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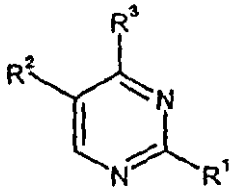
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(54) Title: AMINOPYRIMIDINES AS SORBITOL DEHYDROGENASE INHIBITORS



(I)

(57) Abstract

This invention is directed to sorbitol dehydrogenase inhibitory compounds of formula (I), wherein $R^1$, $R^2$ and $R^3$ are as defined in the specification. This invention is also directed to pharmaceutical compositions containing those compounds and methods of treating or preventing diabetic complications, particularly diabetic neuropathy, diabetic nephropathy, diabetic microangiopathy, diabetic macroangiopathy and diabetic cardiomyopathy by administering such compounds to a mammal suffering from diabetes and therefor at risk for developing such complications. This invention is also directed to pharmaceutical compositions comprising a combination of a compound of formula (I) of this invention with an aldose reductase inhibitor and to methods of treating or preventing diabetic complications therewith. This invention is also directed to pharmaceutical compositions comprising a combination of a compound of formula (I) of this invention with an NHE-1 inhibitor and to methods of treating cardiomyopathy and other heart-related problems therewith. This invention is also directed to certain intermediates used in the synthesis of the compounds of formula (I) and to processes for preparing those intermediates.

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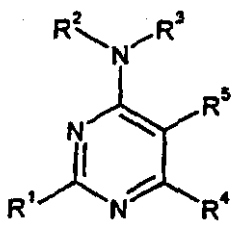
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# AMINOPYRIMIDINES AS SORBITOL DEHYDROGENASE INHIBITORS

The present invention relates to novel pyrimidine derivatives and to the use of such derivatives and related compounds to inhibit sorbitol dehydrogenase (SDH), lower fructose levels, or treat or prevent diabetic complications such as diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic microangiopathy and diabetic macroangiopathy in mammals. This invention also relates to pharmaceutical compositions containing such pyrimidine derivatives and related compounds. This invention also relates to pharmaceutical compositions comprising a combination of a sorbitol dehydrogenase inhibitor of formula I and an aldose reductase inhibitor and to the use of such compositions to treat or prevent diabetic complications in mammals. This invention also relates to pharmaceutical compositions comprising a combination of a sorbitol dehydrogenase inhibitor of formula I and an NHE-1 inhibitor and to the use of such compositions to reduce tissue damage resulting from ischemia, and particularly to prevent perioperative myocardial ischemic injury.

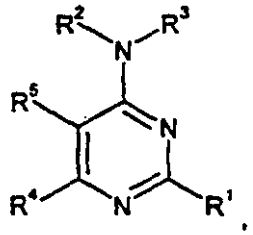
S. Ao et al., Metabolism, 40, 77-87 (1991) have shown that significant functional improvement in the nerves of diabetic rats (based on nerve conduction velocity) occurs when nerve fructose levels are pharmacologically lowered, and that such improvement correlates more closely with the lowering of nerve fructose than the lowering of nerve sorbitol. Similar results were reported by N. E. Cameron and M. A. Cotter, Diabetic Medicine, 8, Suppl. 1, 35A-36A (1991). In both of these cases, lowering of nerve fructose was achieved using relatively high does of aldose reductase inhibitors, which inhibit the formation of sorbitol, a precursor of fructose, from glucose via the enzyme aldose reductase.

U.S. Patent Nos. 5,138,058 and 5,215,990, which are hereby incorporated by reference, each disclose compounds of the formula



where $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are as disclosed therein. Said compounds are disclosed as having utility as tools in screening for aldose reductase inhibitors due to the sorbitol accumulating activity of said compounds.

Commonly assigned U.S. Patent Nos. 5,728,704 and 5,866,578, which are hereby incorporated by reference, each disclose compounds of the formula A,



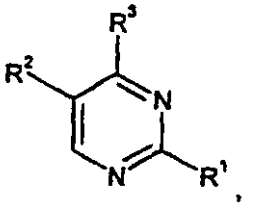
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wherein $R^1$ through $R^5$ are defined as disclosed therein. Further, U.S. 5,728,704 discloses that sorbitol dehydrogenase compounds have utility in the treatment of diabetic complications.

