBAF 的 THF(5mL, 5mmol)溶液处理。将反应混合物在室温下搅拌 1 小时，用盐水稀释并用 EtOAc 萃取。

将合并的有机萃取液用硫酸镁干燥，过滤然后浓缩，将硅胶色谱(1%二氯甲烷→5%甲醇的二氯甲烷溶液)得到 2.46g(94%) (R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-羟基甲基-5-氧代-哌嗪-1-基甲基}-5-氯-吲哚-1-甲酸叔丁酯。质谱：(ESI) m/z 688 $(M+H)^+$。

D: (R)-2-[4-[3-(二苯亚甲基-氨基)-4-氰基苄基]-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。

向 100mL 的烧瓶中加入(R)-2-{4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-羟基甲基-5-氧代-哌嗪-1-基甲基}-5-氯-吲哚-1-甲酸叔丁酯(0.22g, 0.32mmol)、三苯基膦(0.25g, 0.96mmol)和邻苯二甲酰亚胺(0.19g, 1.28mmol)。向其中加入甲苯(2mL)和 THF(2mL)，将此悬浮液用 DEAD (0.15mL, 0.96mmol)于-50℃下进行处理。将反应混合物升温至室温并搅拌 48 小时。将溶液浓缩并进行硅胶色谱(己烷/EtOAc, 5:1→1:1)得到 240mg(93%) (R)-2-[4-[3-(二苯亚甲基-氨基)-4-氰基苄基]-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。质谱：(ESI) m/z 817 $(M+H)^+$。

E: (R)-2-[4-(3-氨基-4-氰基-苄基)-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。

将浓盐酸(12M, 5 滴)于 0℃下加入到(R)-2-[4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(0.24g, 0.3mmol)的甲醇(5mL)溶液中。在 0℃下 2 小时后，将反应混合物浓缩并在 EtOAc 和饱和碳酸氢钠溶液之间进行分配。将分离出的有机相用盐水洗涤，用硫酸镁干燥，过滤然后浓缩。将粗品残余物进行硅胶色谱(己烷/EtOAc, 3:1→1:1)得到 0.13g(67%) (R)-2-[4-(3-氨基-4-氰基-苄

基)-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。质谱:(ESI) m/z 653 $(M+H)^+$。

F: (R)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。

向(R)-2-[4-(3-氨基-4-氰基-苄基)-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(130mg, 0.2mmol)的无水乙醇(7mL)溶液中加入1,3,5-三嗪(162mg, 2mmol)和乙酸(0.11mL, 2mmol)。将溶液加热回流20小时后,将溶液冷却然后浓缩。所得粗产物进行硅胶色谱处理(1%二氯甲烷→10%甲醇的二氯甲烷溶液)得到 100mg(74%) (R)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。质谱:(ESI) m/z 679 $(M+H)^+$。

G: (R)-2-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-异吲哚-1,3-二酮。

将过量的TFA(约30%的二氯甲烷溶液)于0℃下加入到(R)-2-[4-(4-氨基-喹唑啉-7-基甲基)-3-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯(100mg, 0.15mmol)的二氯甲烷(10mL)溶液中。室温下 3 小时后,将反应混合物浓缩得到粗品残余物,将该粗品残余物进行硅胶色谱处理(2%二氯甲烷→20%甲醇的二氯甲烷溶液)得到 90mg(100%) (R)-2-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-异吲哚-1,3-二酮。质谱:(ESI) m/z 580 $(M+H)^+$。

H: (S)-6-氨基甲基-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮(RPR257001A)。

将(R)-2-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-

基甲基)-6-氧代-哌嗪-2-基甲基]-异吲哚-1,3-二酮(1.0g, 1.5mmol)在甲醇(30mL)中的混合物用肼的一水合物(30mL, 75mmol)进行处理。室温下12小时后，将反应混合物浓缩然后溶于含有0.1% TFA的乙腈和水中，制成40mL溶液用于制备HPLC注射。将粗产物通过RP-HPLC纯化，用10%乙腈/水(0.1% TFA)至80%乙腈/水(0.1% TFA)进行梯度洗脱，将适当的产物馏分合并然后冷冻干燥得到0.91g (89%)白色固体状(S)-6-氨基甲基-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮。质谱：(ESI) m/z 450 $(M+H)^+$。

实施例1512

(S)-N-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-乙酰胺

向(S)-6-氨基甲基-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-哌嗪-2-酮(15mg, 0.022mmol)和过量三乙胺的DMF(0.5mL)溶液中于0℃下加入乙酸酐(0.008mL)。室温下1小时后，将反应混合物用水和乙腈稀释得到10mL溶液。将粗产物通过RP-HPLC进行纯化，用10%乙腈/水(0.1% TFA)至80%乙腈/水(0.1% TFA)进行梯度洗脱，将适当的产物馏分合并然后冷冻干燥得到11mg (82%)白色固体状(S)-N-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-乙酰胺。质谱：(ESI) m/z 492 $(M+H)^+$。

按照上面实施例描述的方法，通过将C(6)-氨基甲基模板与适当的亲电试剂进行偶联反应制备如下化合物。

实施例	化合物名称	m/z (M+H)
1513	(S)-呋喃-2-甲酸[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-酰胺	544

1514	(S)-N-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-甲酰胺	477
1515	(S)-1-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-3-乙基-脲	521
1516	(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-脲	492
1517	(S)-5-溴-嘧吩-2-磺酸[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-酰胺	675
1518	(S)-1-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-3-苯基-脲	569
1519	(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-氨基甲酸异丙酯	536
1520	(S)-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-氨基甲酸甲酯	507
1521	(S)-N-[1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-氧代-哌嗪-2-基甲基]-甲磺酰胺	528

实施例 1522

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-吗啉-4-基甲基-哌嗪-2-酮

A: (R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲酰基-5-氧代-

哌嗪-1-甲酸烯丙酯。

将(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-羟基甲基-5-氧代-哌嗪-1-甲酸烯丙酯(2.4g, 4.7mmol)的 DMSO(8mL)和三乙胺(4mL)溶液在0℃下用 SO_3.Py (3.76g, 24mmol)进行处理。室温下 20 小时后，将混合物用水稀释并用 EtOAc 萃取。将合并的有机萃取液用饱和氯化铵溶液和水稀释，用硫酸镁干燥然后浓缩。粗品(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲酰基-5-氧代-哌嗪-1-甲酸烯丙酯(约2.3g)不经进一步的纯化直接用于随后的反应。质谱：(ESI) m/z 507 $(M+H)^+$。

B: (S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-吗啉-4-基甲基-5-氧代-哌嗪-1-甲酸烯丙酯。

向(R)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-甲酰基-5-氧代-哌嗪-1-甲酸烯丙酯(0.25g, 0.49mmol)、吗啉(0.21mL, 2.5mmol)和粉末状 4Å 分子筛(0.5g)的 1,2-二氯乙烷(5mL)混合物中于0℃加入三乙酰氧基硼氢化钠(0.31g, 1.5mmol)。室温下 12 小时后，将反应混合物用饱和碳酸氢钠溶液处理并用二氯甲烷萃取。将合并的有机萃取液用盐水洗涤，用硫酸镁干燥，过滤然后浓缩。将粗产物进行硅胶色谱(2%二氯甲烷→5%甲醇的二氯甲烷溶液)得到 210mg(73%) (S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-吗啉-4-基甲基-5-氧代-哌嗪-1-甲酸烯丙酯。质谱：(ESI) m/z 578 $(M+H)^+$。

C: (S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-吗啉-4-基甲基-5-氧代-哌嗪-1-甲酸。

按照前面实施例的描述，用四(三苯基膦)钯和吗啉对(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-吗啉-4-基甲基-5-氧代-哌嗪-1-甲酸烯丙酯进行 Alloc 脱保护，以 100%的收率得到(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-吗啉-4-基甲基-5-氧代-哌嗪-1-甲酸。质谱：(ESI) m/z 494 $(M+H)^+$。

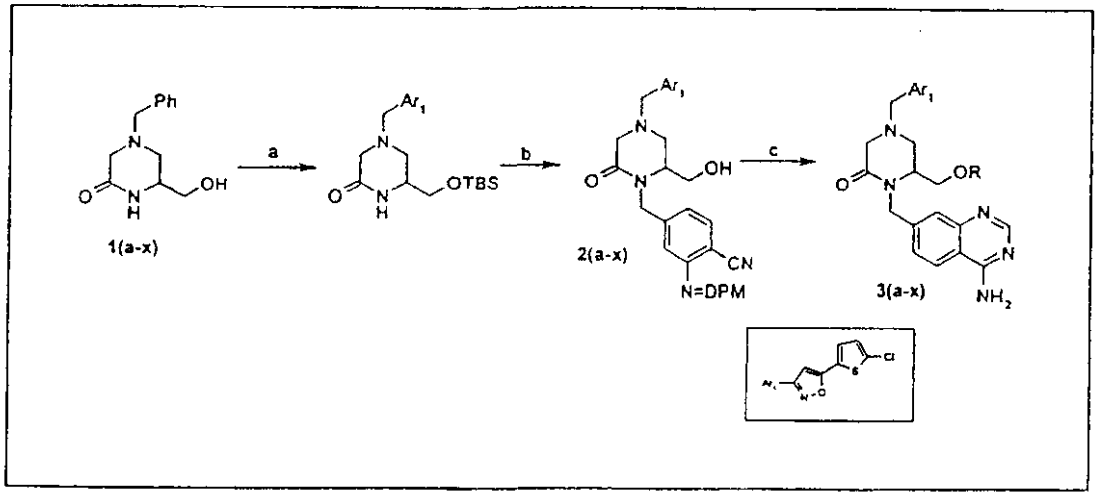
D: (S)-2-[4-(3-氨基-4-氰基-苄基)-3-吗啉-4-基甲基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。

按照前面实施例所描述的方法将(S)-4-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-3-吗啉-4-基甲基-5-氧代-哌嗪-1-甲酸烯丙酯与2-溴甲基-5-氯-吲哚-1-甲酸叔丁酯进行偶联并用HCl/MeOH对二苯基亚甲基进行脱保护，以43%的收率得到(S)-2-[4-(3-氨基-4-氰基-苄基)-3-吗啉-4-基甲基-5-氧代-哌嗪-1-基甲基]-5-氯-吲哚-1-甲酸叔丁酯。质谱: (ESI) m/z 593 $(M+H)^+$。

E: (S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-吗啉-4-基甲基-哌嗪-2-酮(RPR256996A)。

按照前面实施例所描述的方法形成氨基喹唑啉并随后进行Boc脱保护得到(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(5-氯-1H-吲哚-2-基甲基)-6-吗啉-4-基甲基-哌嗪-2-酮。质谱: (ESI) m/z 520 $(M+H)^+$。

反应方案10 C(6)-烷氧基甲基取代的异噁唑基甲基抑制剂的合成方案



试剂: (a). 1. TBSCl, 咪唑。2. $Pd(OH)_2$, 甲醇, H_2。3. NaH, Ar_1CH_2Br, THF。(b). 1. NaH, 4-溴甲基-2-二苯基亚甲基氨基苯甲腈, THF。2. TBAF, THF。(c). 1. NaH, RBr, THF。2. 浓盐酸, 甲醇。3. 1,3,5-

三嗪，AcOH，乙醇，回流。

实施例 1523

(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-甲氧基甲基-哌嗪-2-酮

A：(R)-4-苄基-6-(叔丁基-二甲基-硅烷氧基甲基)-哌嗪-2-酮。

将(R)-4-苄基-6-羟基甲基-哌嗪-2-酮(9g，41mmol)和咪唑(4.2g，62mmol)的二氯甲烷(80mL)溶液在 0℃下用 TBSCl (6.24g，42mmol)处理。在室温下 1 小时后，将该混合物浓缩，用 EtOAc 稀释，过滤除去大部分三乙胺盐酸盐。将溶液浓缩得到 12.8 g (93%)粗品(R)-4-苄基-6-(叔丁基-二甲基-硅烷氧基甲基)-哌嗪-2-酮，其不经进一步的纯化直接用于随后的反应。质谱：(ESI) m/z 335 $(M+H)^+$。

B：(R)-6-(叔丁基-二甲基-硅烷氧基甲基)-哌嗪-2-酮。

向(R)-4-苄基-6-(叔丁基-二甲基-硅烷氧基甲基)-哌嗪-2-酮(2.1g，6.3mmol)的甲醇(80mL)溶液中加入 10%吸附于碳上的氢氧化钯(0.3g)。将反应混合物在气囊氢气压力下室温氢化 20 小时。将反应混合物用硅藻土垫过滤，将滤液浓缩得到 1.36g(88%) (R)-6-(叔丁基-二甲基-硅烷氧基甲基)-哌嗪-2-酮。质谱：(ESI) m/z 245 $(M+H)^+$。

C：(R)-6-(叔丁基-二甲基-硅烷氧基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-哌嗪-2-酮。

向(R)-6-(叔丁基-二甲基-硅烷氧基甲基)-哌嗪-2-酮(1.36g，5.6mmol)和碳酸钾(3.1g，22mmol)的无水 DMF(10mL)混合物中于 0℃下加入 3-溴甲基-5-(5-氯-噻吩-2-基)-异噁唑(1.72g，6.2mmol)。室温下 2 小时后，将反应混合物用 EtOAc 和水稀释然后分层。将有机相用水、盐水洗涤两次，用硫酸镁干燥，过滤然后浓缩。将粗品残余物进行硅胶色谱处理(二氯甲烷→10%甲醇的二氯甲烷溶液)得到 2.55g(100%) (R)-6-(叔丁基-二甲基-硅烷氧基甲基)-4-[5-(5-氯-

噻吩-2-基)-异噁唑-3-基甲基]-哌嗪-2-酮。^{1}H NMR (300 MHz, $CDCl_3$) δ 27 (d, J=4.2Hz, 1H), 6.95 (d, J=4.2Hz, 1H), 6.35 (s, 1H), 6.09 (s, 1H), 3.7-3.45 (m, 5H), 3.33 (d, J=16Hz, 1H), 3.14 (d, J=16Hz, 1H), 2.76 (dd, J=15, 3.6Hz, 1H), 2.4-2.33 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H) ppm。质谱: (ESI) m/z 442 $(M+H)^+$。

D: (R)-2-(二苯亚甲基-氨基)-4-{2-(叔丁基-二甲基-硅烷氧基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈。

向(R)-6-(叔丁基-二甲基-硅烷氧基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-哌嗪-2-酮 (2.55g, 5.7mmol)在 THF:DMF(5:1, 25mL)混合物中的溶液中于0℃下加入氢化钠(60%矿物油分散液, 0.32g, 8mmol), 随后加入 2-(二苯亚甲基-氨基)-4-溴甲基-苯甲腈(2.35g, 6.3mmol)。在0℃下0.5小时后, 将反应混合物用饱和氯化铵稀释并用 EtOAc 萃取。将合并的有机萃取液用水洗涤(两次), 用硫酸镁干燥, 过滤然后浓缩。粗品(R)-2-(二苯亚甲基-氨基)-4-{2-(叔丁基-二甲基-硅烷氧基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈不经进一步的纯化直接用于随后的反应。

E: (R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-羟基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈。

将(R)-2-(二苯亚甲基-氨基)-4-{2-(叔丁基-二甲基-硅烷氧基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈的 THF (30mL)溶液用 1.0M TBAF 的 THF 溶液(7mL, 7mmol)处理。将反应混合物室温搅拌0.5小时, 浓缩然后进行硅胶色谱(二氯甲烷→4%甲醇的二氯甲烷溶液)得到 3.3g(95%) (R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-羟基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈。^{1}H NMR (300 MHz, $CDCl_3$)

δ 79 (d, J=7.2Hz, 2H), 7.6-7.2 (m, 10H), 6.95 (d, J=4.1Hz, 1H), 6.90 (d, J=6.9Hz, 1H), 6.62 (s, 1H), 6.31 (s, 1H), 5.15 (d, J=15.4Hz, 1H), 3.96 (d, J=15.4Hz, 1H), 3.75-3.6 (m, 5H), 3.2-2.9 (m, 3H), 2.51 (dd, J=11.7, 2.8Hz, 1 H) ppm。质谱: (ESI) m/z 622 $(M+H)^+$。

F: (R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-羟基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈(0.15g, 0.24mmol)的 THF/DMF (5:1, 6mL)溶液中于 0℃下加入 60%氢化钠的矿物油分散液(26mg, 0.68mmol), 15 分钟后加入 MeI (0.018mL, 0.29mmol)。室温下 1 小时后, 将混合物用饱和氯化铵水溶液处理并用 EtOAc 萃取。将合并的有机萃取液用硫酸镁干燥, 过滤然后浓缩。粗品(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈不经进一步的纯化直接用于随后的反应。

G: (R)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈。

将浓盐酸(12M, 5 滴)于 0℃下加入到(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈的甲醇(5mL)溶液中。室温下 1 小时后, 将反应混合物浓缩并在 EtOAc 和饱和碳酸氢钠溶液之间进行分配。将分离出的有机相用盐水洗涤, 用硫酸镁干燥, 过滤然后浓缩。将粗品残余物进行硅胶色谱(二氯甲烷→5%甲醇的二氯甲烷溶液)得到 90mg(79%) (R)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈。质谱: (ESI) m/z 472 $(M+H)^+$。

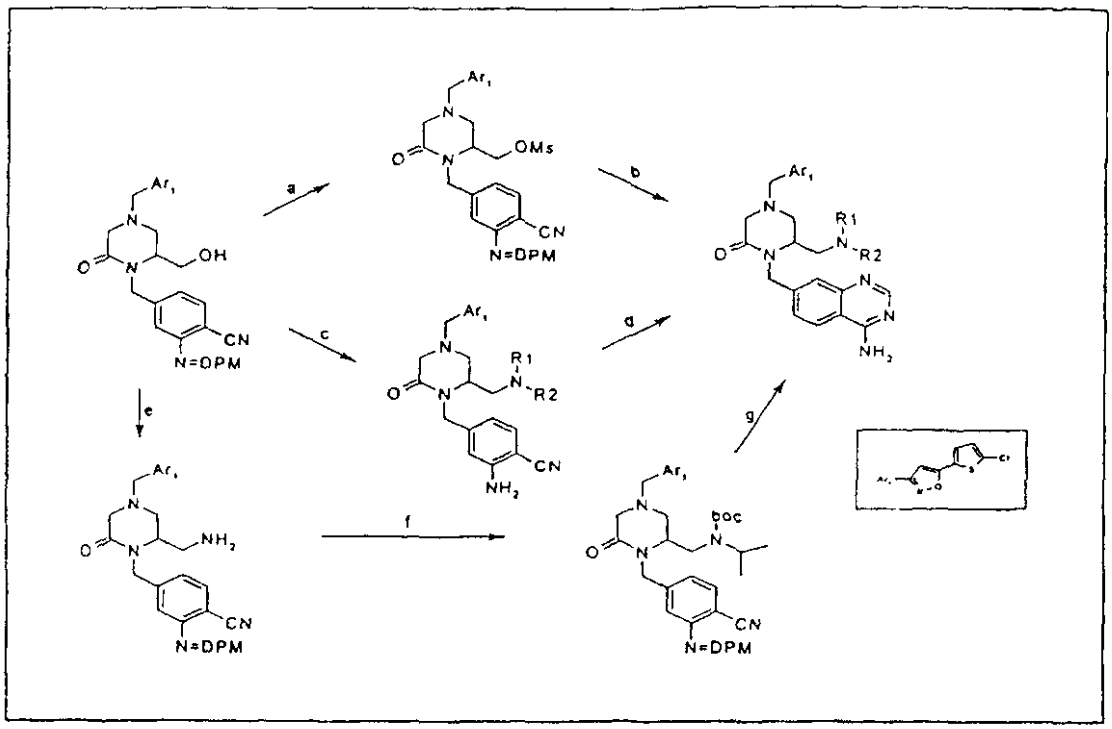
H: (R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-甲氧基甲基-哌嗪-2-酮(RPR257852A)。

向(R)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲氧基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈(90mg, 0.19mmol)的无水乙醇(3mL)溶液中加入 1,3,5-三嗪(0.16g, 1.9mmol)和乙酸(0.11mL, 1.9mmol)。将该溶液加热至回流。15小时后, 将溶液浓缩并用水和乙腈稀释得到 10mL 溶液。将粗产物通过 RP-HPLC 纯化, 用10%乙腈/水(0.1% TFA)至 80%乙腈/水(0.1% TFA)进行梯度洗脱, 将适当的产物馏分合并然后冷冻干燥得到 75mg (79%)白色固体状(R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯噻吩-2-基)-异噁唑-3-基甲基]-6-甲氧基甲基-哌嗪-2-酮。质谱: (ESI) m/z 499 $(M+H)^+$。

按照以上实施例中描述的方法, 将 C(6)-羟基甲基模板用适当的亲电试剂进行O-烷基化反应制备如下化合物。

实施例	化合物名称	m/z (M+H)
1524	(6R)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-乙氧基甲基-哌嗪-2-酮	513
1525	(6R)-1-(4-氨基-喹唑啉-7-基甲基)-6-苄氧基甲基-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-哌嗪-2-酮	575

反应方案 11 C(6)-烷基氨基甲基取代的异噁唑基甲基抑制剂的合成方案



试剂：(a) Ms_2O, Et_3N, CH_2Cl_2。(b) 1. 胺，DMF，80℃。2. 浓盐酸，甲醇；3. 1,3,5-三嗪，AcOH，乙醇，回流。(c) 1. PDC. 2. 胺，$NaB(OAc)_3H$，4A MS，甲醇。3. 参见(b. 2)。(d) 参见(b. 3)。(e) 1. 邻苯二甲酰亚胺，PPh_3，DEAD，THF。2. 肼。(f) 1. 丙酮，$NaB(OAc)_3H$，4A MS。2. Boc_2O，THF。(g) 1. 参见(b. 2-3)，2. TFA，CH_2Cl_2。

实施例 1526

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-吡咯烷-1-基甲基-哌嗪-2-酮

A：(R)-甲磺酸 1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲酯。

向(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-羟基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈(1.89g，3.04mmol)和三乙胺(2.1mL，15.2mmol)的 CH_2Cl_2(25mL)溶液中加入甲磺酸酐(815mg，4.68mmol)。搅拌 3 小时后，蒸除二氯甲烷并将残

余物在乙酸乙酯和水之间进行分配。将乙酸乙酯层依次用水和盐水洗涤，用硫酸钠干燥，过滤然后浓缩得到 1.9g(89%)黄色泡沫状(R)-甲磺酸 1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲酯。^{1}H NMR (300 MHz, $CDCl_3$) δ 7 (d, J =7.1 Hz, 2H), 7.14-7.52 (m, 10H), 6.94 (d, J =4.0 Hz, 1H), 6.88 (dd, J=8.0, 1.4 Hz, 1H), 6.63 (d, J =1.3 Hz, 1H), 6.53 (s, 1H), 5.12 (d, J =15.1 Hz, 1H), 4.41 (dd, J =10.0, 8.9 Hz, 1H), 4.05-4.16 (m, 1H), 3.91 (d, J =15.1 Hz, 1H), 3.68 (d, J =3.5 Hz, 2H), 3.53 (d, J =16.7 Hz, 1H), 3.21-3.29 (m, 1H), 2.94-3.14 (m, 2H), 2.94 (s, 3H), 2.32-2.38 (m, 1H) ppm。质谱：(ESI) m/z 700 $(M+H)^+$。

B：(S)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-氧代-6-吡咯烷-1-基甲基-哌嗪-1-基甲基}-苯甲腈。

将(R)-甲磺酸 1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲酯(1.5g, 2.14mmol)、吡咯烷(2mL, 24mmol)和碳酸钾(1.55g, 11.2mmol)的混合物于 80℃加热 2 小时。将反应液用乙酸乙酯稀释，然后依次用水和盐水洗涤，用硫酸钠干燥，过滤然后浓缩得到 1.5g (>100%)油状(S)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-氧代-6-吡咯烷-1-基甲基-哌嗪-1-基甲基}-苯甲腈粗品。质谱：(ESI) m/z 675 $(M+H)^+$。

C：(S)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-氧代-6-吡咯烷-1-基甲基-哌嗪-1-基甲基}-苯甲腈。

将(S)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯噻吩-2-基)-异噁唑-3-基甲基]-2-氧代-6-吡咯烷-1-基甲基-哌嗪-1-基甲基}-苯甲腈(1.5g, 2.14mmol)在 0℃下溶于甲醇(20mL)和二氯甲烷(5mL)的混合物中并用 TFA (4mL)处理。将反应液升温至室温，搅拌 2 小时后进行

硅胶色谱(二氯甲烷至10%甲醇/二氯甲烷)得到880mg (两步的总收率85%)棕色胶状(S)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-氧代-6-吡咯烷-1-基甲基-哌嗪-1-基甲基}-苯甲腈。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.29 (m, 2H,), 6.93 (d, J =4.0 Hz, 1 H), 6.73 (d, J =1.0 Hz, 1H), 6.56 (dd, J =8.0, 1.4 Hz, 1H), 6.29 (s, 1H), 4.94 (d, J =15.1 Hz, 1H), 4.11 (d, J =15.0 Hz, 1H), 3.72-3.89 (m, 1H), 3.69-3.74 (m, 2H), 3.59 (d, J =17.9 Hz, 1H), 3.27 (d, J =12.7 Hz, 1H), 2.58-2.65 (m, 6H), 2.01-2.07 (m, 4H) ppm。

D: (S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-吡咯烷-1-基甲基-哌嗪-2-酮。

将(S)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-氧代-6-吡咯烷-1-基甲基-哌嗪-1-基甲基}-苯甲腈(880 mg, 1.72mmol)、HOAc (950μL, 16.6mmol)和 1,3,5-三嗪(1.40g, 17.2mmol)的无水乙醇(20mL)溶液加热回流 16 小时。经硅胶色谱(CH_2Cl_2 至 20%甲醇/CH_2Cl_2)得到 800mg (86%)白色固体状(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯噻吩-2-基)-异噁唑-3-基甲基]-6-吡咯烷-1-基甲基-哌嗪-2-酮。^{1}H NMR (300 MHz, DMSO-d_6) δ 10.3 (br s, 1 H), 9.81 (d, J =29. 3 Hz, 2H), 8.79 (s, 1 H), 8.40 (d, J =8.6 Hz, 1 H), 7.54-7.65 (m, 3H), 7.27 (d, J =4.0 Hz, 1H), 6.96 (s, 1H), 5.18 (d, J =16.6 Hz, 1H), 4.41 (d, J =16.6 Hz, 1 H), 3.39-3.88 (m, 8H), 3.08-3.39 (m, 2H), 2.75 (d, J =11.2 Hz, 1H), 1.80-1.98 (m, 4H) ppm. 质谱: (ESI) m/z 538 $(M+H)^+$。

实施例 1527

(R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-N-(2-异丙氧基-乙基)-甲

脒和(6R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-N-(2-异丙氧基-乙基)-甲酰胺

A: (R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲酰基-6-氧代-哌嗪-1-基甲基}-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-羟基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈(0.8g, 1.3mmol)和4Å分子筛(1g)的二氯甲烷(20mL)溶液中加入PDC (0.98g, 2.6mmol)。室温下1小时后，将反应混合物进行硅胶色谱(CH_2Cl_2至1%甲醇/CH_2Cl_2)得到 520mg (65%) (R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲酰基-6-氧代哌嗪-1-基甲基}-苯甲腈。

B: (R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-[(2-异丙氧基-乙基氨基)-甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-甲酰基-6-氧代-哌嗪-1-基甲基}-苯甲腈(280mg, 0.45mmol)、2-氨基乙基异丙基醚(230mg, 2.3mmol)和4Å分子筛(300mg)的1,2-二氯乙烷(3mL)溶液中加入$NaBH(OAc)_3$ (290mg, 1.35mmol)。搅拌16小时后，滤除分子筛并用二氯甲烷洗涤。将滤液用碳酸氢钠水溶液和盐水洗涤，干燥($MgSO_4$)，过滤，然后浓缩得到(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-[(2-异丙氧基-乙基氨基)-甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈，其不经进一步纯化直接用于随后的反应。

C: (R)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-[(2-异丙氧基-乙基氨基)-甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁

唑-3-基甲基]-2-[(2-异丙氧基乙基氨基)-甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈在甲醇(4mL)和二氯甲烷(1mL)的混合物中的溶液中于0℃下加入浓盐酸(5滴)。搅拌20分钟后，将反应液浓缩然后用饱和碳酸氢钠溶液和乙酸乙酯稀释。将分出的有机相用盐水洗涤，干燥($MgSO_4$)，过滤然后浓缩。将粗品残余物进行硅胶色谱(二氯甲烷至5%甲醇的二氯甲烷溶液)得到80mg (33%)的(R)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-[(2-异丙氧基-乙基氨基)-甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈。质谱：(ESI) m/z 543$(M+H)^+$。

D：(R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-N-(2-异丙氧基-乙基)-甲脒和(R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-N-(2-异丙氧基-乙基)-甲酰胺。

向(R)-2-氨基-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-[(2-异丙氧基-乙基氨基)-甲基]-6-氧代-哌嗪-1-基甲基}-苯甲腈(80mg, 0.15mmol)的无水乙醇(5mL)溶液中加入1,3,5-三嗪(0.13g, 2.2mmol)和乙酸(0.1mL, 2.2mmol)。将溶液于90℃加热20小时然后浓缩。将粗产物通过RP-HPLC纯化，用10%乙腈/H_2O(0.1% TFA)至80%乙腈/H_2O(0.1% TFA)进行梯度洗脱得到10mg(11%) (R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-N-(2-异丙氧基-乙基)-甲脒。质谱：(ESI) m/z 597 $(M+H)^+$，和25mg(28%) (R)-N-{1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-N-(2-异丙氧基-乙基)-甲酰胺。质谱：(ESI) m/z 598 $(M+H)^+$。

按照上述实施例的描述通过类似方式制备如下化合物。

实施例	化合物名称	m/z (M+H)
1528	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-吡咯烷-1-基甲基-哌嗪-2-酮	538
1529	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-哌啶-1-基甲基-哌嗪-2-酮	552
1530	(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-[(环戊基-甲基-氨基)-甲基]-哌嗪-2-酮	566

实施例 1531

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-(异丙基氨基-甲基)-哌嗪-2-酮

A: (R)-2-(二苯亚甲基-氨基)-4-[4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-{4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-羟基甲基-6-氧代-哌嗪-1-基甲基}-苯甲腈(2.00g, 3.22mmol)、三苯基膦(2.55g, 9.72mmol)和邻苯二甲酰亚胺(1.86g, 12.6mmol)在 THF (15mL)和甲苯(15mL)的混合物中的溶液中于-70℃下滴加 DEAD (1.45mL, 9.66mmol)。升温至室温并搅拌 16 小时后,进行硅胶色谱(5:1 己烷/EtOAc 至 1:2 己烷/EtOAc)得到 4.7g (>100%)黄色固体状(R)-2-(二苯亚甲基-氨基)-4-[4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈。质谱: (ESI) m/z 751 $(M+H)^+$。

B: (S)-4-{2-氨基甲基-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲

基]-6-氧代哌嗪-1-基甲基}-2-(二苯亚甲基-氨基)-苯甲腈。

向(R)-2-(二苯亚甲基-氨基)-4-[4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-(1,3-二氧代-1,3-二氢-异吲哚-2-基甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(4.7g, 3.22mmol)的甲醇(40mL)溶液中于0℃下加入一水合肼(2mL, 41mmol)。升温至室温并搅拌16小时后，将反应液用水稀释并用乙酸乙酯萃取。将乙酸乙酯层用盐水洗涤，用硫酸钠干燥，过滤然后浓缩。经硅胶色谱处理(二氯甲烷至4%甲醇/二氯甲烷)得到1.13g (两步的收率为57%)橙色固体状(S)-4-{2-氨基甲基-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-1-基甲基}-2-(二苯亚甲基-氨基)-苯甲腈。^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.78 (m, 2H), 7.36-7.53 (m, 4H), 7.22-7.29 (m, 4H), 7.12-7.18 (m, 2H), 6.93 (d, *J* = 3.9 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.60 (d, *J* = 1.2 Hz, 1H), 6.30 (s, 1H), 5.05 (d, *J* = 15.4 Hz, 1H), 4.00 (d, *J* = 15.4 Hz, 1H), 3.46-3.71 (m, 3H), 3.09 (d, *J* = 16.4 Hz, 1H), 2.98 (d, *J* = 11.8 Hz, 1H), 2.66-2.91 (m, 2H), 2.64-2.75 (m, 1H), 2.37-2.42 (m, 1H) ppm. 质谱：(ESI) *m/z* 621 $(M+H)^+$.

C: (S)-2-(二苯亚甲基-氨基)-4-[4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-(异丙基氨基-甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈。

向(S)-4-{2-氨基甲基-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-1-基甲基}-2-(二苯亚甲基-氨基)-苯甲腈(1.13g, 1.82mmol)、冰乙酸(104μL, 1.82mmol)和丙酮(200μL, 2.7mmol)的溶液中加入三乙酰氧基硼氢化钠(553mg, 2.60mmol)。搅拌16小时后，用饱和碳酸氢钠终止反应然后用乙酸乙酯萃取。将乙酸乙酯层用盐水洗涤，用硫酸钠干燥，过滤然后浓缩得到1.09g (90%)黄色泡沫状(S)-2-(二苯亚甲基-氨基)-4-[4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-(异丙基氨基-甲基)-6-氧代-哌嗪-1-基甲基]-苯甲

腈。质谱：(ESI) m/z 663 $(M+H)^+$。

D：(R)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯。

向(S)-2-(二苯亚甲基-氨基)-4-[4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-2-(异丙基氨基-甲基)-6-氧代-哌嗪-1-基甲基]-苯甲腈(1.34g, 2.02mmol)、三乙胺(560μL, 4.04mmol)和 DMAP (26mg, 0.20mmol)的 THF (15mL)溶液中于 0℃下加入 Boc-酐(485mg, 2.22mmol)。升温至室温并搅拌 2 小时后，加入 Boc-酐(144mg, 0.660mmol)。将反应液搅拌 48 小时，然后用水稀释并用乙酸乙酯萃取。将乙酸乙酯层用盐水洗涤，用硫酸钠干燥，过滤然后浓缩得到 1.55g (100%)黄色固体状(R)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯。^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.73 (m, 2H), 7.33-7.50 (m, 4H), 7.19-7.30 (m, 4H), 7.11-7.18 (m, 2H), 6.89-6.95 (m, 2H), 6.81 (s, 1H), 6.28 (s, 1 H), 4.98-5.07 (m, 1H), 3.89-4.05 (m, 1 H), 3.63 (s, 2H), 3.20-3.60 (m, 5H), 2.76-2.89 (m, 2H), 2.14-2.23 (m, 1H), 1.32-1.54 (m, 9H), 1.03-1.17 (m, 6H) ppm。质谱：(ESI) m/z 763 $(M+H)^+$。

E：(R)-{1-(3-氨基-4-氰基-苄基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯。

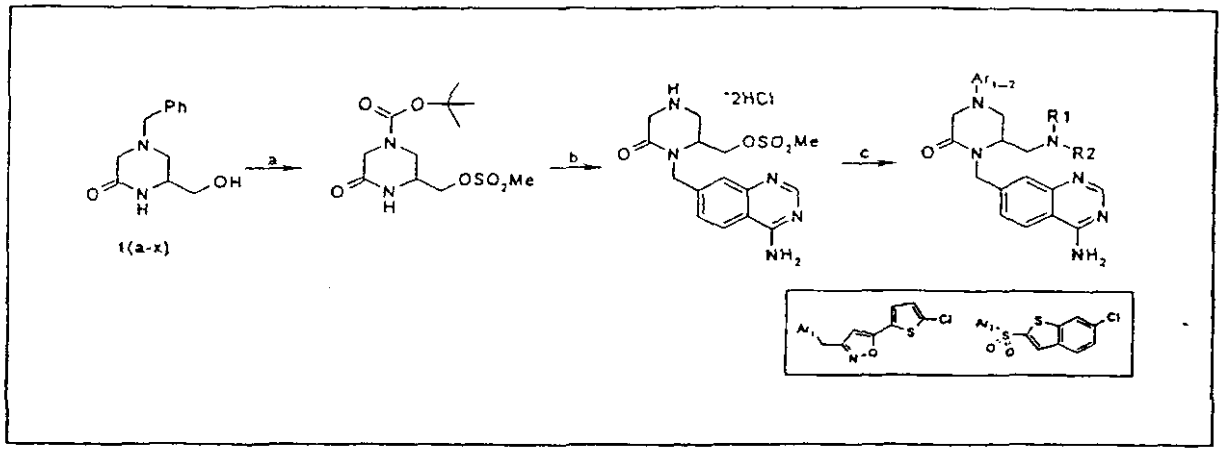
向(R)-{1-[3-(二苯亚甲基-氨基)-4-氰基-苄基]-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯(1.55g, 2.02mmol)在甲醇(10mL)和 THF (5mL)的混合物中的溶液中于 0℃下加入浓盐酸(2 滴)。搅拌 45 分钟后，加入浓盐酸(3 滴)，将反应液升温至室温并继续搅拌 1.5 小时。经硅胶色谱

(CH_2Cl_2至10%甲醇/CH_2Cl_2)得到350mg (两步的收率为29%)白色固体状(R)-{1-(3-氨基-4-氰基-苄基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯。质谱: (ESI) m/z 599 $(M+H)^+$。

F: (S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-(异丙基氨基-甲基)-哌嗪-2-酮。

将(R)-{1-(3-氨基-4-氰基-苄基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-氧代-哌嗪-2-基甲基}-异丙基-氨基甲酸叔丁酯(350mg, 0.584mmol)、冰乙酸(340μL, 5.94mmol)和1,3,5-三嗪(492g, 6.07mmol)的无水乙醇(10mL)溶液加热回流16小时。蒸除乙醇, 将残余物溶于二氯甲烷(10mL), 冷却至0℃并用TFA (4mL)处理。室温搅拌16小时, 然后将混合物浓缩并通过RP-HPLC纯化, 用10%乙腈/H_2O (0.1% TFA)至70%乙腈/H_2O (0.1% TFA)进行梯度洗脱。合并适当的产物馏分然后冷冻干燥得到188mg (50%)白色固体状(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-6-(异丙基氨基-甲基)-哌嗪-2-酮的TFA盐。^1H NMR (300 MHz, DMSO-d_6) δ 9.79 (d, J =13 Hz, 2H), 8.81 (s, 1H), 8.65 (br s, 1 H), 8.50 (br s, 1 H), 8.38 (d, J =8.5 Hz, 1H), 7.53-7.63 (m, 3H), 7.29 (d, J =4.0 Hz, 1H), 6.94 (s, 1H), 5.17 (d, J =16.7 Hz, 1H), 4.39 (d, J =16.7 Hz, 1H), 3.78 (AB四重峰, J =30.0, 14.4 Hz, 2H), 3.46-3.62 (m, 3H), 3.33 (t, J =5.8 Hz, 1H), 3.09-3.25 (m, 3H), 2.72 (d, J =10.2 Hz, 1 H), 1.14-1.23 (m, 6H) ppm。质谱: (ESI) m/z 526 $(M+H)^+$。