Pyrimidine derivatives of the formula I, as defined below, and their pharmaceutically acceptable salts, lower fructose levels in the tissues of mammals affected by diabetes (e.g., nerve, kidney and retina tissue) and are useful in the treatment and prevention of the diabetic complications referred to above. These compounds, or their metabolites *in vivo*, are inhibitors of the enzyme sorbitol dehydrogenase, which catalyzes the oxidation of sorbitol to fructose.

## SUMMARY OF THE INVENTION

The present invention is directed to a compound of the formula I



I

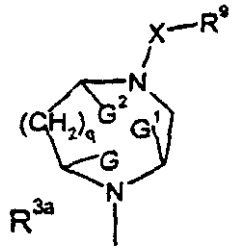
a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

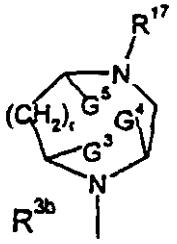
$R^1$ is formyl, acetyl, propionyl, carbamoyl or $-C(OH)R^4R^5$;

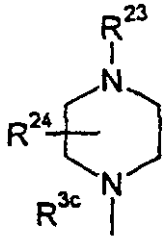
$R^4$ and $R^5$ are each independently hydrogen, methyl, ethyl or hydroxy-($C_1$-$C_3$)alkyl;

$R^2$ is hydrogen, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy;

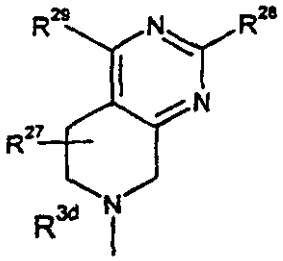
$R^3$ is a radical of the formula

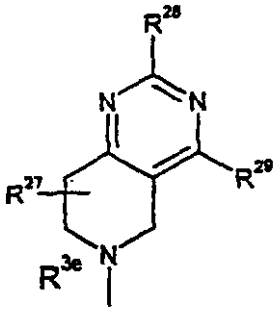


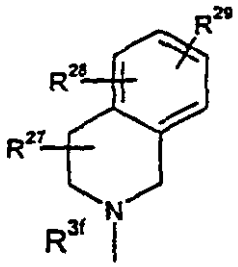
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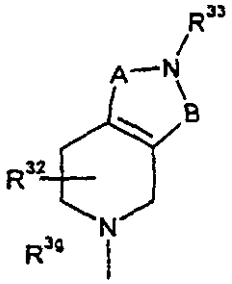
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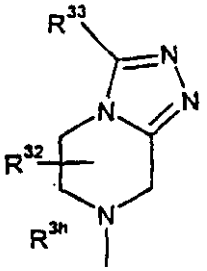


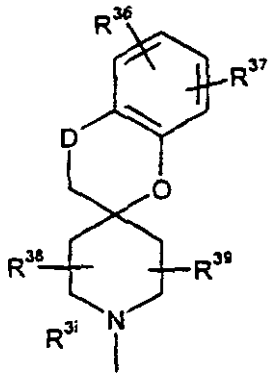
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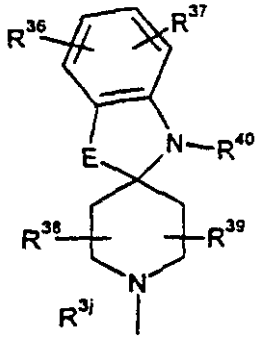
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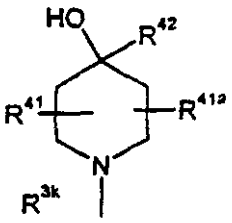
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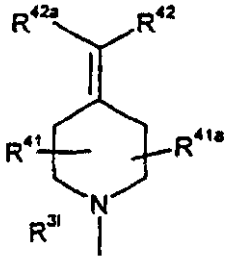