反应方案 12 C(6)-烷基氨基甲基取代的抑制剂的甲磺酸化方案



试剂：(a) 1. Ms_2O, Et_3N, CH_2Cl_2。2. $Pd(OH)_2$, 甲醇, H_2。3. Boc_2O, Et_3N, THF。(b) 1. NaH, 4-氨基-7-溴甲基喹唑啉, THF。2. HCl, 甲醇。(c) 1. Et_3N, Ar_1Br 或 Ar_2SO_2Cl, CH_2Cl_2。2. 胺, DMF, K_2CO_3, 80 ℃。

实施例 1532

(S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[(2-甲氧基-乙基氨基)-甲基]-哌嗪-2-酮

A: (R)-甲磺酸 4-苄基-6-氧代-哌嗪-2-基甲酯。

向(R)-4-苄基-6-羟基甲基-哌嗪-2-酮(2.0g, 9.3mmol)的二氯甲烷(20mL)溶液中于 0℃下加入三乙胺(5.2mL, 37mmol), 随后加入甲磺酸酐(3.24g, 19mmol)。室温下 1 小时后, 将反应混合物用饱和氯化铵溶液处理然后用二氯甲烷萃取。将合并的有机萃取液用盐水洗涤, 干燥($MgSO_4$), 过滤然后浓缩得到 2.6g (94%) (R)-甲磺酸 4-苄基-6-氧代-哌嗪-2-基甲酯, 其不经进一步的纯化直接用于随后的反应。^1H NMR (300 MHz, $CDCl_3$) δ 7.3-7.26 (m, 5H), 6.18 (br s, 1H), 4.32-4.16 (m, 2H), 3.8-3.7 (m, 1H), 3.61 (d, J =12.9 Hz, 1H), 3.52 (d, J =12.9 Hz, 1H), 3.32 (d, J =16 Hz, 1H), 3.0 (s, 3H), 2.7-2.6 (m, 2H) ppm。质谱: (ESI) m/z 299 $(M+H)^+$。

B: (R)-甲磺酸 6-氧代-哌嗪-2-基甲酯。

向(R)-甲磺酸 4-苄基-6-氧代-哌嗪-2-基甲酯(2.9g, 9.7mmol)的甲醇(50mL)溶液中加入 10%氢氧化钯/碳(1g)。将该多相混合物在气囊氢气压力下室温氢化 20 小时。将反应混合物用硅藻土垫过滤然后将滤液浓缩得到(R)-甲磺酸 6-氧代-哌嗪-2-基甲酯，其不经进一步的纯化直接用于随后的反应。质谱: (ESI) m/z 209 $(M+H)^+$。

C: (R)-3-甲磺酰氧基甲基-5-氧代-哌嗪-1-甲酸叔丁酯。

向(R)-甲磺酸6-氧代-哌嗪-2-基甲酯和碳酸氢钠(2.44g, 29mmol)的 THF/水(5:1, 20mL)悬浮液中于 0℃下加入 Boc-酐(2.75g, 12.6mmol)。室温下 24 小时后，将反应混合物用饱和碳酸氢钠溶液稀释并用乙酸乙酯萃取。将合并的有机萃取液用饱和氯化铵溶液和盐水洗涤，干燥($MgSO_4$)，过滤，然后浓缩。经硅胶色谱(1%至 10%甲醇的二氯甲烷溶液)得到 1.8g(35%) (R)-3-甲磺酰氧基甲基-5-氧代-哌嗪-1-甲酸叔丁酯。^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (br s, 1H), 4.3-4.1 (m, 3H), 3.94 (d, J =19 Hz, 1H), 3.82-3.75 (m, 2H), 3.55 (dd, J =14.6, 4.6 Hz, 1H), 3.09 (s, 3H), 1.48 (s, 9H) ppm。质谱: (ESI) m/z 617 $(2M+H)^+$。

D: (R)-4-(4-氨基-喹唑啉-7-基甲基)-3-甲磺酰氧基甲基-5-氧代-哌嗪-1-甲酸叔丁酯。

向(R)-3-甲磺酰氧基甲基-5-氧代哌嗪-1-甲酸叔丁酯(1.8g, 5.8mmol)的 DMF(20mL)溶液中于 0℃下加入氢化钠(60%的矿物油分散液, 0.35g, 8.7mmol)，15分钟后加入4-氨基-7-溴甲基-喹唑啉(1.52g, 6.4mmol)。室温下 1 小时后，将反应混合物用饱和氯化铵处理并用乙酸乙酯萃取。将合并的有机萃取液用水洗涤(两次)，干燥($MgSO_4$)，过滤然后浓缩。将粗产物进行硅胶色谱(5%至 20%甲醇的二氯甲烷溶液)得到 1.72g(63%) (R)-4-(4-氨基-喹唑啉-7-基甲基)-3-甲磺酰氧基甲基-5-氧代-哌嗪-1-甲酸叔丁酯。质谱: (ESI) m/z 466

$(M+H)^+$。

E: (R)-甲磺酸 1-(4-氨基-喹唑啉-7-基甲基)-6-氧代-哌嗪-2-基甲酯。

0℃下，向(R)-4-(4-氨基-喹唑啉-7-基甲基)-3-甲磺酰氧基甲基-5-氧代哌嗪-1-甲酸叔丁酯(1.72g, 3.7mmol)的甲醇(80mL)溶液中通入无水氯化氢气体 15 分钟。室温下 6 小时后，将反应混合物浓缩并用甲醇和乙醚研磨得到 1.54g (R)-甲磺酸 1-(4-氨基-喹唑啉-7-基甲基)-6-氧代-哌嗪-2-基甲酯的盐酸盐，其不经进一步纯化直接用于随后的反应。^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (s, 1 H), 8.32 (d, J =4.0 Hz, 1 H), 7.78 (s, 2H), 5.05 (br s, 1 H), 4.56 (br s, 1H), 4.46 (br s, 1H), 4.27 (br s, 1H), 4.07 (br s, 2H), 3.76 (br s, 2H), 3.11 (s, 3H) ppm. 质谱: (ESI) m/z 366 $(M+H)^+$。

F: (R)-甲磺酸 1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲酯。

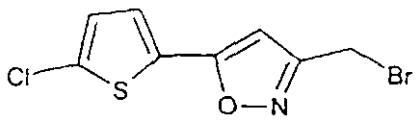
向(R)-甲磺酸 1-(4-氨基-喹唑啉-7-基甲基)-6-氧代-哌嗪-2-基甲酯-HCl (0.48g, 1.1mmol)的 DMF (3mL)溶液中于 0℃下加入三乙胺(0.92mL, 6.6mmol)，随后加入6-氯-苯并[b]噻吩-2-磺酰氯(330mg, 1.32mmol)。室温下 0.5 小时后，将反应混合物用水稀释形成固体，滤出固体并用乙醚洗涤。粗品(R)-甲磺酸 1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲酯(0.7g, 100%)不经进一步纯化直接用于随后的反应。^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 7.72 (br s, 1H), 7.59 (d, J =9.9 Hz, 1H), 7.51 (s, 1H), 7.32 (d, J =9.9 Hz, 1H), 5.15 (d, J =16 Hz, 1H), 4.45-4.30 (m, 3H), 4.07 (d, J =18 Hz, 1H), 3.85-3.70 (m, 3H), 3.25 (s, 3H), 3.25-3.15 (m, 1H)。质谱: (ESI) m/z 596 $(M+H)^+$。

G: (S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[(2-甲氧基-乙基氨基)-甲基]-哌嗪-2-酮

将(R)-甲磺酸 1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-氧代-哌嗪-2-基甲酯(100mg, 0.17mmol)和 2-氨基乙基甲基醚(1ml)在 DMF (2ml)中的混合物于 100℃加热 24 小时。将反应混合物浓缩然后进行硅胶色谱(5%至 20%甲醇的二氯甲烷溶液)得到20mg(20%) (S)-1-(4-氨基-喹唑啉-7-基甲基)-4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-[(2-甲氧基-乙基氨基)-甲基]-哌嗪-2-酮。^{1}H NMR (300 MHz, DMSO-d_6) ↗ 9.77 (br.s, 2H), 8.96 (br.s, 2H), 8.81 (s, 1H), 8.39 (s, 1H), 8.31 (d, J =8.6 Hz, 1H), 8.22 (s, 1H), 8.11 (d, J =8.7 Hz, 1H), 7.65-7.58 (m, 3H), 5.14 (d, J =16.8 Hz, 1H), 4.44 (d, J =16.8 Hz, 1H), 4.10-3.80 (m, 5H), 3.68 (d, J =16.2 Hz, 1H), 3.61 (t, J =4.8 Hz, 2H), 3.50-3.20 (m, 4H), 3.32 (s, 3H) ppm。质谱: (ESI) m/z 575 $(M+H)^+$。

甲基卤化物的制备

3-溴甲基-5-(5-氯-噻吩-2-基)-异噁唑的制备



A 部分. 4-(5-氯-噻吩-2-基)-2,4-二氧代-丁酸乙酯。

将氢化钠(60%的矿物油分散液, 2.43g, 60.8mmol)在 0℃及氮气氛下分两次加入到 2-乙酰基-5-氯噻吩(4.88g, 30.4mmol)的 150ml 无水甲苯溶液中。将混合物在 0℃下搅拌 10 分钟, 然后通过注射器加入草酸二乙酯(6.20 ml, 45.6mmol)。将所得混合物在 0℃下搅拌 30 分钟, 然后逐渐加热至 140℃并回流 1 小时。减压蒸除溶剂, 向残余物中加入 250ml 水并用乙酸乙酯(75ml x 2)洗涤, 将含水的部分冷却至 0℃并向其中加入 2N HCl 直至 pH =2, 用乙酸乙酯萃取酸化的含水

部分(100 ml x 4)，将合并的有机部分用盐水洗涤，用硫酸镁干燥。蒸除溶剂得到 7.10g (90%)棕色固体状所需产物，其不经进一步纯化直接用于随后的反应。^{1}H NMR (CD_3OD) δ 1.36 (t, 3H, J =7.1 Hz), 4.35 (q, 2H, J =7.1 Hz), 6.95 (s, 1H), 7.15 (m, 1H), 7.87 (m, 1H)。

B 部分. 5-(5-氯-噻吩-2-基)-异噁唑-3-甲酸乙酯。

将 4-(5-氯-噻吩-2-基)-2,4-二氧代-丁酸乙酯(5.40g, 20.7mmol)和羟胺盐酸盐(5.04g, 72.5mmol)在 150ml 无水乙醇中的混合物回流 3 小时。减压蒸除溶剂，向残余物中加入 150 水，然后加入氢氧化铵(28-30%)直至 pH=7。然后将含水混合物用乙酸乙酯萃取(75ml x 3)，将合并后的有机部分用盐水洗涤然后用硫酸镁干燥。蒸除溶剂后，将粗产物通过快速柱色谱纯化(10%乙酸乙酯/己烷)，得到 4.35g (82%)浅色固体状所需产物。^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3H, J =7.1 Hz), 4.44 (q, 2H, J =7.1 Hz), 6.71 (s, 1H), 6.95 (d, 1H, J =4.0 Hz), 7.31 (d, 1H, J =4.0 Hz)。

C 部分. [5-(5-氯-噻吩-2-基)-异噁唑-3-基]-甲醇。

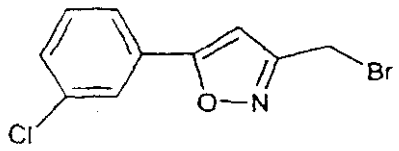
将硼氢化钠(3.20g, 84.4mmol)于 0℃下加入到 5-(5-氯-噻吩-2-基)-异噁唑-3-甲酸乙酯(4.35g, 16.9mmol)的 80ml 无水乙醇溶液中，然后将混合物室温搅拌 12 小时。减压蒸除乙醇，将残余物加入水(100ml)中，然后加入氯化铵水溶液以消耗过量的 $NaBH_4$。将产物用乙酸乙酯萃取(75ml x 3)，将合并后的有机部分用盐水洗涤，用硫酸镁干燥然后蒸除溶剂得到 3.53g (97%)白色固体状所需产物。^{1}H NMR ($CDCl_3$) δ 4.78 (s, 2H), 6.40 (s, 1H), 6.94 (d, 1 H, J =3.9 Hz), 7.27 (d, 1H, J =3.9 Hz)。

D 部分. 3-溴甲基-5-(5-氯-噻吩-2-基)-异噁唑。

将 NBS (3.19g, 17.9mmol)于 0℃下加入到[5-(5-氯-噻吩-2-

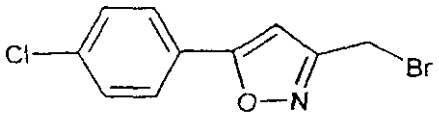
基)-异噁唑-3-基]-甲醇(3.50g, 16.2mmol)和三苯基膦(4.68g, 17.9mmol)在80ml无水二氯甲烷中的混合物中。将混合物室温搅拌1小时。蒸除溶剂，将残余物通过快速柱色谱纯化(10%乙酸乙酯/己烷)得到4.0g (89%)白色固体状产物。^{1}H NMR ($CDCl_3$) δ 4.42 (s, 2H), 6.42 (s, 1H), 6.95 (d, 1H, J =4.0 Hz), 7.28 (d, 1H, J =4.0 Hz)。

3-溴甲基-5-(3-氯-苯基)-异噁唑的制备



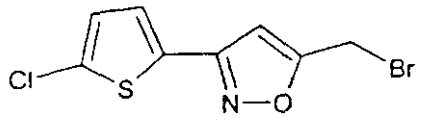
按照关于3-甲基-5-(5-氯-噻吩-2-基)-1H-吡唑描述的方法制备3-溴甲基-5-(3-氯-苯基)-异噁唑。^{1}H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.64 (s, 1H), 7.41-7.43 (m, 2H), 7.64-7.67 (m, 1H), 7.77 (m, 1H)。

3-溴甲基-5-(4-氯苯基)-异噁唑的制备



按照关于3-甲基-5-(5-氯-噻吩-2-基)-1H-吡唑描述的方法制备3-溴甲基-5-(4-氯苯基)-异噁唑。^{1}H NMR ($CDCl_3$) δ 4.45 (s, 2H), 6.60 (s, 1H), 7.44 (d, 2H, J=8.6 Hz), 7.70 (d, 2H, J=8.6 Hz).

5-溴甲基-3-(5-氯-噻吩-2-基)-异噁唑的制备



方法 I:

A 部分. 5-氯-噻吩-2-甲醛肟。

将 5-氯-2-噻吩甲醛(1.36g, 9.28mmol)和羟胺盐酸盐(0.71g, 10.2mmol)在 8ml 吡啶中的混合物室温搅拌过夜。减压蒸除吡啶, 将残余物通过快速柱色谱纯化(5%-10%乙酸乙酯的二氯甲烷溶液), 得到 1.02g (68%)白色固体状产物。^{1}H NMR (CD_3OD) δ 6.94 (d, 1H, J=4.0 Hz), 7.14 (d, 1H, J=4.0 Hz), 7.60 (s, 1H), 8.81 (宽峰, 1H, OH)。

B 部分. 5-溴甲基-3-(5-氯-噻吩-2-基)-异噁唑

将 N-氯代琥珀酰亚胺(0.28g, 2.10mmol)于室温及氮气氛下加入到 5-氯-噻吩-2-甲醛肟(0.33g, 2.04mmol)的 10ml 无水 DMF 溶液中, 接着加入 2 滴吡啶。将混合物室温搅拌 1 小时, 于 60℃搅拌 3 小时, 然后将混合物冷却至 0℃并向其中加入炔丙基溴(80wt.%的甲苯溶液, 2.30ml, 20.4mmol), 然后在 25 分钟内缓慢滴加三乙胺(0.29ml, 2.04mmol)的 2.5ml DMF 溶液。将反应混合物升温至室温, 搅拌 18 小时, 用水(200ml)稀释, 用乙酸乙酯(50ml x 3)萃取, 将合并后的有机部分用水(100ml x 2)和盐水洗涤, 用硫酸镁干燥。蒸除溶剂后, 将粗产物通过快速柱色谱纯化(5%-10%乙酸乙酯/己烷), 得到 0.28g (49%)白色固体状所需产物。^{1}H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.51 (s, 1H), 6.92 (d, 1H, J =3.9 Hz), 7.19 (d, 1H, J =3.9 Hz)。

方法 II:

A 部分. 3-(5-氯-噻吩-2-基)-异噁唑-5-甲酸乙酯。

将 N-氯代琥珀酰亚胺(0.32g, 2.41mmol)在室温及氮气氛下加入

到 5-氯噻吩-2-甲醛肟(0.39g, 2.41mmol)的 10ml 无水 DMF 溶液中，接着加入 2 滴吡啶。60℃下搅拌 3 小时后，将混合物冷却至 0℃并向其中加入丙炔酸甲酯(1.0ml, 12.1mmol)，然后在 30 分钟内缓慢加入三乙胺(0.34ml, 2.41mmol)的 2.5ml DMF 溶液。将反应液升温至室温并搅拌 12 小时，用水(200ml)稀释，用乙酸乙酯(50ml x 2)萃取，将合并后的有机部分用水和盐水洗涤，用硫酸镁干燥。蒸除溶剂后，将粗产物通过快速柱色谱纯化(3%-10%乙酸乙酯/己烷)，得到 0.19g (32%)白色固体状所需产物。^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 6.95 (d, 1H, J=3.9 Hz), 7.11 (s, 1H), 7.26 (d, 1H, J=3.9 Hz)。

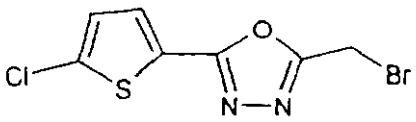
B 部分. [3-(5-氯-噻吩-2-基)-异噁唑-5-基]-甲醇。

将硼氢化钠(0.14g, 3.90mmol)于 0℃下加入到 3-(5-氯-噻吩-2-基)-异噁唑-5-甲酸乙酯(0.19g, 0.78mmol)的 15ml 无水甲醇悬浮液中。然后将混合物于 0℃及氮气氛下搅拌，室温搅拌半小时。减压蒸除甲醇，将残余物加入水(50ml)中，加入氯化铵水溶液直至 pH =7。将产物用乙酸乙酯(30ml x 2)萃取，将合并后的有机部分用盐水洗涤，用硫酸镁干燥，蒸除溶剂得到 0.14g (83%)白色固体状所需产物。^{1}H NMR ($CDCl_3$) δ 4.79 (s, 2H), 6.44 (s, 1H), 6.92 (d, 1H, J =3.9 Hz), 7.19 (d, 1H, J =3.9 Hz)。

C 部分. 3-溴甲基-5-(5-氯-噻吩-2-基)-异噁唑。

将 N-溴代琥珀酰亚胺(0.14g, 0.78mmol)于 0℃及氮气氛下加入到[3-(5-氯-噻吩-2-基)-异噁唑-5-基]-甲醇(0.14g, 0.65mmol)和三苯基膦(0.21g, 0.78mmol)在 15ml 无水二氯甲烷中的混合物中。然后将混合物室温搅拌 1 小时。蒸除溶剂，将残余物通过快速柱色谱纯化(10%乙酸乙酯/己烷)得到 0.13g (72%)白色固体状产物。^{1}H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.51 (s, 1H), 6.92 (d, 1H, J =3.9 Hz), 7.19 (d, 1 H, J =3.9 Hz)。