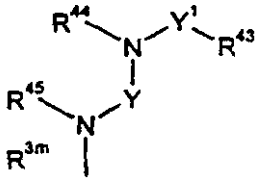


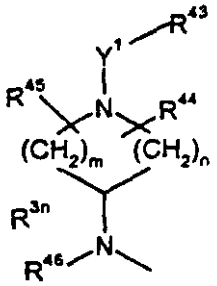


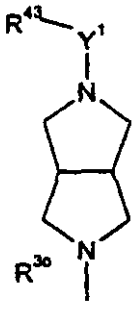


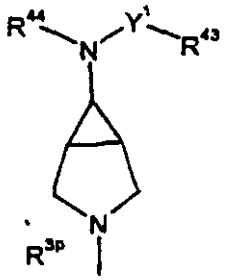




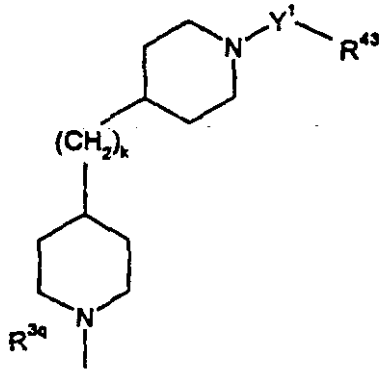








or



;

wherein said radical of formula $R^{3a}$ is additionally substituted on the ring by $R^6$, $R^7$ and $R^8$;

said radical of formula $R^{3b}$ is additionally substituted on the ring by $R^{18}$, $R^{19}$ and $R^{20}$;

G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or

G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or

$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;

q is 0 or 1;

X is a covalent bond, -(C=$NR^{10}$)-, oxycarbonyl, vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl, vinylenylsulfonyl, sulfinyl-($C_1$-$C_4$)alkylenylcarbonyl, sulfonyl-($C_1$-$C_4$)alkylenylcarbonyl or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl and thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar; said vinylenylsulfonyl and said vinylenylcarbonyl in the definition of X are optionally substituted independently on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; and said carbonyl($C_0$-$C_4$)alkylenylcarbonyl in the definition of X is optionally substituted indepedently with up to three ($C_1$-$C_4$)alkyl, benzyl or Ar;

$R^{10}$ is hydrogen or ($C_1$-$C_4$)alkyl;

$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_3$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro; provided that when q = 0 and X is a covalent bond, oxycarbonyl or ($C_1$-$C_4$)alkylenylcarbonyl, then $R^9$ is not ($C_1$-$C_6$)alkyl;

Ar and $Ar^1$ are independently a fully saturated, partially saturated or fully unsaturated five- to eight-membered ring optionally having up to four heteroatoms selected

independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated five- to seven-membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five to seven membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially saturated, fully saturated ring or fully unsaturated monocyclic ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

Ar and $Ar^1$ are optionally independently substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to a total of four substituents independently selected from $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$; wherein $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are each taken separately and are each independently halo, formyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)alkylenyloxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, $C(OH)R^{15}R^{16}$, naphthyl, phenyl, imidazolyl, pyridyl, triazolyl, morpholinyl, ($C_0$-$C_4$)alkylsulfamoyl, N-($C_0$-$C_4$)alkylcarbamoyl, N,N-di-($C_1$-$C_4$)alkylcarbamoyl, N-phenylcarbamoyl, N-($C_1$-$C_4$)alkyl-N-phenylcarbamoyl, N,N-diphenyl carbamoyl, ($C_1$-$C_4$)alkylcarbonylamido, ($C_3$-$C_7$)cycloalkylcarbonylamido, phenylcarbonylamido, piperidinyl, pyrrolidinyl, piperazinyl, cyano, benzimidazolyl, amino, anilino, pyrimidyl, oxazolyl, isoxazolyl, tetrazolyl, thienyl, thiazolyl, benzothiazolyl, pyrrolyl, pyrazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, 8-($C_1$-$C_4$)alkyl-3,8-diaza[3.2.1]bicyclooctyl, 3,5-dioxo-1,2,4-triazinyl, phenoxy, thiophenoxy, ($C_1$-$C_4$)alkylsulfanyl, ($C_1$-$C_4$)alkylsulfonyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said naphthyl, phenyl, pyridyl, piperidinyl, benzimidazolyl, pyrimidyl, thienyl, benzothiazolyl, pyrrolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, thiophenoxy, anilino and phenoxy in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five

fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from ($C_1$-$C_4$)alkyl; said pyrrolidinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from hydroxy, hydroxy-($C_1$-$C_3$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to three substituents independently selected from ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, ($C_0$-$C_4$)alkylsulfamoyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said triazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said tetrazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy-($C_2$-$C_3$)alkyl or ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; and said phenyl and pyridyl which are optionally substituted on piperazine in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

$R^{11}$ and $R^{12}$ are taken together on adjacent carbon atoms and are $-CH_2OC(CH_3)_2OCH_2-$ or $-O-(CH_2)_p-O-$, and $R^{13}$ and $R^{14}$ are taken separately and are each independently hydrogen or ($C_1$-$C_4$)alkyl;

p is 1, 2 or 3;

$R^{15}$ and $R^{16}$ are taken separately and are each independently hydrogen, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; or $R^{15}$ and $R^{16}$ are taken separately and $R^{15}$ is hydrogen and $R^{16}$ is ($C_3$-$C_6$)cycloalkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, imidazolyl, benzothiazolyl or benzoxazolyl; or $R^{15}$ and $R^{16}$ are taken together and are ($C_3$-$C_6$)alkylene;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 0; $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently $(C_1$-$C_4)$alkyl; or

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_1$-$C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1$-$C_6)$alkyl;

$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl and $Ar^2$-$(C_0$-$C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy,

amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, pyrimidyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$Ar^2$ is independently defined as set forth for Ar and $Ar^1$ above;

said $Ar^2$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{23}$ is $CONR^{25}R^{26}$ or $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen ($C_1$-$C_4$)alkyl or $Ar^3$-($C_0$-$C_4$)alkylenyl and $R^{26}$ is $Ar^3$-($C_0$-$C_4$)alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

$R^{24}$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro;

$Ar^3$ is independently defined as set forth for Ar and $Ar^1$ above;
said $Ar^3$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;
$R^{27}$ is hydrogen or $(C_1-C_4)$alkyl;
$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro, $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$; said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and thiophenoxy in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{30}$ and $R^{31}$ are each independently hydrogen, $(C_1-C_4)$alkyl, $(C_3-C_7)$cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; or
$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
A is N optionally substituted with hydrogen or $(C_1-C_4)$alkyl and B is carbonyl; or

A is carbonyl and B is N optionally substituted with hydrogen or $(C_1-C_4)$alkyl;
$R^{32}$ is hydrogen or $(C_1-C_4)$alkyl;
$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl; said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl *in the definition of* $R^{33}$ *are optionally substituted with up to three phenyl, phenoxy,* $NR^{34}R^{35}$, halo, hydroxy, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{34}$ and $R^{35}$ are each independently hydrogen, $(C_1-C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
D is CO, CHOH or $CH_2$;
E is O, NH or S;
$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, $(C_1-C_6)$alkylamino, di-$(C_1-C_6)$alkylamino, pyrrolidino, piperidino, morpholino, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, hydroxy-$(C_1-C_4)$alkyl, $Ar^4$, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or $(C_1-C_4)$-alkyl;
$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; or
$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are $-O-(CH_2)_t-O-$;
t is 1, 2 or 3;
Y is $(C_2-C_6)$alkylene;
$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or $(C_1-C_4)$alkyl;
m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;
k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is $(C_3-C_7)$cycloalkyl, $Ar^5$-$(C_0-C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1-C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1-C_6)$alkyl and $Ar^5$-$(C_0-C_4)$alkylenyl; or

$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;

$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

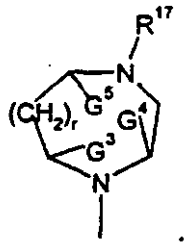
$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3-C_7)$cycloalkyl, $Ar^6$-$(C_0-C_3)$alkylenyl, $Ar^6$-$(C_2-C_4)$alkenyl, $Ar^6$-carbonyl or $(C_1-C_6)$alkyl optionally substituted with up to five fluoro;

$Ar^6$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^6$ is optionally independently substituted as set forth for Ar and $Ar^1$ above; and $R^{41}$ and $R^{41a}$ are each independently hydrogen or $(C_1-C_4)$alkyl.