5-(5-氯噻吩-2-基)-2-溴甲基-[1,3,4]噁二唑的制备



A 部分. 5-氯-噻吩-2-甲酸 N-乙酰基-酰肼。

将 2.0M 草酰氯的二氯甲烷(82ml)于 0℃下加入到搅拌中的 5-氯-噻吩-2-甲酸(13.33g)和 DMF (0.1ml)的二氯甲烷(150ml)溶液中，25 分钟后，升温至室温并搅拌 1 小时。蒸除二氯甲烷得到油状物(酰氯)，将其溶于 THF (40ml)。将形成的溶液在室温及氮气氛下加入到搅拌中的乙酰肼(6.08g)的 THF (100ml)溶液中，然后加入碳酸钾(22.66g)。室温搅拌 4 小时。真空蒸除 THF 得到固体并将其溶于甲醇(120ml)。滤除沉淀出的固体；将所得溶液浓缩得到标题产物(17.90g)，收率 100%。^{1}HNMR (CD_3OD) ppm 7.34 (d, H), 6.85 (d, H), 2.00 (s, 3H)。

B 部分. 5-(5-氯-噻吩-2-基)-2-甲基-[1,3,4]噁二唑

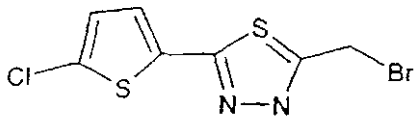
将 5-氯-噻吩-2-甲酸 N-乙酰基-酰肼(1.11g)和 P_2O_5 (18.0g)的混合物于 110℃加热 20 小时。冷却至室温，加入冰(200g)以溶解 P_2O_5。将深色的溶液用水稀释至 400ml，用乙醚(2 x 30ml)萃取。将合并的有机溶液用盐水洗涤然后用硫酸镁干燥。浓缩后得到 0.62g 产物，收率 61%。^{1}HNMR ($CDCl_3$) ppm 7.45 (d, H), 6.93 (d, H), 2.56 (s, 3H)。

C 部分. 5-(5-氯-噻吩-2-基)-2-溴甲基-[1,3,4]噁二唑

将 5-(5-氯-噻吩-2-基)-2-甲基-[1,3,4]-噁二唑(937mg)、NBS (800mg)和苯过氧化物(330mg)的四氯化碳(100ml)溶液回流过夜。将反应混合物浓缩得到固体残余物，将其进行硅胶色谱，用 5-10%乙酸乙酯作为洗脱剂。以 50%的收率得到纯净产物(429mg)。^{1}HNMR ($CDCl_3$)

ppm 7.55 (d, H), 6.98 (d, H), 4.58 (s, 2H)。

5-(5-氯噻吩-2-基)-2-溴甲基-[1,3,4]噻二唑的制备



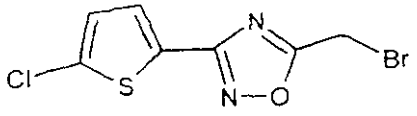
A 部分. 5-(5-氯-噻吩-2-基)-2-甲基-[1,3,4]噻二唑

将 5-氯-噻吩-2-甲酸 N-乙酰基-酰肼(1.18g)和 Lowesson's 试剂(2.18g)的二甲苯(40ml)溶液于 140℃搅拌 1 小时。将该热的溶液转移到硅胶色谱柱上。冷却后，用己烷洗涤以除去二甲苯。将固体进行硅胶色谱，用 20%乙酸乙酯作为洗脱剂。以约 100%的收率得到纯净的产物(1.18g)。^{1}HNMR ($CDCl_3$) ppm 7.25 (d, H), 6.93 (d, H), 2.78 (s, 3H)。

B 部分. 5-(5-氯-噻吩-2-基)-2-溴甲基-[1,3,4]噻二唑的制备

将 5-(5-氯-噻吩-2-基)-2-甲基-[1,3,4]噻二唑(937mg)、NBS (800mg)和苯过氧化物(330mg)的四氯化碳(100ml)溶液回流过夜。浓缩得到固体，将其进行硅胶色谱，用 10%乙酸乙酯作为洗脱剂。以 54%的收率得到纯净的产物(672mg)。^{1}HNMR ($CDCl_3$) ppm 7.31 (d. H), 6.96 (d, H), 4.80 (s, 2H)。

5-溴甲基-3-(5-氯-噻吩-2-基)-[1,2,4]噁二唑的制备



A 部分. 5-氯-噻吩-2-甲醛肟。

将 5-氯-2-噻吩甲醛(1.36g, 9.28mmol)、羟胺盐酸盐(0.71g, 10.2mmol)在 8ml 吡啶中的混合物室温搅拌过夜。减压蒸除吡啶，将

残余物通过快速柱色谱纯化(5%-10%乙酸乙酯的二氯甲烷溶液)得到1.02g(68%)白色固体状产物。^{1}H NMR (CD_3OD) δ 6.94 (d, 1H, J=4.0 Hz), 7.14 (d, 1H, J=4.0 Hz), 7.60 (s, 1H), 8.81 (宽峰, 1H, OH)。

B 部分. 5-氯-噻吩-2-甲腈。

将 5-氯-噻吩-2-甲醛肟(2.20g, 13.6mmol)的 30ml 无水乙酸酐溶液回流 24 小时; 减压蒸除过量的乙酸酐。将所得残余物加入 100ml 水中, 用氢氧化铵中和并用乙酸乙酯(50ml x 3)萃取。将合并的有机部分用盐水洗涤。蒸除溶剂后, 将残余物通过快速柱色谱纯化(10%乙酸乙酯的己烷溶液); 得到 1.50g(77%)无色油状的所需产物。^{1}H NMR ($CDCl_3$) d, J =4.1 Hz), 6.95 (1H, d, J =4.0 Hz)。

C 部分. 5-氯-N-羟基-噻吩-2-甲脒。

将羟胺盐酸盐(1.10g, 15.7mmol)和氢氧化钠(0.63g, 15.7mmol)在 20ml 乙醇和 1ml 水中的混合物加入到 5-氯噻吩-2-甲腈(1.50g, 10.4mmol)的 20ml 乙醇溶液中。将混合物回流 12 小时。减压蒸除溶剂, 将残余物通过快速柱色谱纯化(2%甲醇的二氯甲烷溶液); 得到 1.65g (90%)白色固体状所需产物。^{1}H NMR (CD_3OD) δ 7.52 (1H, d, J =4.1 Hz), 7.00-7.01 (1H, m)。

D 部分. 3-(5-氯-噻吩-2-基)-[1,2,4]噁二唑-5-甲酸乙酯。

将吡啶(0.14 ml, 1.70mmol)滴加到 5-氯-N-羟基噻吩-2-甲脒(0.15g, 0.85mmol)和氯氧代乙酸乙酯(ethyl chlorooxoacetate)(0.19 ml, 1.70mmol)在 10ml 无水氯仿中的混合物中。将反应液回流 16 小时; 减压蒸除溶剂。将残余物加入 50ml 水中并用乙酸乙酯(15ml x 2)萃取; 将有机部分用盐水洗涤然后用硫酸镁干燥。浓缩后, 将粗产物通过快速柱色谱纯化(5%乙酸乙酯的己烷溶液); 得到 0.11g(50%)无色油状所需产物。^{1}H NMR ($CDCl_3$) δ 7.67-7.69 (1H, m), 6.99 (1H,

d, J =4.1 Hz), 4.56 (2H, q, J =7.1 Hz), 1.48 (3H, t, J =7.1 Hz)。

E 部分. [3-(5-氯-噻吩-2-基)-4,5-二氢-[1,2,4]噁二唑-5-基]-甲醇。

将硼氢化钠(0.080g, 2.20mmol)于 0℃下加入到 3-(5-氯-噻吩-2-基)-[1,2,4]噁二唑-5-甲酸乙酯(0.11g, 0.43mmol)的 10ml 无水甲醇溶液中。将反应液于 0℃下搅拌 30 分钟, 减压蒸除溶剂并将残余物用 30ml 水稀释。将该含水溶液用乙酸乙酯(20ml x 2)萃取, 将合并后的有机部分用盐水洗涤, 用硫酸镁干燥然后浓缩得到粘稠油状的所需产物(0.085g, 91%)。^{1}H NMR (CD_3OD) δ 7.25-7.28 (1H, m), 6.99-7.01 (1H, m), 5.61-5.62 (1H, m), 3.54-3.59 (2H, m)。

F 部分. [3-(5-氯-噻吩-2-基)-[1,2,4]噁二唑-5-基]-甲醇。

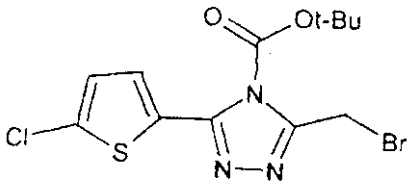
将 N-氯代琥珀酰亚胺(0.052g, 0.39mmol)于 50℃及氮气氛下加入到[3-(5-氯-噻吩-2-基)-4,5-二氢-[1,2,4]噁二唑-5-基]-甲醇(0.085g, 0.39mmol)的 4.0ml 无水 DMF 溶液中。然后将混合物于 50℃搅拌 40 分钟, 倒入 50ml 水中并用乙酸乙酯(15ml x 3)萃取。将合并后的有机部分用水和盐水洗涤然后用硫酸镁干燥; 蒸除溶剂得到白色固体状产物(0.082g, 96%)。^{1}H NMR (CD_3OD) δ 7.61 (1H, d, J =4.0 Hz), 7.09 (1H, d, J=3.9Hz), 4.86 (2H, s)。

G 部分. 5-溴甲基-3-(5-氯-噻吩-2-基)-1,2,4-噁二唑。

将 N-溴代琥珀酰亚胺(0.082g, 0.46mmol)于 0℃及氮气氛下加入到 3-(5-氯-噻吩-2-基)-[1,2,4]噁二唑-5-基]-甲醇(0.082g, 0.38mmol)和三苯基膦(0.12g, 0.46mmol)在 10ml 无水二氯甲烷中的混合物中。将反应液于 0℃搅拌 30 分钟, 然后升温至室温 1 小时。蒸除溶剂,将残余物通过快速柱色谱纯化(5%-10%乙酸乙酯的己烷溶液); 得到 0.030g (47%)无色油状的产物。还回收到了原料(0.036g)。^{1}H NMR

($CDCl_3$) δ 7.58 (1H, d, J =4.0 Hz), 6.97 (1H, d, J =4.0 Hz), 4.51 (2H, s)。

5-(5-氯-噻吩-2-基)-3-溴甲基-4-甲酸叔丁酯[1,2,4]三唑的制备



A 部分. N,N'-(5-氯-噻吩-2-羧基)-乙酰基-酰肼

将乙酸酐(1.62g)和 1.9M Et_3Al (25.3ml)的甲苯溶液室温搅拌 20 分钟。于室温下缓慢加入 5-氯-2-氰基噻吩(3.14g)的甲苯(55ml)溶液然后于 85℃搅拌过夜。将反应液冷却至室温，用 4 滴水终止反应然后室温搅拌 20 分钟.加入水(30ml),滤出固体并用热甲醇(3 x 30ml)洗涤。将滤液浓缩；固体用乙醇重结晶得到白色固体状产物(2.88g, 61%)。^{1}HNMR (CD_3OD) ppm 7.35 (d, H), 6.92 (d, H), 2.01 (s, 3H)。

B 部分. 5-(5-氯-噻吩-2-基)-2-甲基-4H-[1,2,4]三唑

将 N,N'-(5-氯-噻吩-2-羧基)-乙酰基-酰肼(1.80g)于 180℃加热 20 分钟然后冷却得到白色固体状产物(1.15g, 100%)。^{1}HNMR ($CDCl_3$) ppm 7.48 (d, H), 6.96 (d, H), 4.86 (s, NH) 2.46 (s, 3H)。

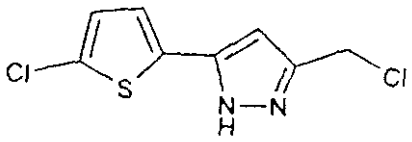
C 部分. 5-(5-氯-噻吩-2-基)-2-甲基-4-甲酸叔丁酯[1,2,4]三唑

将 5-(5-氯-噻吩-2-基)-2-甲基-4H-[1,2,4]三唑(1.09g)、$(BOC)_2O$ (1.43g)和 DMAP (0.14g)的溶液室温搅拌过夜。蒸除 THF 得到油状物，将其溶于二氯甲烷(40ml)，用 1N 盐酸和水洗涤。用硫酸镁干燥后，将有机层浓缩得到纯净产物(1.64g, 100%)。^{1}HNMR ($CDCl_3$) ppm 7.50 (d, H), 6.89 (d, H), 2.69 (s, 3H), 1.64 (s, 9H)。

D 部分. 5-(5-氯-噻吩-2-基)-3-溴甲基-4-甲酸叔丁酯[1,2,4]三唑

将 5-(5-氯-噻吩-2-基)-2-甲基-4-甲酸叔丁酯[1,2,4]三唑(1.16g)、NBS (1.14g)和苯过氧化物(0.27mg)的四氯化碳(50ml)溶液回流过夜。浓缩得到固体，将其进行硅胶色谱，用 5-10%乙酸乙酯作为洗脱剂。以 43%的收率得到纯净的产物(0.91g)。^{1}HNMR ($CDCl_3$) ppm 7.56 (d, H), 6.92 (d, H), 4.76 (s, 2H), 1.70 (s, 9H)。

5-氯甲基-3-(5-氯-噻吩-2-基)-1H-吡唑的制备



A 部分. 4-(5-氯-噻吩-2-基)-2,4-二氧代-丁酸乙酯。

将氢化钠(60%矿物油分散液，2.43g，60.8mmol)于 0℃及氮气氛下分两次加入到 2-乙酰基-5-氯噻吩(4.88g，30.4mmol)的 150ml 无水甲苯溶液中。将混合物于 0℃下搅拌 10 分钟后，通过注射器加入草酸二乙酯(6.20ml，45.6mmol)，将所得混合物在 0℃下搅拌 30 分钟，然后逐渐加热至 140℃并回流 1 小时。减压蒸除溶剂，向残余物中加入 250ml 水然后用乙酸乙酯(75ml x 2)洗涤，将含水的部分冷却至 0℃并向其中加入 2N 盐酸直至 pH =2，用乙酸乙酯萃取酸化的含水部分(100ml x 4)，将合并后的有机部分用盐水洗涤并用硫酸镁干燥。蒸除溶剂得到 7.10g (90%)棕色固体状所需产物，其不经进一步纯化直接用于随后的反应。^{1}H NMR (CD_3OD) δ 1.36 (t, 3H, J =7.1 Hz), 4.35 (q, 2H, J =7.1 Hz), 6.95 (s, 1H), 7.15 (m, 1H), 7.87 (m, 1H)。

B 部分. 4-(5-氯-噻吩-2-基)-2H-吡唑-3-甲酸乙酯。

将肼(0.30ml，9.44mmol)于 0℃下加入到 4-(5-氯-噻吩-2-基)-2,4-二氧代-丁酸乙酯(1.64g，6.30mmol)的 80ml 无水乙醇溶液中。

将混合物升温至室温，加入数滴乙酸然后将混合物于 90℃搅拌 1 小时。减压蒸除溶剂，将残余物加入 100ml 水中，然后用乙酸乙酯(50ml x 3)萃取。将合并的有机部分用盐水洗涤然后用硫酸镁干燥。蒸除溶剂后，将粗产物通过快速柱色谱纯化(10%至 20%乙酸乙酯/己烷)；得到 0.53g (33%)白色固体状所需产物。^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, J =7.1 Hz), 4.39 (q, 2H, J =7.1 Hz), 6.87 (d, 1H, J=3.9 Hz), 6.94 (s, 1 H), 7.11 (d, 1H, J =3.9 Hz), 11.6 (宽峰, 1H)

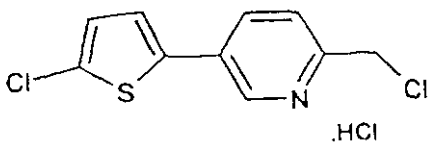
C 部分. [5-(5-氯-噻吩-2-基)-2H-吡唑-3-基]-甲醇。

将二异丁基氢化铝(1.5M 的甲苯溶液，6.80ml，10.1mmol)于 0℃及氮气氛下滴加到 4-(5-氯-噻吩-2-基)-2H-吡唑-3-甲酸乙酯(0.52g，2.03mmol)的 40ml 无水四氢呋喃溶液中。将混合物于 0℃下搅拌半小时，然后室温搅拌半小时。用甲醇(0.80ml)于-10℃下终止反应；加入 100ml 10%酒石酸钠钾溶液。将含水混合物用乙酸乙酯(50ml x 3)萃取；将合并后的有机部分用盐水洗涤，用硫酸镁干燥然后浓缩得到 0.43g(99%)白色固体状所需产物。^{1}H NMR (CD_3OD) δ 4.61 (s, 2H), 6.46 (s, 1H), 6.92 (d, 1H, J =3.7 Hz), 7.13 (d, 1H, J =3.9 Hz)。

D 部分. 5-氯甲基-3-(5-氯-噻吩-2-基)-1H-吡唑。

将 N-氯代琥珀酰亚胺(0.30g，2.24mmol)于 0℃及氮气氛下加入到[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基]-甲醇(0.40g，1.86mmol)和三苯基膦(0.59g，2.24mmol)的 40ml 无水四氢呋喃和 40ml 无水氯仿溶液中。将混合物于 0℃下搅拌 10 分钟，然后升温至室温半小时。蒸除溶剂，将残余物通过快速柱色谱纯化(15%乙酸乙酯/己烷)，得到 0.29g(67%)白色固体状产物。^{1}H NMR ($CDCl_3$加少量 CD_3OD) δ 4.58 (s, 2H), 6.42 (s, 1H), 6.84 (d, 1H, J =3.9 Hz), 7.03 (d, 1H, J =3.8 Hz)。

2-氯甲基-5-(5-氯-噻吩-2-基)-吡啶盐酸盐的制备



A 部分. 2-甲基-5-三氟甲基磺酰氧基-吡啶

将 2-甲基-5-羟基吡啶(7.4g, 67.80mmol)悬浮在 40mL 吡啶中。于 5℃下滴加三氟甲磺酸酐(20g, 70.89mmol)。在该温度下 30 分钟后，将形成的溶液室温搅拌 12 小时。将反应混合物用 200mL 乙酸乙酯稀释，用 1N 盐酸(3 x 200mL)和盐水(200mL)洗涤，用硫酸镁干燥然后浓缩。得到无色液体状标题化合物(12.6g, 77%)。$C_7H_6F_3O_3S$ MS $(M+H)^+$ =242

B 部分. 5-(5-氯-噻吩-2-基)-2-甲基-吡啶

氮气氛下，向 2-甲基-5-三氟甲基磺酰氧基-吡啶(4.82g, 20mmol)的 60mL DMF 溶液中加入 5-氯噻吩-2-硼酸(4g, 24.6mmol)、四(三苯基膦)钯(0) (1g, 0.86mmol)和磷酸钾(6.36g, 30mmol)。将该混合物于 100℃加热 6 小时，冷却然后用 200mL 乙酸乙酯稀释。将乙酸乙酯溶液用水(2 x 200mL)和盐水(200mL)洗涤，用硫酸镁干燥然后浓缩。将所得残余物通过硅胶柱色谱纯化，用环己烷 70%/AcOEt 30%洗脱。得到浅黄色固体状标题化合物(3g, 71%)。$C_{10}H_8NClS$ MS $(M+H)^+$ =210, Cl 花样

C 部分. 5-(5-氯-噻吩-2-基)-2-甲基-吡啶-1-氧化物

向 5-(5-氯-噻吩-2-基)-2-甲基-吡啶(1.3g, 6.35mmol)的 50mL 二氯甲烷溶液中于 5℃下分批加入 70%氯过氧苯甲酸(1.67g, 6.77mmol)。将所得溶液室温搅拌 2 小时然后真空浓缩。将所得固体加入乙酸乙酯(100mL)中，用 0.5N 氢氧化钠(2 x 50mL)和盐水(50mL)洗涤。将有机层用硫酸镁干燥然后浓缩得到白色固体状标题化合物

(1.25g, 71%)。$C_{10}H_8OClNS$ MS $(M+H)^+$ =226, Cl 花样

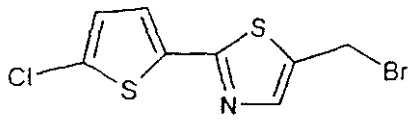
D 部分. 5-(5-氯-噻吩-2-基)-2-羟基甲基-吡啶

向 5-(5-氯-噻吩-2-基)-2-甲基-吡啶-1-氧化物(1.25g, 5.54mmol)的 20mL 二氯甲烷溶液中滴加三氟乙酸酐(1.6mL, 14.07mmol)。将该溶液室温搅拌 2 小时, 浓缩然后真空干燥。将所得固体加入 20mL 二氯甲烷和 30mL 2M 碳酸钾水溶液中。将该两相的混合物于室温下剧烈搅拌 6 小时。分出水相并用二氯甲烷萃取两次。将有机相合并, 用硫酸镁干燥然后浓缩。将所得粗产物通过硅胶柱色谱纯化, 用乙酸乙酯洗脱。得到浅黄色固体状标题化合物(1g, 80%)。$C_{10}H_8OClNS$ MS $(M+H)^+$ =226, Cl 花样

E 部分. 2-氯甲基-5-(5-氯-噻吩-2-基)-吡啶盐酸盐

将 5-(5-氯-噻吩-2-基)-2-羟基甲基-吡啶(550mg, 2.44mmol)的 20mL 亚硫酰氯溶液回流 2 小时然后真空浓缩。将所得固体用乙醚洗涤 3 次然后真空干燥。得到绿色固体状标题化合物(600mg, 88%), 其不经进一步纯化直接使用。$C_{10}H_7ClNS$ MS $(M+H)^+$ =244, Cl 花样。

5-溴甲基-2-(5-氯-噻吩-2-基)-噻唑的合成



A 部分. 5-氯噻吩-2-甲酰胺

向 5-氯噻吩-2-甲酸(5g, 30.75mmol)的 100mL 二氯甲烷溶液中加入草酰氯(3.2mL, 36.90mmol)和 10 滴 DMF。室温下 2 小时后, 将溶液真空浓缩并将残余物加入 100mL THF 中。将 NH_3 气流通过该反应液 10 分钟, 然后将悬浮液搅拌 1 小时 30 分钟。加入水并真空蒸除 THF。将固体过滤, 用水和环己烷洗涤然后真空干燥。得到白色固体状标题

化合物(4.7g, 95%)。C_5H_4OClNS。

B部分. 5-氯噻吩-2-硫代甲酰胺

将 5-氯噻吩-2-甲酰胺(4.24g, 26.2mmol)和五硫化磷(2.33g, 5.25mmol)在80mL甲苯中混合并将该反应混合物回流5小时。冷却后滤除黑色固体。将滤液用活性炭处理并再次过滤。将黄色溶液用硫酸镁干燥然后浓缩。将所得粗产物通过硅胶柱色谱进行纯化, 用氯仿95%/甲醇 5%洗脱。得到黄色固体状标题化合物(1.71g, 37%)。$C_5H_4ClNS_2$。

C部分. 2-(5-氯-噻吩-2-基)-噻唑-5-甲酸甲酯

将 5-氯噻吩-2-硫代甲酰胺(546mg, 3.08mmol)和氯甲酰基乙酸甲酯(663mg, 纯度95%, 4.6mmol)溶于4.5mL甲醇中并将所得混合物回流3小时, 然后补加氯甲酰基乙酸甲酯(288mg, 纯度95%, 2mmol)。回流20小时后, 将反应混合物真空浓缩。将所得粗产物通过硅胶柱色谱进行纯化, 用环己烷99%/EtOAc 1%洗脱。得到白色固体状标题化合物(203mg, 25%)。$C_9H_6ClNO_2S_2$。

D部分. 2-(5-氯-噻吩-2-基)-5-羟基甲基-噻唑

向搅拌中的 2-(5-氯-噻吩-2-基)-噻唑-5-甲酸甲酯(194mg, 0.748mmol)的 12mL 甲醇悬浮液中于室温加入 $NaBH_4$ (300mg, 7.9mmol)。2小时后, 补加 $NaBH_4$ (300mg, 7.9mmol)并将反应混合物室温搅拌2小时。向其中加入水并真空蒸除甲醇。将所得水溶液用0.1N盐酸中和并用EtOAc萃取; 将有机层用硫酸镁干燥然后真空浓缩。标题化合物(173mg, 85%)不经进一步纯化直接使用。$C_8H_6ClNOS_2$。

E部分. 5-溴甲基-2-(5-氯-噻吩-2-基)-噻唑

向 2-(5-氯-噻吩-2-基)-5-羟基甲基-噻唑(90mg, 0.39mmol)的5mL二氯甲烷溶液中于0℃下加入三苯基膦(122mg, 0.467mmol)和N-

溴代琥珀酰亚胺(83mg, 0.467mg)。在0℃下搅拌10分钟后，将反应混合物升温至室温30分钟。真空蒸除溶剂并将所得粗产物通过硅胶柱色谱进行纯化，用环己烷90%/AcOEt 10%洗脱得到标题化合物(31mg, 27%)。$C_8H_5BrClNS_2$。

用前述实施例的制备例和方法中所描述的甲基卤化物制备如下抑制剂:

实施例1533

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-吡啶-2-基甲基]-哌嗪-2-酮三-三氟乙酸盐

向2-氯甲基-5-(5-氯-噻吩-2-基)-吡啶盐酸盐(600mg, 2.13mmol)的25mL DMF溶液中加入1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮(500mg, 1.94mmol)，随后加入N-乙基二异丙基胺(1.5ml, 8.61mmol)。将该混合物室温搅拌2天，用100mL水稀释。搅拌1小时后，滤除黄色固体，用水充分洗涤然后真空干燥。将固体通过硅胶柱色谱进行纯化，先用二氯甲烷洗脱，再用10%甲醇-二氯甲烷洗脱，随后通过RP-HPLC进行纯化，用50%乙腈/水(0.1% TFA)的混合物进行洗脱。收集适当的馏分并冷冻干燥得到白色固体状标题化合物(467mg, 收率29%)。$C_{23}H_{21}OClN_6S$ MS $(M+H)^+$ =465, Cl花样。^1H NMR (1H, DMSO) 9.82 (d, J=17Hz, 2H); 8.90 (d, J=3Hz, 1H); 8.82 (s, 1H); 8.41 (d, J=10Hz, 1H); 8.12 (dd, J=2Hz, J=9Hz, 1H); 7.70 (s, 1H); 7.63 (d, J=9Hz, 1H); 7.58 (s, 1H); 7.56 (m, 1H); 7.22 (dd, J=1Hz, J=4Hz, 1H); 4.78 (s, 2H); 4.34 (s, 2H); 3.82 (s, 2H); 3.50 (m, 2H); 3.48 (m, 2H)。

用前述实施例的制备例和方法中所描述的甲基卤化物制备如下抑制剂:

实施例 1534

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.37 (1H, d, J=8.6Hz), 7.55-7.61 (3H, m), 7.27-7.29 (1H, m), 6.89 (1H, s), 4.80 (1H, d, J=16.1Hz), 4.65 (1H, d, J=16.0Hz), 4.00 (1H, d, J=14.6Hz), 3.78-3.83 (4H, m), 3.36 (2H, s), 3.27 (3H, s), 3.06-3.10 (1H, m), 2.67-2.68 (1H, m)。MS(离子喷雾) $[M+H]^+$ 499/501, Cl 花样。

实施例 1535

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-3-(S)-丙基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.74 (2H, bs), 8.81 (1H, s), 8.37 (1H, d, J=8.5Hz), 7.54-7.61 (3H, m), 7.28-7.29 (1H, m), 6.88 (1H, s), 4.64-4.76 (2H, m), 3.91 (1H, d, J=14.4Hz), 3.71 (1H, d, J=14.4Hz), 3.27-3.30 (2H, m), 3.13 (1H, t, J=4.7Hz), 3.01-3.05 (1H, m), 2.61-2.65 (1H, m), 1.80-1.86 (2H, m), 1.39-1.52 (1H, m), 1.13-1.27 (1H, m), 0.80-0.85 (3H, m)。MS(离子喷雾) $[M+H]^+$ 497/499, Cl 花样。

实施例 1536

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-3-(S)-甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J=8.6Hz), 7.59-7.61 (2H, m), 7.52 (1H, s), 7.29 (1H, d, J=4.0Hz), 6.92 (1H, s), 4.63-4.70 (2H, m), 3.95 (1H, d, J=14.5Hz), 3.76 (1H, d, J=14.5Hz), 3.24-3.32 (3H, m), 2.97-3.05 (1H, m), 2.60-2.70 (1H, m), 1.40 (3H, d, J=6.8Hz)。

MS(离子喷雾) $[M+H]^+$ 469/471, Cl 花样。

实施例 1537

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.81 (1H, bs), 9.77 (1H, s), 8.80 (1H, s), 8.38 (1H, d, J=8.5Hz), 7.59-7.62 (2H, m), 7.24 (1H, d, J=3.9Hz), 7.04 (1H, s), 4.71 (2H, s), 3.91 (2H, s), 3.30-3.34 (4H, m), 2.82-2.85 (2H, m)。MS(离子喷雾)$[M+H]^+$ 455/457, Cl 花样。

实施例 1538

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.73 (2H, bs), 8.80 (1H, s), 8.37 (1H, d, J=8.6Hz), 7.55-7.62 (3H, m), 7.24-7.26 (1H, m), 7.00 (1H, s), 4.80 (1H, d, J=16.2Hz), 4.65 (1H, d, J=16.0Hz), 4.10 (1H, d, J=15.6Hz), 3.98 (1H, d, J=15.6Hz), 3.78-3.86 (3H, m), 3.33 (2H, s), 3.28 (3H, s), 3.10-3.14 (1H, m), 2.66-2.73 (1H, m)。MS(离子喷雾)$[M+H]^+$ 499/501, Cl 花样。

实施例 1539

1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-3-甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J=8.6Hz), 7.59-7.62 (2H, m), 7.51 (1H, s), 7.25 (1H, d, J=3.9Hz), 7.03 (1H, s), 4.69 (2H, s), 4.05 (1H, d, J=15.6Hz), 3.94 (1H, d, J=15.5Hz), 3.34-3.36 (1H, m), 3.20-3.26 (2H, m), 3.04-3.08 (1H, m), 2.65-2.71 (1H, m), 1.40 (3H, d, J=6.8Hz)。

MS(离子喷雾)[M+H]$^+$ 469/471, Cl 花样。

实施例 1540

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.81 (1H, s), 9.77 (1H, s), 8.80 (1H, s), 8.36 (1H, d, J=8.6Hz), 7.58-7.62 (2H, m), 7.26 (1H, d, J=3.9Hz), 7.10 (1H, d, J=3.9Hz), 6.62 (1H, s), 4.73 (2H, s), 3.95 (2H, s), 3.50 (2H, s), 3.38 (2H, s), 3.02 (2H, s)。MS(离子喷雾)[M+H]$^+$ 454/456, Cl 花样。

实施例 1541

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]-3-(S)-甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J=8.6Hz), 7.60 (1H, d, J=8.6Hz), 7.54 (1H, s), 7.25 (1H, d, J=3.9Hz), 7.09 (1H, d, J=3.9Hz), 6.61 (1H, s), 4.64 -4.77 (2H, m), 3.98-4.10 (1H, m), 3.79-3.92 (1H, m), 3.25-3.46 (3H, m), 3.09-3.20 (1H, m), 2.70-2.85 (1H, m), 1.47 (3H, d, J=6.6Hz)。MS(离子喷雾)[M+H]$^+$ 468/470, Cl 花样。

实施例 1542

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]-3-(S)-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300MHz, DMSO) δ 9.73 (2H, bs), 8.80 (1H, s), 8.36 (1H, d, J=8.6Hz), 7.60 (1H, d, J=8.6Hz), 7.54 (1H, s), 7.23 (1H, d, J=3.9Hz), 7.07 (1H, d, J=3.9Hz), 6.56 (1H, s), 4.81 (1H, d, J=16.1Hz), 4.64 (1H, d, J=16.1Hz), 3.65-4.00 (5H, m), 3.26-3.38 (5H, m), 3.04-3.16 (1H, m), 2.55-2.64 (1H, m)。

MS(离子喷雾)$[M+H]^+$ 498/500, Cl 花样。

实施例 1543

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(3-氯-苯基)-4H-[1,2,4]三唑-3-基甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.79 (s, 2H), 8.80 (s, H), 8.37 (d, H), 8.04 (s, H), 7.95 (m, H), 7.47-7.68 (m, 4H), 4.57-5.94 (m, 4H), 4.40 (s, H), 4.11 (m, 2H), 3.42-3.84 (m, 4H), 3.37 (s, 3H)。MS: (M+H), 493, 495。

实施例 1544

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(3-氯-苯基)-4H-[1,2,4]三唑-3-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.80 (s, 2H), 8.79 (s, H), 8.36 (d, H), 8.00 (s, H), 7.91 (s, H), 7.43-7.68 (d, H), 4.75 (m, 5H), 4.05-4.83 (m, 4H), 3.10-4.02 (m, 6H)。MS: (M+H), 449, 451。

实施例 1545

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.81 (s, 2H, NH_2), 8.80 (s, H), 8.36 (d, H), 7.65 (s, H), 7.58 (d, H), 7.56 (d, 4H), 7.14 (d, H), 4.75 (s, 2H), 4.54 (s, 2H), 4.04 (s, 2H), 3.43-3.70 (m, 4H)。MS: (M+H), 455, 457。

实施例 1546

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.79 (s, 2H, NH_2), 8.76 (s, H), 8.37 (d, H),

7.63 (s, H), 7.57 (d, H), 7.54 (d, H), 7.18 (d, H), 4.52-4.94 (m, 4H), 4.34 (s, 2H), 4.03 (m, 2H), 3.45-3.80 (m, 4H), 3.37 (s, 3H)。MS: (M+H), 499, 501。

实施例 1547

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(4-氯-苯基)-4H-[1,2,4]三唑-3-基甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.78 (s, 2H, NH2), 8.77 (s, H), 8.35 (d, H), 8.00 (d, H), 7.61 (s, H), 7.52 (m, 3H), 4.57-5.93 (m, 4H), 4.38 (m, H), 4.10 (m, 2H), 3.45-3.84 (m, 4H), 3.39 (s, 3H)。MS: (M+H), 493, 495。

实施例 1548

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基-[1,3,4]噁二唑-2-基甲基]-(s)-3-甲基-哌嗪-2-酮二-三氟乙酸盐

1H NMR: (DMSO-d_6) 9.76 (d, 2H, NH2), 8.75 (s, H), 8.35 (d, H), 7.64 (d, H), 7.57 (d, H), 7.55 (s, H), 7.25 (d, H), 4.43-4.80 (m, 4H), 4.72-3.84 (m, H), 3.10-3.55 (m, 4H), 1.55 (d, 3H)。MS: (M+H), 470, 472。

实施例 1549

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-(s)-3-甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.78 (d, 2H, NH2), 8.85 (s, H), 8.36 (d, H), 8.01 (s, H, NH), 7.94 (d, H), 7.63 (s, H), 7.60 (d, H), 7.54 (d, H), 4.50-4.86 (m, 4H), 4.22 (m, H), 3.40-3.84 (m, 4H), 1.68 (d, 3H)。MS: (M+H), 463, 465。

实施例 1550

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.76 (s, 2H, NH2), 8.76 (s, H), 8.36 (d, H), 7.65 (d, H), 7.59 (s, H), 7.57 (d, H), 7.26 (d, H), 5.74 (q, 2H), 4.35-4.55 (m, 3H), 3.00-4.00 (m, 9H 包括 s, 3H)。MS: (M+H), 500, 502。

实施例 1551

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基-[1,3,4]噁二唑-2-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.78 (d, 2H, NH2), 8.79 (s, H), 8.35 (s, H), 7.66 (d, H), 7.63 (s, H), 7.56 (d, H), 7.29 (d, H), 4.72 (s, 2H), 4.56 (s, 2H), 3.85 (s, 2H), 3.32-3.52 (d, 4H)。MS: (M+H), 456, 458。

实施例 1552

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(4-氯-苯基)-4H-[1,2,4]三唑-3-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.80 (d, 2H, NH2), 8.78 (s, H), 8.37 (d, H), 8.00 (d, 2H), 7.66 (s, H), 7.60 (d, H), 7.56 (d, 2H), 4.78 (s, 2H), 4.60 (s, 2H), 4.10 (s, 2H), 3.45-3.72 (m, 4H)。MS: (M+H), 449, 451。

实施例 1553

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基-[1,3,4]噻二唑-2-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.80 (d, 2H, NH2), 8.79 (s, H), 8.36 (d, H), 7.72 (d, H), 7.64 (s, H), 7.60 (d, H), 7.22 (d, H), 4.53-5.87 (m, 4H), 4.80-4.96 (m, 2H), 3.31-3.64 (m, 4H)。MS: (M+H),

472, 474。

实施例 1554

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-甲氧基甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.77 (s, 2H, NH2), 8.79 (s, H), 8.37 (d, H), 7.66 (d, H), 7.60 (d, H), 7.58 (s, H), 7.22 (d, H), 4.52-4.87 (m, 5H), 3.94-4.00 (m, 9H)。MS: (M+H), 516, 518。

实施例 1555

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-甲基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.78 (d, 2H, NH2), 8.81 (s, H), 8.37 (d, H), 7.68 (d, H), 7.60 (d, H), 7.68 (s, H), 7.21 (d, H), 4.50-4.85 (m, 5H), 3.10-3.90 (m, 4H), 1.52 (d, 3H)。MS: (M+H), 486, 488。

实施例 1556

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-丙基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.74 (s, 2H, NH2), 8.79 (s, H), 8.36 (d, H), 7.62 (d, H), 7.57 (d, H), 7.55 (s, H), 7.16 (d, H), 4.58-4.83 (m, 3H), 4.40 (q, 2H), 2.80-3.53 (m, 4H), 1.67-2.00 (m, 2H), 1.15-1.60 (m, 2H), 0.85 (t, 3H)。MS: (M+H), 514, 516。

实施例 1557

1-(4-氨基-喹唑啉-7-基甲基-4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-3-基甲基]-(s)-3-乙基-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR: (DMSO-d_6) 9.85 (s, 2H, NH2), 8.80 (s, H), 8.38 (d, H),

7.66 (d, H), 7.64 (d, H), 7.56 (s, H), 7.17 (d, H), 4.75 (m, 3H), 4.35 (q, 2H), 2.80-3.45 (m, 4H), 1.80-1.12 (m, 2H), 0.88 (t, 3H)。MS: (M+H), 500, 502。

实施例 1558

1-(4-氨基-喹唑啉-7-基甲基)-4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-哌嗪-2-酮二-三氟乙酸盐

^{1}H NMR (300 MHz, DMSO) δ 9.75 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J=8.6Hz), 7.55-7.63 (3H, m), 7.29 (1H, d, J=4.0Hz), 6.92 (1H, s), 4.71 (2H, s), 3.74 (2H, s), 3.18-3.29 (4H, m), 2.76-2.78 (2H, m)。MS (离子喷雾) $[M+H]^+$ 455/457, Cl 花样。