A preferred group of compounds of formula I, designated Group A, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

$R^3$ is



;

substituted by $R^{18}$, $R^{19}$ or $R^{20}$;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen, r is 0 and $R^{18}$ is hydrogen, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl or phenyl optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; $R^{19}$ and $R^{20}$ are each independently $(C_1-C_4)$alkyl;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; and $R^{18}$ is hydrogen, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl or phenyl optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1-C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1-C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1-C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

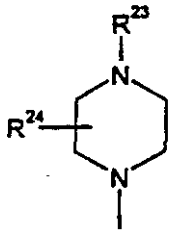
$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1-C_6)$alkoxycarbonyl, $(C_1-C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1-C_6)$alkylsulfonyl, $(C_1-C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1-C_6)$alkyl;

$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1-C_6)$alkyl, $(C_3-C_7)$cycloalkyl and $Ar^2$-$(C_0-C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, morpholinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, pyrimidyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro.

Another preferred group of compounds of formula I, designated Group B, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

$R^3$ is



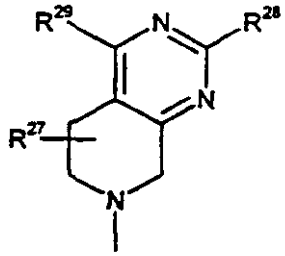
;

$R^{23}$ is $CONR^{25}R^{26}$, $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen $(C_1\text{-}C_4)$alkyl or $Ar^3\text{-}(C_0\text{-}C_4)$alkylenyl and $R^{26}$ is $Ar^3\text{-}(C_0\text{-}C_4)$alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

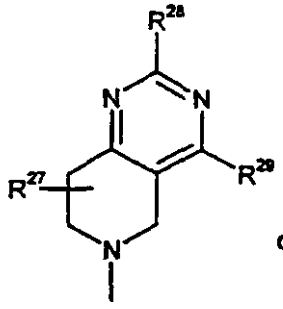
$R^{24}$ is hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxycarbonyl or phenyl optionally substituted by up to three $(C_1\text{-}C_4)$alkyl optionally substituted with up to five fluoro, $(C_1\text{-}C_4)$alkoxy optionally substituted with up to five fluoro, hydroxy, halo or hydroxy-$(C_1\text{-}C_3)$alkyl.

Another preferred group of compounds of formula I, designated Group C, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

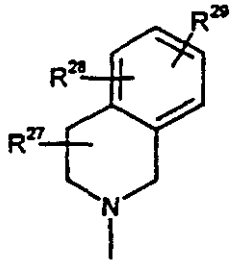
$R^3$ is



,



or



.

$R^{27}$ is hydrogen or $(C_1\text{-}C_4)$alkyl;

$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl optionally substituted with up to five fluoro, $(C_1\text{-}C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$;

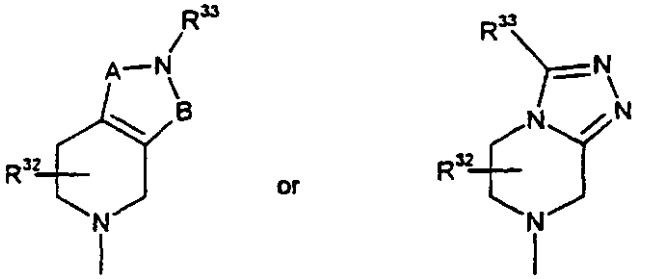
said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and thiophenoxy in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$R^{30}$ and $R^{31}$ are each independently hydrogen, ($C_1$-$C_4$)alkyl, ($C_3$-$C_7$)cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, or hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro.