实施例 1559

1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-吡啶-5-基-甲基]-哌嗪-2-酮三-三氟乙酸盐

A 部分. 2-溴-5-吡啶甲醛

向 2,5-二溴吡啶(1g, 4.22mmol)的 10mL THF 溶液中于-78℃下加入 n-BuLi (1.7mL, 2.5N 的己烷溶液, 4.25mmol)。在该温度下 15 分钟后, 加入 DMF (0.49mL, 6.33mmol)并将反应混合物搅拌 15 分钟。加入甲醇并将该溶液用 AcOEt 稀释, 用水、盐水洗涤, 用硫酸镁干燥然后浓缩。将所得粗产物通过硅胶柱色谱纯化, 先用庚烷 90%/AcOEt 10%洗脱, 再用庚烷 85%/AcOEt 15%洗脱。得到黄色固体状标题化合物(146mg, 18%)。C_5H_4OBrN MS $(M+H)^+$= 185, Br 花样。

B 部分. 2-(5-氯-噻吩-2-基)-5-吡啶甲醛

向 2-溴-5-吡啶甲醛(140mg, 0.756mmol)的 5mL DME 溶液中于氮气氛下加入 5-氯噻吩-2-硼酸(131mg, 0.806mmol)、四(三苯基-膦)钯(0) (47mg, 0.041mmol)和碳酸钠(0.7mL 2M 的水溶液)。将该混合物回流 5 小时然后真空浓缩, 然后加入乙酸乙酯中。将该溶液用水、

盐水洗涤，用硫酸镁干燥然后浓缩。将所得粗产物通过硅胶柱色谱进行纯化，先用庚烷 95%/AcOEt 5%洗脱，再用庚烷 90%/AcOEt 10%洗脱。得到黄色固体状标题化合物(137mg，81%)。$C_{10}H_6OClNS$ MS $(M+H)^+$=224，Cl 花样。

C 部分. 1-(4-氨基-喹唑啉-7-基甲基)-4-[2-(5-氯-噻吩-2-基)-吡啶-5-基-甲基]-哌嗪-2-酮三-三氟乙酸盐

向 1-(4-氨基-喹唑啉-7-基甲基)-哌嗪-2-酮(20mg，0.078mmol)的 5mL 乙腈溶液中加入 2-(5-氯-噻吩-2-基)-5-吡啶甲醛(17mg，0.078mmol)、三乙酰氧基硼氢化钠(33mg，0.156mmol)和 2mL AcOH。将该混合物室温搅拌过夜，然后用乙酸乙酯稀释，用饱和碳酸氢钠水溶液和盐水洗涤，用硫酸镁干燥然后浓缩。将产物通过 RP-HPLC 纯化，用 10%乙晴/水(0.1% TFA)至 80%乙晴/水(0.1%TFA)进行梯度洗脱。收集适当的馏分然后冷冻干燥得到白色固体状标题化合物(2mg，收率 3%)。$C_{23}H_{21}OClN_6S$ MS $(M+H)^+$=465，Cl 花样。

实施例 1560

4-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐

向 2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(0.33g，1.0mmol)和 Et_3N(0.34mL，2.4mmol)的 MeCN(40mL)溶液中加入 3-溴甲基-5-(5-氯-噻吩-2-基)-异噁唑的 MeCN(10mL)溶液。将该溶液在室温下搅拌过夜然后浓缩至干。然后将残余物用 20% TFA/DCM (40mL)处理过夜。将溶液浓缩。将残余物用 RP-HPLC 纯化得到白色固体状产物(0.23g，0.35mmol)。^1H NMR (DMSO) δ 14.6 (br，1H)，12.7 (s，1H)，9.14 (s，1H)，8.36 (d，1H)，7.86 (d，1H)，7.61 (d，1H)，7.33 (d，1H)，6.93 (s，1H)，6.87 (s，2H)，4.75 (s，2H)，3.75 (s，2H)，3.36 (t，2H)，3.23 (s，2H)，2.75 (t，2H)。MS M+1：428，430。

实施例 1561

4-[5-(5-氯-噻吩-2-基)-4H-[1,2,4]三唑-3-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐

标题化合物按照类似的方法从 2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯和 3-溴甲基-5-(5-氯-噻吩-2-基)-[1,2,4]三唑-4-甲酸叔丁酯制备。^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.68 (s, 1H), 9.20 (s, 1H), 8.36 (d, 1H), 7.88 (d, 1H), 7.48 (d, 1H), 7.20 (d, 1H), 6.89 (s, 1H), 4.74 (s, 2H), 3.90 (s, 2H), 3.38 (m, 4H), 2.81 (t, 2H)。MS M+1: 428, 430。

实施例 1562

[5-(5-氯-噻吩-2-基)-[1,3,4]噁二唑-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

标题化合物按照类似方法从 2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯和 2-溴甲基-5-(5-氯-噻吩-2-基)-[1,3,4]噁二唑制备。^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.67 (s, 1H), 9.19 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.69 (d, 1H), 7.32 (d, 1H), 6.88 (s, 1H), 4.75 (s, 2H), 4.01 (s, 2H), 3.35 (s, 2H), 3.14 (m, 4H), 2.85 (t, 2H)。MS M+1: 429, 431。

实施例 1563

4-[5-(5-氯-噻吩-2-基)-噁唑-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐

标题化合物按照类似方法从 2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯和 2-溴甲基-5-(5-氯-噻吩-2-基)-噁唑制备。^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.7 (s, 1H), 9.16 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.49 (s, 1H), 7.30 (d, 1H), 7.20 (d, 1H), 6.87 (s, 1H), 4.74 (s, 2H), 3.79 (s, 2H), 3.30

(t, 2H), 3.25 (s, 2H), 2.89 (t, 2H)。MS M+1 : 428, 430。

实施例 1564

4-[5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑-2-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐

标题化合物按照类似方法从 2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁基酯和 2-溴甲基-5-(5-氯-噻吩-2-基)-[1,3,4]噻二唑制备。^{1}H NMR (DMSO) δ 14.5 (br, 1H), 12.7 (s, 1H), 9.18 (s, 1H), 8.37 (d, 1H), 7.87 (d, 1H), 7.69 (d, 1H), 7.26 (d, 1H), 6.87 (s, 1H), 4.75 (s, 2H), 4.05 (s, 2H), 3.33 (t, 2H), 3.14 (s, 2H), 2.80 (t, 2H)。MS M+1 : 445, 447。

实施例 1565

4-[5-(5-氯-噻吩-2-基)-2H-吡唑-3-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐

标题化合物按照类似方法从 2-(2-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯和 5-氯甲基-3-(5-氯-噻吩-2-基)-1H-吡唑制备。^{1}H NMR (CD_3OD) δ 8.71 (s, 1H), 8.10 (d, 1H), 7.37 (d, 1H), 7.13 (d, 1H), 6.93 (d, 1H), 6.55 (s, 1H), 6.48 (s, 1H), 4.75 (s, 2H), 3.69 (s, 2H), 3.37 (t, 2H), 3.24 (s, 2H), 2.72 (t, 2H)。MS M+1: 427, 429。

实施例 1566

1-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐

A 部分. 2-(3-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯。

向哌嗪-2-酮 (2.5g, 25mmol) 和 DIEA (5.2mL, 30mmol) 的 MeCN(50mL)溶液中缓慢加入炔丙基溴(4.5g, 80%的甲苯溶液)。将该

溶液室温搅拌过夜。滤除白色固体将滤液浓缩得到残余物。将上述残余物与(3-碘-吡啶-4-基)-氨基甲酸叔丁酯(6.4g, 20mmol)、$Pd(PPh_3)_4Cl_2$(0.70g, 1mmol)、CuI (0.12g, 0.6mmol)和三乙胺(14mL, 100mmol)的 DMF(100mL)溶液混合。将该混合物于 100℃加热 1.5 小时, 然后将其冷却至 50℃。加入 DBU(7.5mL, 50mmol)。将混合物于 50℃搅拌 1.5 小时然后将其浓缩得到残余物。将该残余物用活性碳在二氯甲烷中处理并用水洗涤。将由二氯甲烷层得到的粗产物通过快速柱色谱纯化,用5-6%甲醇/二氯甲烷洗脱得到米黄色泡沫状物质(1.1g, 3.3mmol)。^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.20 (d, 1H), 7.86 (d, 1H), 6.64 (s, 1H), 6.02 (s, 1H), 3.98 (s, 2H), 3.38 (m, 2H), 2.77 (t, 2H)。MS M+1: 331。

B 部分. 1-[5-(5-氯-噻吩-2-基)-异噁唑-3-基甲基]-4-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮二-三氟乙酸盐。

将 2-(3-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(0.066g, 0.20mmol)的 THF(5mL)溶液用氢化钠(0.010g, 60%, 0,24mmol)处理 15 分钟。向其中加入 Bu_4NI 并将混合物搅拌 15 分钟。然后加入 3-溴甲基-5-(5 氯-噻吩-2-基)-异噁唑(0.056g, 0.20mmol)。将混合物在室温下搅拌 4 小时然后浓缩成残余物。然后将残余物用 20% TFA/DCM (4mL)处理 4 小时并再次浓缩。将残余物通过 RP HPLC 纯化得到白色固体状标题化合物(0.0033g, 0.005mmol)。^{1}H NMR (DMSO) δ 14.5 (br, 1H), 12.8 (s, 1H), 9.20 (s, 1H), 8.37 (d, 1H), 7.84 (d, 1H), 7.62 (d, 1H), 7.28 (d, 1H), 6.94 (s, 1H), 6.80 (s, 1H), 4.57 (s, 2H), 3.86 (s, 2H), 3.3 (m, 2H), 3.19 (s, 2H), 2.74 (m, 2H)。MS M+1: 428, 430。

实施例 1567

4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(R)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 2-甲氧羰基-6-氯苯并[b]噻吩。

向 4-氯-2-硝基苯甲醛(18g, 97mmol)的 DMF(100mL)溶液中加入粉末状的碳酸钾(16g, 116mmol), 接着加入甲硫基羟乙酸酯(8.7mL, 97mmol)。将混合物于 75℃加热 2 小时,然后冷却至室温并倒入水(2L)中。收集所形成的黄色沉淀并干燥得到标题化合物(21g, 93mmol)。可将产物用乙醇/水中重结晶。^{1}H NMR ($CDCl_3$, 300MHz) δ 8.03 (s, 1H), 7.85 (s, 1H), 7.80 (d, 1H), 7.39 (d, 1H), 3.95 (s, 3H)。

B. 2-羧基-6-氯苯并[b]噻吩。

将 5N 氢氧化钠(50mL)加入到 2-甲氧羰基-6-氯苯并[b]噻吩(12.57g, 55.45mmol)的甲醇(30mL)溶液中, 然后将其升温至 80℃并加热 4 小时。将反应混合物冷却并用浓盐酸酸化至 pH 约为 3。将形成的沉淀用水洗涤, 然后于 50℃下用五氧化二磷真空干燥得到标题化合物(11.52g, 54.18mmol)。^{1}H NMR (DMSO-d_6, 300MHz) δ 8.21 (s, 1H), 8.11 (s, 1H), 8.00 (d, 1H), 7.50 (d, 1H)。

C. 6-氯苯并[b]噻吩。

将铜(5.58g, 87.9mmol)加入到2-羧基-6-氯苯并[b]噻吩(17.8g, 83.7mmol)的喹啉(70mL)溶液中, 将其于 180℃加热 1.5 小时。然后将反应混合物冷却至室温并倒入 500g 冰中。冰溶化后, 将混合物用硅藻土过滤并将滤液用浓盐酸酸化。将水溶液用乙醚萃取 3 次, 将合并的醚层先用 2N 盐酸洗涤, 然后用盐水洗涤。将有机层用硫酸镁干燥, 过滤然后浓缩。将所得粗产物用 50%EtOAc/己烷进行色谱处理得到标题化合物(12.48g, 74.30mmol)。^{1}H NMR ($CDCl_3$, 300MHz) δ 7.88 (s, 1H), 7.72 (d, 1H), 7.43 (d, 1H), 7.35 (dd, 1H), 7.31 (dd, 1H)。

D. 6-氯苯并[b]噻吩-2-磺酰氯。

向 6-氯苯并[b]噻吩(12.5g, 74.4mmol)的 250mL THF 溶液中于 -78℃加入 n-BuLi(29.7mL 2.5M 的己烷溶液, 74.4mmol)。1 小时后,

通过干冰冷凝器向该溶液中滴加二氧化硫。在 1 小时的时间内加完后，将溶液搅拌 1 小时然后升温至室温过夜。将反应混合物浓缩，将残余物悬浮在己烷(500mL)中并将其冷却至 0℃。向溶液中加入 SO_2Cl_2(7.2mL，89.3mmol)，将所得悬浮液升温至室温并搅拌 4 小时。将反应混合物真空浓缩并将残余物溶于 EtOAc。将有机溶液用饱和碳酸氢钠水溶液和饱和氯化钠水溶液洗涤。将有机层用硫酸镁干燥，过滤然后浓缩。可将粗产物通过柱色谱纯化，用己烷洗脱得到白色固体状标题化合物(18.3g，70.3mmol)。^{1}H NMR ($CDCl_3$，300MHz) δ 8.11 (s，1H)，7.88 (m，2H)，7.50 (m，1H)。

E. 3-碘吡啶-4-基胺。

将碘化钾(19.48g，117.4mmol)和碘(18.37g，72.3mmol)的水(77mL)溶液通过加液漏斗滴加到回流中的 4-氨基吡啶(9.21g，97.8mmol)和碳酸钠(6.12g，57.7mmol)的水(35mL)溶液中。加完后，将混合物回流搅拌 2 小时，然后将其冷却至室温并用乙酸乙酯萃取。将合并的有机层用饱和硫代硫酸钠溶液(3 次)和盐水洗涤，然后用硫酸镁干燥，过滤并浓缩得到标题产物(8.37g，38.0mmol)和微量的黄色/橙色固体状的二碘化合物。该产物不经进一步的纯化直接用于随后的步骤。^{1}H NMR ($CDCl_3$，300 MHz) δ 8.70 (s，1H)，8.10 (d，1H)，6.55 (d，1H)，4.60 (bs，2H)。

F. (3-碘吡啶-4-基)-氨基甲酸叔丁酯。

将二碳酸二叔丁酯(20.7g，94.8mmol)加入到 3-碘吡啶-4-基胺(19.0g，86.4mmol)的 THF(86mL)溶液中。将所得溶液在室温下搅拌 2 小时然后浓缩。将残余物用乙酸乙酯稀释，用饱和碳酸氢钠溶液和盐水洗涤。将有机层用硫酸镁干燥，过滤然后浓缩。将残余物用柱色谱进行纯化，用 1% EtOAc/二氯甲烷洗脱得到标题产物和少量 BOC-保护的二碘化合物。将此混合物用乙醚/己烷研磨除去不希望得到的化合物，标题产物留在溶液中。滤除固体并将滤液浓缩得到标题产物

(18.95g, 59.2mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.05 (bs, 1H), 1.55 (s, 9H)。

此外，还可以按照如下描述制备(3-碘吡啶-4-基)-氨基甲酸叔丁酯:

G. 吡啶-4-基-氨基甲酸叔丁酯。

将二碳酸二叔丁酯(43.3, 0.20mmol)在室温下滴加到 4-氨基吡啶(18.68g, 0.20mol)的 THF(300mL)溶液中。3 小时后，将反应混合物真空浓缩并将残余物通过色谱纯化，用 EtOAc 洗脱得到白色固体状标题化合物(38.7g, 0.20mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, 2H), 7.40 (d, 2H), 6.65 (bs, 1H), 1.5 (s, 9H)。

H. (3-碘吡啶-4-基)-氨基甲酸叔丁酯。

将 nBuLi (255.2mL 2.5M 的己烷溶液, 0.64mol)于-78℃下加入到 xxx (38.7g, 0.20mol)和 TMEDA (95mL, 0.64mol)的 THF (400mL)溶液中。加完后，将反应混合物升温至-20℃并搅拌 1.5 小时。然后将该混合物再次冷却至-78℃，将 I_2 (81g, 0.32mol)的 THF (100mL)溶液滴加到该反应器中。加完后，将所得溶液升温至室温并搅拌 1 小时。将反应混合物用水处理，然后倒入 EtOAc 中。将有机层用水、饱和硫代硫酸钠(2 次)和盐水洗涤，用硫酸镁干燥，过滤然后浓缩。将粗品固体通过色谱纯化，用 20% EtOAc/己烷洗脱得到白色固体状标题化合物(58g, 0.18mol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.05 (bs, 1H), 1.55 (s, 9H)。

I. 4-[(甲氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯。

将 4-噁唑烷醛(75g, 0.33mol)、甘氨酸甲酯盐酸盐(166.25g, 1.32mol)和无水甲醇(915mL)于氮气氛中加入到 2L 的三颈烧瓶中并在冰水浴中冷却至 5℃。30 分钟后，通过加液漏斗在 10 分钟内加入 1M

$NaBH_3CN$的 THF (381ml, 0.38mol)溶液。在加料过程中反应液的温度升至 8℃。将反应液升温至 23℃。在 23℃3 小时后, TLC (2:1, 庚烷:EtOAc)显示反应结束。减压除去溶剂得到油状白色固体。向该固体中加入 MTBE (500mL)和饱和碳酸氢钠水溶液并搅拌至所有固体溶解。进行相分离并分出 MTBE 层。将水相用 200mL MTBE 萃取。将合并的有机相用水(100mL)洗涤,用硫酸镁干燥然后减压蒸发得到亮黄色油状标题化合物(90g, 0.30mol)。MS (ESI) m/z 303 (M^++1, 100); ^1H NMR ($CDCl_3$) δ 3.95 (s, 2H), 3.75 (m, 1H), 3.70 (s, 3H), 3.45 (s, 2H), 2.7 (m, 2H), 1.5 (m, 15H)。

J. 4-[(苄氧羰基-甲氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯。

将 4-[(甲氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(88g, 0.29mol)、二氯甲烷(1.1L)和三乙胺(38.3g, 0.38mol)于氮气氛中加入到 2L 的三颈烧瓶中。将溶液冷却至 5℃并通过加液漏斗滴加氯甲酸苄酯。加料需要 30 分钟, 然后将反应液的温度升至 10℃。使反应在 2-5℃进行 1.5 小时, 然后于 20℃进行 2 小时, 此时的 TLC (2:1, 庚烷:EtOAc)显示反应完成。反应完成后, 向该混合物中加入氯化铵(300mL)水溶液并进行分层。将有机层用硫酸镁干燥, 过滤然后减压蒸发得到浑浊的黄色油状物。将 MTBE (100mL)加入到该油状物中并将该混合物用硅藻土垫过滤。减压蒸除溶剂得到澄清的黄色油状标题化合物(128.5g, 0.29mol)。MS (ESI) m/z 437 (M^+ +1, 60), 459 (M^++Na, 40); ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.15 (d, 2H), 4.00 (m, 5H), 3.75 (d, 2H), 3.65 (d, 2H), 3.25 (m, 1H), 1.5 (m, 15H)。

K. [(2-氨基-3-羟基-丙基)-苄氧羰基-氨基]-乙酸甲酯盐酸盐。

将甲醇(1.2L)加入到 2L 的三颈烧瓶中。向甲醇中通入无水氯化氢气体直至温度稳定在 55℃。将该溶液冷却至 20℃并加入 4-[(苄氧羰

基-甲氧羰基甲基-氨基)-甲基]-2,2-二甲基-噁唑烷-3-甲酸叔丁酯(125g, 0.28mol)。将该溶液于20-23℃搅拌15小时。于25-30℃下减压蒸出0.9-1L溶剂。在冷却时开始从溶液中析出固体沉淀,于是加入1L MTBE,将该混合物冷却至5℃然后过滤得到米黄色固体。将该物质置于真空烘箱中于45℃和21英寸Hg的真空下干燥。干燥后得到米黄色固体状标题化合物(79.3g, 0.24mol)。MS (ESI) m/z 297 (M^+ +1, 100)。^{1}H NMR ($CDCl_3$) δ 8.10 (s, 3H), 7.30 (m, 5H), 5.15 (d, 2H), 4.40 (s, 1H), 4.15 (m, 2H), 3.95 (m, 1H), 3.70 (m, 5H), 3.50 (s, 2H)。

L. 3-(R)-羟基甲基-5-氧代-哌嗪-1-甲酸苄酯。

将甲醇(790ml)、[(2-氨基-3-羟基-丙基)-苄氧羰基-氨基]-乙酸甲酯(79g, 0.24mol)、水(79mL)和碳酸钾(99.5g, 0.72mol)加入到1L的三颈烧瓶中。将混合物用机械搅拌器高速搅拌6小时直至TLC (2:1, 庚烷:EtOAc)显示反应完成。反应完成后,将反应液用水(600mL)稀释然后用二氯甲烷(3 X 800mL)洗涤。将合并的二氯甲烷层用硫酸镁干燥,过滤然后减压蒸除溶剂得到粘稠琥珀色的油状标题化合物(60g, 0.23mol)。MS (ESI) m/z 265 (M^+ +1, 70), 306 (M^+ +乙腈, 90); ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H), 7.30 (s, 5H), 5.15 (s, 2H), 4.4 (s, 1H), 4.15 (dd, 2H), 3.85 (m, 2H), 3.55 (m, 3H), 3.40 (m, 1H)。

M. 3-(R)-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸苄酯。

将3-(R)-羟基甲基-5-氧代-哌嗪-1-甲酸苄酯(17.6g, 66.7mmol)、咪唑(5.9g, 86.7mmol)和叔丁基二甲基氯硅烷(8.2g, 54.4mmol)在二氯甲烷(450mL)中室温搅拌2小时。将反应混合物过滤,将滤液真空浓缩然后通过色谱纯化,用2%甲醇/二氯甲烷洗脱得到无色油状的标题化合物(20.6g, 54.4mmol)。^{1}H NMR ($CDCl_3$, 300 MHz)

δ 7.35 (s, 5H), 6.40 (bs, 1H), 5.13 (s, 2H), 4.30 (d, 1H), 4.01 (d, 1H), 3.78-3.95 (m, 1H), 3.53-3.71 (m, 2H), 3.49 (m, 1H), 3.22 (m, 1H), 0.93 (s, 9H), 0.1 (s, 6H)。MS

N. 3-(R)-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-4-丙-2-炔基-哌嗪-1-甲酸苄酯。

向 3-(R)-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-哌嗪-1-甲酸苄酯(20.6g, 54.5mmol)的 DMF/THF(50mL/250mL)溶液中于 0℃下缓慢加入氢化钠(2.29g, 57.2mmol)。搅拌10分钟后,加入炔丙基溴(6mL, 54.5mmol)并将所得溶液搅拌 1 小时。然后将反应混合物升温至室温, 2 小时后, 用水终止反应然后倒入 EtOAc 中。将有机层用水(两次)和盐水洗涤, 用硫酸镁干燥, 过滤然后浓缩。将所得粗产物进行色谱处理, 用 30% EtOAc/己烷洗脱得到油状标题产物(18.2g, 43.7mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 1H), 5.20 (s, 2H), 4.78 (d, 1H), 4.28-4.45 (m, 2H), 3.90-4.01 (m, 2H), 3.63-3.78 (m, 3H), 3.30 (dd, 1H), 2.28 (m, 1H), 0.90 (s, 9H), 0.05 (s, 6H)。MS

O. 3-(R)-羟基甲基-5-氧代-4-丙-2-炔基-哌嗪-1-甲酸苄酯。

向 3-(R)-(叔丁基-二甲基-硅烷氧基甲基)-5-氧代-4-丙-2-炔基-哌嗪-1-甲酸苄酯(18.2g, 43.7mmol)的 THF(300mL)溶液中加入乙酸(2.77mL, 48.1mmol), 接着向该溶液中滴加 nBu_4NF(48.1mL 1M 的 THF 溶液, 48.1mmol)。3 小时后, 将反应混合物用水处理并倒入 EtOAc 中。将有机层用水和盐水洗涤, 用硫酸镁干燥, 过滤然后浓缩。将所得残余物通过色谱纯化, 用 5%甲醇/二氯甲烷洗脱得到油状标题产物(12.5g, 41.4mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 5H), 5.18 (bs, 2H), 4.30-4.61 (m, 3H), 3.85-4.01 (m, 2H), 3.70-3.89 (m, 2H), 3.50-3.60 (bd, 1H), 3.20-3.40 (bd, 1H), 2.61 (bs, 1H), 2.28 (m, 1H)。ESI MS $[M+H]^+$=303。

P. 3-(R)-甲氧基甲基-5-氧代-4-丙基-2-炔基-哌嗪-1-甲酸苄酯。

向3-(R)-羟基甲基-5-氧代-4-丙-2-炔基-哌嗪-1-甲酸苄酯(10g, 33.1mmol)的 THF/DMF (300mL/80mL)溶液中于 0℃下加入氢化钠(1.39g, 34.8mmol)。5分钟后，加入 MeI (2.27mL, 36.4mmol)并将反应混合物搅拌20分钟，然后升温至室温。将溶液搅拌2小时，然后用水处理并倒入 EtOAc 中。将有机层用水和盐水洗涤，用硫酸镁干燥，过滤并浓缩。将所得残余物通过色谱纯化，用 30% EtOAc/己烷洗脱得到无色油状标题产物(7.5g, 23.7mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 5H), 5.18 (s, 2H), 4.75 (d, 1H), 4.41 (m, 1H), 4.28 (d, 1H), 3.75-3.95 (m, 3H), 3.51 (bs, 2H), 3.20-3.48 (m, 4H), 2.22 (m, 1H)。ESI MS $[M+H]^+$=317。

Q. 2-(4-苄氧基羰基-2-(R)-甲氧基甲基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯。

将 3-(R)-甲氧基甲基-5-氧代-4-丙基-2-炔基-哌嗪-1-甲酸苄酯(7.2g, 22.8mmol)、(3-碘吡啶-4-基)-氨基甲酸叔丁酯(7.3g, 22.8mmol)、CuI (0.13g, 0.68mmol)、$Pd(PPh_3)_2Cl_2$ (0.80g, 1.14mmol)和三乙胺(12.7mL, 91.1mmol)在 DMF(100mL)中于 100℃加热3小时，然后将其冷却至 50℃。加入 DBU (6.8mL, 45.6mmol)并将所得混合物搅拌1小时。将反应混合物冷却至室温并倒入 EtOAc 中。将有机层用水(两次)和盐水洗涤然后用硫酸镁干燥，过滤然后浓缩。将粗产物用 100% EtOAc 或 2%甲醇/二氯甲烷纯化得到泡沫状的浅黄色固体状标题化合物(9.0g, 17.7mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.42 (d, 1H), 7.90 (d, 1H), 7.31-7.39 (m, 5H), 6.38 (s, 1H), 5.04 (AB, 2H), 5.21 (bs, 2H), 4.30 (AB multiplet, 2H), 4.42 (d, 1H), 3.20-3.68 (m, 5H), 1.71 (s, 9H)。ESI MS $[M+H]^+$=509。

R. 2-(2-(R)-甲氧基甲基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]

吡啶-1-甲酸叔丁酯。

将 2-(4-苄氧羰基-2-(R)-甲氧基甲基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(9.0g, 17.7mmol)的 5%甲酸/甲醇(100mL)溶液于氩气氛下加入到湿的 Pd 黑(10g, 94.0mmol)中。30 分钟(在此期间内有大量的气泡产生)后，将混合物用硅藻土过滤并将滤液用饱和碳酸氢钠中和。将滤液真空浓缩，将所得溶液用二氯甲烷萃取。将合并的有机层用盐水洗涤，用硫酸镁干燥，过滤然后浓缩得到泡沫状的浅黄色固体状标题产物(5.94g, 15.9mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.41 (d, 1H), 7.88 (d, 1H), 6.45 (s, 1H), 5.02 (AB, 2H), 3.71 (dd, 1H), 3.64 (d, 2H), 3.50-3.58 (m, 2H), 3.30 (dd, 1H), 3.34 (s, 3H), 3.20 (dd, 1H), 1.71 (s, 9H)。HRMS 测量值 375.2013，计算值 375.2027。ESI MS $[M+H]^+$=375。

S. 2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-(R)-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯。

将 2-(2-(R)-甲氧基甲基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(5.94g, 15.9mmol)、6-氯苯并[b]噻吩-2-磺酰氯(4.24g, 15.9mmol)和三乙胺(2.4mL, 17.2mmol)在乙腈(120mL)中于室温下搅拌 5 小时。将反应混合物浓缩至干，然后用二氯甲烷将其吸附在硅胶上进行色谱处理，用 EtOAc 洗脱得到白色固体状标题化合物(6.4g, 10.6mmol)。^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.41 (d, 1H), 7.82-7.91 (m, 4H), 7.50 (dd, 1H), 6.25 (s, 1H), 5.01 (AB, 2H), 4.19 (AB, 2H), 3.62-3.72 (m, 4H), 3.38 (s, 3H), 3.02 (d, 1H), 1.70 (s, 9H)。ESI MS $[M+H]^+$=605, 607, Cl 花样。

T. 4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(R)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮。

在 0℃下向 EtOAc (300 mL)中通入 HCl(气体) 20 分钟时溶液饱

和。然后向其中加入 2-[4-(6-氯-苯并[b]噻吩-2-磺酰基)-2-(R)-甲氧基甲基-6-氧代-哌嗪-1-基甲基]-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(5.5g, 9.2mmol)，将悬浮液于0℃搅拌1小时然后升温至室温。再次向浆液中通入 HCl (气体)，此时反应瓶开始变热。随后加入甲醇(60mL)，溶液变为澄清。1小时后，分析 RP-HPLC 表明仍有明显量的原料，于是在室温下向溶液中通入 HCl (气体) 30 分钟。将反应混合物搅拌 10 小时，然后向溶液中通入氮气 30 分钟。将该混合物浓缩至干并将所得粗产物通过 RP-HPLC (Metachem monochrom 10 微米 C-18 柱)纯化，并在 18 分钟内用 20-70%乙腈/水(HCl, pH=2.8)以 70mL/min 的流速梯度洗脱，收集用约 45%乙腈/水(HCl, pH=2.8)洗脱的馏份。将适当的馏分冷冻干燥得到盐酸盐形式的标题产物。^{1}H NMR ($CDCl_3$, 300MHz) δ 11.82 (s, 1H), 8.89 (d, 1H), 8.15 (m, 1H), 7.80-7.85 (m, 3H), 7.77 (d, 1H), 7.41 (d, 1H), 6.75 (s, 1H), 4.90 (AB, 2H), 4.01 (AB, 2H), 3.91 (d, 1H), 3.62-3.78 (m, 3H), 3.34 (s, 3H), 3.13 (d, 1H)。EI MS, $[M+H]^+$=505, 507, Cl 花样。HRMS 测量值 505.0730, 计算值 505.0765。分析($C_{22}H_{21}N_4O_4S_2Cl.HCl.1.5H_2O$)计算值: C, 46.53; H, 4.44; N, 9.87。实测值: C, 46.28; H, 4.43; N, 9.45。> 99% ee (Chiralpak AD, 用 100%乙醇洗脱)。

实施例 1568

4-(6-氯噻吩并[2,3-b]吡啶-2-磺酰基)-6-(R)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

A. 6-氯噻吩并[2,3,b]吡啶-2-磺酰氯

按照实施例1, C部分中描述的方法将6-氯噻吩并[2,3,b]吡啶(J. Het. Chem. (1976), 13, 1197)转化为标题化合物。^{1}H NMR ($CDCl_3$, 300MHz) δ 8.20 (d, 1H), 8.16 (s, 1H), 7.53 (d, 1H)。质谱, M^+ 267, 269, 271 两个 Cl 花样。

B. 4-(6-氯噻吩并[2,3,b]吡啶-2-磺酰基-(R)-6-甲氧基甲基-1-(丁

基羧基吡咯并[3,2,c]吡啶-2-基甲基)-哌嗪-2-酮

将 2-(2-(R)-甲氧基甲基-6-氧代-哌嗪-1-基甲基)-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯(500mg)、6-氯噻吩并[2,3,b]吡啶-2-磺酰氯(360mg)和 19ml 三乙胺在 50ml 乙腈中室温搅拌过夜。将溶液浓缩并在乙酸乙酯和 10%碳酸氢钠之间进行分配。将有机溶液用水洗涤，用硫酸钠干燥，用 2%甲醇/乙酸乙酯进行色谱处理得到 780mg 标题化合物。质谱 M+H=606.2, 608.2(Cl)。^{1}H NMR $CDCl_3$ 8.7 (s, 1H), 8.4 (d, 1H), 8.1 (d, 1H), 7.85 (d, 1H), 7.8 (s, 1H), 7.5 (d, 1H), 6.25 (s, 1H), 5.4 (d, 1H), 4.8 (d, 1H), 4.3 (d, 1H), 4.1 (d, 1H), 3.6-3.7 (m, 4H), 3.4 (s, 3H), 3.05 (d, 1H), 1.7 (s, 9H)。

C. 4-(6-氯-噻吩并[2,3-b]吡啶-2-磺酰基)-6-(R)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮

将 4-(6-氯噻吩并[2,3,b]吡啶-2-磺酰基-(R)-6-甲氧基甲基-1-(丁基羧基吡咯并-[3,2,c]吡啶-2-基甲基)-哌嗪-2-酮(700mg)在 50ml 40%三氟乙酸的二氯甲烷溶液中室温搅拌 2 小时，浓缩并通过 HPLC 纯化得到 560mg 的标题化合物。质谱 M+H=506.2, 508.2(Cl); ^{1}H NMR CD_3OD 8.9 (s, 1H), 8.4 (d, 1H), 8.3 (d, 1H), 8.0 (d, 1H), 7.8, (d, 1H), 7.6 (d, 1H), 6.9 (s, 1H), 5.1 (d, 1H), 4.7 (d, 1H), 4.2 (d, 1H), 3.9 (d, 1H), 3.5-3.8 (m, 4H), 3.3 (s, 3H), 3.2 (d, 1H), HPLC > 98A%。

如下 6-取代的酮基哌嗪化合物用以上描述的合成方法制得。

实施例	名称	m/z [M+H]
1569	4-(5-氯-1H-吲哚-2-磺酰基)-6-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	488, 490 Cl 花样

1570	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(S)-异丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	503, 505 Cl 花样
1571	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-(S)-异丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	479, 481 Cl 花样
1572	4-(6-氯-苯并[b]噻吩-2-磺酰基)-6-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	503, 505 Cl 花样
1573	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-6-(S)-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	479, 481 Cl 花样

如下酮基哌嗪化合物按照上面描述的类似方法制备。

实施例	名称	m/z [M+H]
1574	4-(5-氯-1H-吲哚-2-磺酰基)-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	444, 446 Cl 花样
1575	4-[3-(5-氯-噻吩-2-基)-异噁唑-5-基甲基]-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	428, 430 Cl 花样
1576	4-[4-(5-氯-噻吩-2-基)-苄基]-3-(S)-甲氧基甲基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	481, 483 Cl 花样
1577	1-(4-氨基-喹唑啉-7-基甲基)-4-[3-(5-氯-噻吩-2-基)-苄基]-哌嗪-2-酮	464, 466 Cl 花样
1578	1-(4-氨基-喹唑啉-7-基甲基)-4-[4-(5-氯-噻吩-2-基)-苄基]-哌嗪-2-酮	464, 466 Cl 花样

以下化合物通过上述方法用 3-甲基-4 氨基吡啶(按照 Recueil

1951,70, 571-579 描述的方法制备)作为原料制备。

实施例	名称	m/z [M+H]
1579	4-(6-氯-苯并[b]噻吩-2-磺酰基)-1-(7-甲基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	475, 477 Cl 花样
1580	4-[2-(5-氯-噻吩-2-基)-乙烯磺酰基]-1-(7-甲基-1H-吡咯并[3,2-c]吡啶-2-基甲基)-哌嗪-2-酮	451, 453 Cl 花样

抑制因子 Xa

本文所述的化合物可以抑制凝血级联中的倒数第二个酶，控制因子 Xa 的活性，因此可以抑制凝血。式 1 化合物同时可以抑制游离的因子 Xa 和装配在凝血酶原酶复合物(因子 Xa、因子 Va、钙和磷脂)中的因子 Xa。其通过直接形成抑制剂和酶之间的复合物而达到对因子 Xa 活性的抑制，因此不依赖于血浆辅因子抗凝血酶 III。可以通过将化合物口服给药、连续静脉内输注、静脉内快速浓注或通过其它能够达到预防由于从凝血酶原形成凝血酶而引起的因子 Xa 活性之所需效果的胃肠外途径给药来有效地抑制因子 Xa 的活性。

抗凝疗法可用于治疗和预防静脉和动脉的各种血栓形成疾病。在动脉系统中，异常的血栓形成主要与冠状动脉、脑动脉和外周动脉有关。与这些血管的血栓阻塞有关的疾病主要包括急性心肌梗塞(AMI)、不稳定性心绞痛、血栓栓塞、与溶栓治疗以及经皮冠状动脉成形术(PTCA)、短暂性缺血发作、中风、间歇性跛行和冠状动脉搭桥术(CABG)或外周动脉搭桥术有关的急性血管闭塞。慢性抗凝剂治疗还可能有助于防止 PTCA 和 CABG 后经常发生的动脉腔逐渐变窄(再狭窄)，并有益于维持长期血液透析患者的血管通路开放。对于静脉血管，腹部、膝部和臀部手术后在远端的静脉中常常发生病理性的血栓形成(深部静脉血栓形成，DVT)。DVT 还使患者预先有肺血栓栓塞的较高危险性。系统性、弥漫性血管内凝血(DIC)一般发生在脓毒性休克、某些病毒感染和癌症期间的两种血管系统中。此病症的特征是凝血因子及其血浆

抑制剂的快速消耗，导致在若干器官系统的微血管中形成威胁生命的血块。以上讨论的适应征包括一些、但不是所有可以采用抗凝疗法的可能的临床情形。需要急性或是慢性预防性抗凝疗法的情况是本领域技术人员熟知的。

越来越多的实验证据表明，因子 Xa 的唯一的生物学活性是激活凝血酶原。据信 EPR-1 (效应细胞蛋白酶受体-1，识别因子 Xa)可以通过因子 Xa 介导多种血管壁相互作用。已证实其可以在人脐静脉内皮细胞、大鼠平滑肌细胞和血小板中表达(CR McKenzie 等，Arterioscler Thromb Vasc Biol 16 1285-91 (1996)；以及 F Bono 等，J Cell Physiol 172 36-43 (1997)，AC Nicholson 等，J Biol Chem 271 28407-13 (1996)，J. M. Herbert 等，J Clin Invest 101993-1000 (1998))。该蛋白酶-受体相互作用不仅可以介导凝血酶原酶催化的凝血酶生成，而且还介导多种细胞功能，例如细胞增殖、PDGF 的释放和 DNA 合成。有报道指出，因子 Xa 的致有丝分裂作用取决于因子 Xa 的酶活性(F Bono 等，J Cell Physiol 172 36-43 (1997)，J. M. Herbert 等，J Clin Invest 101 993-1000 (1998))。例如，TAP 可以抑制培养的人和大鼠血管平滑肌细胞的有丝分裂期发生(F Bono 等，J Cell Physiol 172 36-43 (1997))。在兔颈动脉风干损伤模型的研究中，在血管损伤后检测到了 EPR-1 表达的增加。用特异性的因子 Xa 抑制剂(DX-9065a)处理的动物显示出较少的新内膜增生。因子 Xa 在凝血过程中的与其致有丝分裂作用有关的重要调节作用表明因子 Xa 与血管壁腔表面的凝血酶形成有关，并且与动脉粥样化血栓形成过程和导致再狭窄和血管生成的异常血管细胞增殖有关。

这些化合物可单独使用或与其它诊断剂、抗凝剂、抗血小板剂或纤维蛋白分解剂联用。例如，将因子 Xa 活性抑制剂与常规的肝素、低分子量肝素、合成的五糖、直接的凝血酶抑制剂(例如水蛭素、Agratroban (Novastan®)、阿斯匹林、纤维蛋白原受体拮抗剂、抑制素/氯贝特类链激酶、尿激酶和/或组织纤维蛋白溶酶原激活物联合给药。本文所述的化合物可用于在各种动物例如灵长类动物、包括人中

治疗血栓形成并发症。抑制因子 Xa 不仅可用于对患有血栓形成病症的个体进行抗凝治疗，而且还可用于在需要时来抑制凝血，以防止存放的全血凝固和防止在其它用于试验或存放的生物学样品中发生凝血。因此，可将因子 Xa 活性抑制剂加入或者与任何含有或者可能含有因子 Xa 并且需要抑制凝血的介质接触。

除了可用于抗凝疗法外，因子 Xa 抑制剂还可用于治疗或预防凝血酶的生成在其中起生理学作用的其它疾病。例如，据报道凝血酶会影响慢性和变性疾病例如关节炎、癌症、动脉粥样硬化和早老性痴呆的发病率和死亡率，因为它能够通过细胞表面凝血酶受体的特异性裂解和激活、致有丝分裂作用、不同的细胞功能例如细胞增殖(例如导致再狭窄或血管生成的异常血管增殖)、PDGF 的释放和 DNA 合成来调节许多不同的细胞类型。抑制因子 Xa 将可以有效地阻断凝血酶的生成，从而抵消凝血酶对各种细胞类型的作用。

另一方面，本发明提供了对患有或经常遭受可以通过施用因子 Xa 活性抑制剂来改善的生理学情况(例如上文中所描述的那些情况)的人或动物患者进行治疗的方法，该方法包括，向所述患者施用治疗有效量的式 I 或式 II 化合物或含有式 I 或式 II 化合物的组合物。“有效量”是指可以有效抑制因子 Xa 的活性从而产生所需的治疗效果的本发明化合物的量。

本发明还包括含有至少一种式 I 或式 II 化合物以及可药用载体或包衣的药物制剂。

可将药物组合物以适宜的制剂通过局部或全身给药向人和动物给药，包括口服、吸入、直肠、鼻、颊部、舌下、阴道、胃肠外(包括皮下、肌肉内、静脉内、真皮内、鞘内和硬膜外)、脑池内和腹膜内给药。可以理解，优选的途径可能随着例如用药者的病症而变化。

本发明的产物可以以能够通过最适宜的途径进行给药的形式存在，本发明还涉及含有至少一种本发明的产物并且适用于人或兽药的药物组合物。这些组合物可以按照常规方法用一种或多种可药用辅剂或赋形剂制备。辅剂包括稀释剂、无菌含水溶媒和各种无毒的有机溶

剂。组合物可以是片剂、丸剂、颗粒剂、散剂、含水溶液或混悬液、可注射溶液、酏剂或糖浆的形式，并且可以含有一种或多种选自甜味剂、矫味剂、着色剂或稳定剂的物质以得到可药用的制剂。

赋形剂的选择以及赋形剂中活性物质的含量通常根据产物的溶解度和化学性质、具体的给药方式以及药物实践中的规定来确定。例如，赋形剂如乳糖、柠檬酸钠、碳酸钙、磷酸钙和崩解剂如淀粉、藻酸和某些复合硅酸盐以及润滑剂如硬脂酸镁、十二烷基硫酸钠和滑石可用于制备片剂。为了制备胶囊，优选使用乳糖和高分子量的聚乙二醇。当使用含水混悬液时，它可以含有乳化剂或助悬剂。也可以使用稀释剂例如乳糖、乙醇、聚乙二醇、丙二醇、甘油和氯仿或其混合物。

对于胃肠外给药，可以使用本发明的产物在植物油例如芝麻油、花生油或橄榄油或含水-有机溶液例如水和丙二醇、可注射的有机酯例如油酸乙酯中的乳液、混悬液或溶液或可药用盐的无菌含水溶液。本发明产物的盐的溶液特别适用于通过肌肉内或皮下注射给药。可用含水溶液、包括盐在纯净蒸馏水中的溶液进行静脉内给药，条件是对其pH进行适当地调整、对其进行适当地缓冲并用足量的葡萄糖或氯化钠调至等渗以及将其通过加热、辐射或微孔过滤进行灭菌。

含有本发明化合物的适宜组合物可以通过常规方法制备。例如，可将本发明的化合物溶解或悬浮在用于雾化器或混悬液或溶液气雾剂的适宜载体中，或者可以吸附在用于干粉吸入器的适宜固体载体上。

用于直肠给药的固体组合物包括按照已知方法配制的含有至少一种式I或式II化合物的栓剂。

本发明药物组合物中的活性成分的实际剂量水平可以改变，从而达到可以有效获得对于具体患者、组合物和给药方式的理想的治疗反应的量。选择的剂量水平取决于具体化合物的活性、给药途径、所治疗病症的严重程度以及所治疗患者的状况和以前的治疗史。但是，本领域技术人员可以理解，可以从低于达到理想的治疗效果所需的化合物剂量开始，然后逐渐增加剂量直至达到理想的效果。对于成年人，吸入给药的剂量通常为约0.01至约100、优选约0.01至约10mg/kg

体重/天，口服给药为约 0.01 至约 100、优选 0.1 至 70、更优选 0.5 至 10mg/kg 体重/天，静脉内给药为约 0.01 至约 50、优选 0.01 至 10mg/kg 体重/天。在具体情况下，剂量可以根据所治疗对象之间的区别因素来确定，例如年龄、体重、一般健康情况以及可以影响药物效力的其它特征。

本发明的产物可以以所需要的频率进行给药，以获得理想的治疗效果。某些患者可能对较高或较低的剂量反应迅速，因此很小的维持剂量就足够了。对于其它患者，可能需要根据各具体患者的生理需求以每天给药 1 至 4 次的频率进行长期治疗。通常，可将活性产物每天口服给药 1 至 4 次。不言而喻，对于其他患者，可能需要每天给药不超过一或两次。

根据文献中描述的试验，本发明范围内的化合物显示出明显的药理学活性，据信这些试验结果与在人和其它哺乳动物中的药理学活性相关。以下药理学试验结果是本发明化合物的典型特征。

酶试验：

本发明化合物作为因子 Xa、凝血酶、胰蛋白酶、组织纤溶酶原激活物(t-PA)、尿激酶-纤溶酶原激活物(u-PA)、纤溶酶和激活的蛋白 C 的抑制剂的能力通过用纯净的酶测定导致酶活性丧失 50%的抑制剂浓度(IC_{50})进行评估。

所有的酶试验均在室温下在 96 孔微量滴定板中进行，最终的酶浓度为 1nM。因子 Xa 和凝血酶的浓度通过活性部位滴定法来测定，所有其它酶的浓度是基于生产商所提供的蛋白浓度。将本发明的化合物溶于 DMSO，用各自的缓冲液稀释并在 1.25%的最大 DMSO 终浓度下进行试验。将化合物的稀释液加入到含有缓冲液和酶的孔中并预平衡 5 至 30 分钟。通过加入底物引发酶反应，并在 Vmax 微量反应板读数器(Molecular Devices)上于 405nm 下连续监测由于肽-对-硝基酰基苯胺底物水解所产生的颜色 5 分钟。在这些条件下，在所有试验中均使用不到 10%的底物。用测定的起始速率计算出引起对照速率降低 50%

的抑制剂的量(IC_{50})。假定是竞争性抑制动力学，按照 Cheng-Prusoff 方程(IC_{50} =Ki [1+ [S]/Km])测定出表观 Ki 值。

可以用另外的体外试验在正常的人血浆中评估本发明化合物的效力。活化部分凝血激酶时间是基于血浆的凝固试验，该试验依赖于因子 Xa 的就地生成、其装配成凝血酶原酶复合物以及随后的凝血酶和纤维蛋白的生成，其最终导致作为试验终点的凝块的形成。该试验目前在临床上用于监测常用的抗凝药肝素以及正在进行临床评估的直接起作用的抗凝血酶剂的先体外后体内的作用。因此，在该体外试验中的活性被认为是体内抗凝活性的替代指标。

人基于血浆的凝固试验

在 MLA Electra 800 仪器上一式两份地测定活化的部分组织促凝血酶原激酶凝固时间。将体积为 100ml 的柠檬酸化的正常人混合血浆(George Kong Biomedical)加入到含有 100ml 本发明化合物的 Tris/NaCl 缓冲液(pH 7.5)溶液的比色杯中然后置于仪器内。在 3 分钟的加热期过后，仪器自动加入 100ml 活化的 cephaloplastin 试剂(Actin, Dade)，然后加入 100ml 0.035M $CaCl_2$引发凝固反应。通过分光光度法以秒为单位测定凝块的形成。将化合物的效力用引起对照凝固时间加倍所需的浓度来定量表示，所述对照凝固时间是用人血浆在不含本发明化合物的条件下测定的。

还可以用两种非常成熟的急性血管血栓形成动物实验模型来评估本发明化合物的体内抗血栓形成效力。用兔颈静脉血栓形成模型和大鼠颈动脉血栓形成模型来证实这些化合物在人静脉血栓形成和动脉血栓形成的不同动物模型中的抗血栓形成活性。

实验性血浆蛋白结合试验

将化合物溶于 DMSO 制备 10mM 储备液。在含有 0.05M Tris, 0.15M NaCl, 0.1% PEG-8000, pH 7.5 的缓冲液中制备化合物的系列稀释液。在含有 3.45mg/ml 人白蛋白和 2.3mg/ml 纤维蛋白原的上述缓冲液中

制备人 FXa 和底物 Spectrozyme FXa。FXa 试验在室温下在 96 孔微量滴定板中进行，最终的酶浓度和底物浓度分别为 1nM 和 200μM。将化合物稀释液加入到含有缓冲液和 FXa 的孔中然后预保温 30 分钟。通过加入底物 Spectrozyme FXa 引发酶反应，并在 Thermomax 微量滴定板读数器(Molecular Devices, Sunnyvale, CA.)上于 405nm 下连续监测由于从各产色底物释放对-硝基酰基苯胺所产生的颜色 5 分钟。在最终的反应混合物中，白蛋白和纤维蛋白原的浓度分别为 3mg/ml 和 2mg/ml。在该实验条件下，在所有试验中均消耗了不到 10%的底物。用测定的起始速率计算出使对照速率降低 50%所需的抑制剂的量并将其定义为抑制剂的 IC_{50}。假定动力学机制是竞争性抑制，按照 Cheng-Prusoff 方程计算出表观 Ki 值，$Ki = IC_{50}/(1 + [S]/Km)$。

实验性体内兔静脉血栓形成模型：

该模型是文献中公知的富含纤维蛋白的静脉血栓形成的模型，已证实该模型对包括肝素在内的多种抗凝药敏感(重组截短的组织因子途径抑制剂(TFPI 1-161)在实验性静脉血栓形成中的抗血栓形成作用-与低分子量肝素的比较，J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P. B. Ostergaard, J. G. L. Petersen, G. Nielsen 和 U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994))。使用该模型的目的是评估化合物预防在损伤部位体内产生的静脉血栓(凝块)形成和在颈静脉部分郁滞的能力。

将体重为 1.5-2kg 的雄性和雌性新西兰白兔用 35mg/kg 氯胺酮和 5mg/kg 赛拉嗪以 1ml/kg (肌肉内)的体积进行麻醉。对右颈静脉进行插管以输注麻醉剂(氯胺酮/赛拉嗪 17/2.5mg/kg/小时，输注速率为约 0.5ml/小时)和施用试验物质。对右颈动脉进行插管以记录动脉血压和收集血样。用 GAYMAR T-PUMP 将体温保持在 39℃。分离出左颈外静脉并将所暴露的 2-3cm 长的血管上的所有侧枝结扎。在共用颈静脉的分叉点之上对颈内静脉进行插管，插管的顶部在靠近共用颈静脉的前方。用非创伤性血管夹分离出 1cm 长的静脉片段，通过用 18G 针在远

侧夹子的下方在静脉上系结扎线形成相对狭窄。这形成了血流减少的区域和损伤部位的部分郁血。将分离的片段通过颈内静脉中的插管用盐水温和地冲洗 2-3 次。然后将分离的片段用 0.5ml 0.5%聚氧化乙烯醚(W-1)充满 5 分钟。W-1 是一种洗涤剂，它可以破坏该片段的内皮细胞层，从而产生一层用于引发血块形成的血栓形成表面。5 分钟后，从片段中放出 W-1，将片段再次用盐水温和地冲洗 2-3 次。然后移走血管夹，使血液重新流过血管的该部分。使血块形成并使其生长 30 分钟，然后在紧靠狭窄结扎线的下方将静脉切开并检查血流(将没有血流记录为完全阻塞)。然后将整个分离出的静脉片段结扎，取出形成的血块然后称重(湿重)。用试验物质对最终血块重量的影响作为最初的终点。将动物继续保持 30 分钟以获得最终的抗凝药效学测量。药物的给药在用 W-1 损伤血管前 15 分钟开始，并在整个血块形成期和成熟期中持续进行。取 3 份血样(各 3ml)用于评估止血参数：第一份在临施用 W-1 前取；第二份在除去血管夹 30 分钟后取；第三份在实验结束时取。抗血栓形成效力用相对于载体处理的对照动物，在用本发明化合物处理的标本中最终血块重量的减少来表示。

体内大鼠动脉血栓形成模型实验：

因子 Xa 抑制剂对富含血小板的动脉血栓形成的抗血栓形成效力可以用公知的 $FeCl_2$-诱导的大鼠颈动脉血栓形成模型(血栓烷受体拮抗剂与阿斯匹林相比在大鼠动脉和静脉血栓形成模型中的优良活性，W. A. Schumacher, C. L. Heran, T. E. Steinbacher, S. Youssef 和 M. L. Ogletree. Journal of Cardiovascular Pharmacology, 22 526-533 (1993)；由氯化铁诱导的大鼠动脉血栓形成模型，K. D. Kurtz, B. W. Main, 和 G. E. Sandusky. Thrombosis Research, 60, 269-280 (1990)；抑制凝血酶在大鼠动脉血栓形成模型中的影响，R. J. Broersma, L. W. Kutcher 和 E. F. Heminger. Thrombosis Research 64, 405-412 (1991))来评估。该模型广泛用于评估各种物质、包括肝素和直接起作用的凝血酶抑制剂的抗血栓形成潜力。

将重量为 375-450g 的 Sprague Dawley 大鼠用戊巴比妥钠

(50mg/kg，腹膜内)麻醉。在达到可接受的麻醉水平后，刮去颈部前侧表面的毛并准备进行无菌手术。连接心电图的电极并在整个实验过程中监测 II 导联。将右股静脉和股动脉用 PE-50 管插管，分别用于给药本发明的化合物和获取血样并监测血压。在颊部的前侧表面进行正中线切开术。暴露气管并用 PE-240 管进行插管以确保导气管的开放。分离出右颈动脉并在血管上绕两圈 4-0 丝的缝线以便于器械操作。在血管周围放置电磁流量探针(0.95-1.0mm 管腔)以测量血流量。在探针的远侧在血管下方放置一个 4 x 4mm 的石蜡膜带以便将血管和周围的肌肉床分离。在测定了基线流量后，将预先用 35% $FeCl_2$饱和的 2 x 5mm 的滤纸带置于探针下游的血管上方 10 分钟然后移走。$FeCl_2$可以扩散到下方的动脉片段内并造成引起急性血栓形成的脱内皮化。在贴了浸有 $FeCl_2$的滤纸后，对血压、颈动脉血流量和心率监测 60 分钟。在血管阻塞后(定义为达到零血流量)，或者如果仍保持开放，在粘贴滤纸 60 分钟后，将动脉在近心端和损伤区域的远端进行结扎然后将血管切除。取出血栓然后立即称重并记录为研究的最初终点。

在手术器械操作后，抽取对照血样(B1)。所有的血样均从动脉插管收集并与柠檬酸钠混合以防止凝血。在每次取血样后，将插管用 0.5ml 0.9%盐水冲洗。将本发明的化合物在施用 $FeCl_2$前 5 分钟开始静脉内给药。将从施用 $FeCl_2$到颈动脉血流量达到零之间的时间记录为达到阻塞的时间(TTO)。对于未在 60 分钟内阻塞的血管，将 TTO 指定为 60 分钟。在施用 $FeCl_2$ 5 分钟后，抽取第二份血样(B2)。在接触 $FeCl_2$ 10 分钟后，从血管上移走滤纸并在实验的剩余时间内对动物进行监测。在达到零血流量后，抽取第三份血样(B3)，然后取出血块并称重。在前肢的脚趾垫上进行模板出血时间测定并同时获取血样。对所有血样进行的凝血项目包括活化部分凝血激酶时间(APTT)和凝血酶原时间(PT)。在某些情况下，本发明的化合物可以口服给药。将大鼠用常规的方法用手固定，然后将化合物通过胃内管饲法用 18 号弯曲给药针头进行给药(体积为 5ml/kg)。胃内给药 15 分钟后，将动物麻醉并按照以上描述进行器械操作。然后按照上述方法进行实验。

实验性犬静脉内和胃内给药实验

使用任意性别的小猎犬(9-13kg)来评估本发明化合物在静脉内和胃内给药后的药效学作用。这些实验的血样通过头部静脉的静脉穿刺术获得。在弃除了抽取的最初 0.5ml 血后，将 4.5ml 对照血样抽入到含有 0.5ml 柠檬酸三钠的冰冷的塑料注射器中。给药后，通过将样品直接抽入到含有 0.1ml 柠檬酸三钠的冰冷的塑料注射器中在各时间点取 0.9ml 血液(在弃除了最初的 0.5ml 血液后)。

对于静脉内实验，将化合物施用到与采血样用的前肢相对的前肢的头静脉内。将化合物溶于盐水(0.5ml/kg 体重)然后以静脉内快速浓注的方式给药。在给药后的特定时间点获取给药后的血样。

对于胃内实验，将化合物(在 0.5%甲基纤维素和 1%吐温-80 中，1ml/kg 给药体积)通过胃内饲管进行给药。按照以上描述获取给药前的对照血样并在给药后的特定时间点获取给药后的血样。

凝血时间。用血小板缺乏的血浆来测定活化部分凝血激酶时间(APTT)和凝血酶原时间(PT)，这两个时间用 Microsample Coagulation Analyzer (MCA210, Bio Data Corp, Horsham, PA)和 Dade®试剂(组织促凝血酶原激酶-C+和肌动蛋白® FS 激活的 PTT 试剂，Baxter Diagnostics, Inc., Deerfield, IL)。

因子 Xa 的先体外后体内抑制作用。通过产色的方法用 American Diagnostica (Greenwich, CT)提供的试剂(牛因子 Xa 和 spectrozyme Xa)分析了因子-Xa 抑制活性。用 SPECTRAmax 微量滴定板分光光度计和 Softmax Pro 软件(Molecular Devices Corp., Sunnyvale, CA)测定光密度(Vmax, 405 nm)的改变速度。对 Xa 活性的抑制作用按照下式测定：Xa 活性的抑制百分比 = 1-(含抑制剂样品的 Vmax/给药前的对照样品的 Vmax) × 100。

本领域技术人员很容易理解，本发明非常适于实现本发明的目的并获得所提到的以及内在的那些结果和优点。本文中所描述的化合物、组合物和方法是作为优选实施方案的代表而提出的，或者是用来举例说明的，并不是想要限定本发明的范围。

可以通过其它特定的方式实现本发明而不背离本发明的精神或基本属性。