Yet another preferred group of compounds of formula I, designated Group D, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

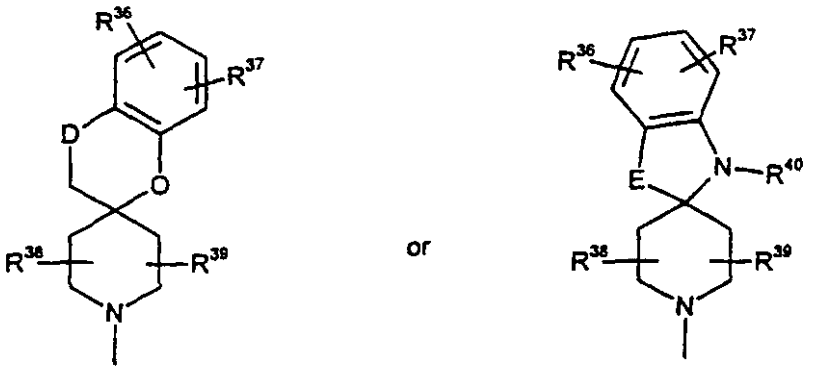
$R^3$ is



A is N optionally substituted with hydrogen or $(C_1-C_4)$alkyl and B is carbonyl; or
A is carbonyl and B is N optionally substituted with hydrogen or $(C_1-C_4)$alkyl;
$R^{32}$ is hydrogen or $(C_1-C_4)$alkyl;
$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl; said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl in the definition of $R^{33}$ are optionally substituted with up to three phenyl, phenoxy, $NR^{34}R^{35}$, halo, hydroxy, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{34}$ and $R^{35}$ are each independently hydrogen, $(C_1-C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro.

Still another preferred group of compounds of formula I, designated Group E, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

$R^3$ is



D is CO, CHOH or $CH_2$;

E is O, NH or S;

$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, $(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, pyrrolidino, piperidino, morpholino, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl, $Ar^4$, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or $(C_1$-$C_4)$-alkyl;

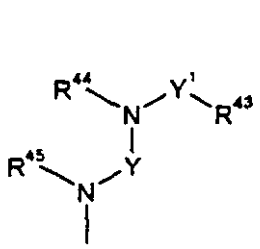
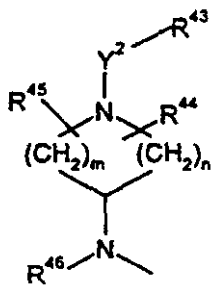
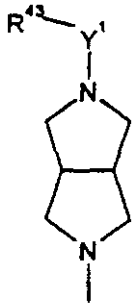
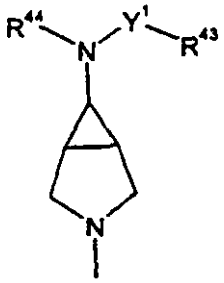
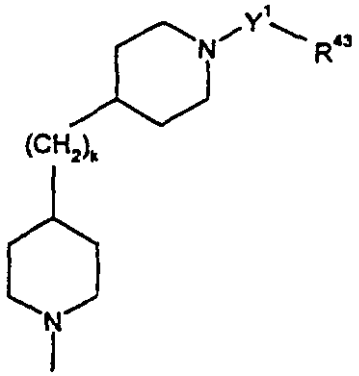
$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or

$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are -O-$(CH_2)_t$-O-;

t is 1, 2 or 3.

Still another preferred group of compounds of formula I, designated Group F, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

$R^3$ is





or

;

Y is $(C_2\text{-}C_6)$alkylene;

$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or $(C_1\text{-}C_4)$alkyl;

m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;

k is 0 to 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is $(C_3\text{-}C_7)$cycloalkyl, $Ar^5\text{-}(C_0\text{-}C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1\text{-}C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1\text{-}C_6)$alkyl and $Ar^5\text{-}(C_0\text{-}C_4)$alkylenyl; or

$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy,

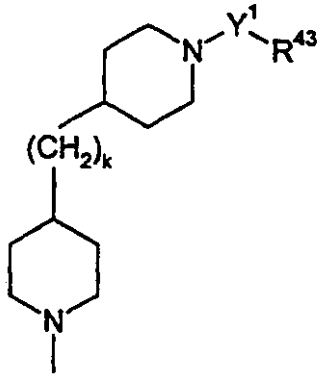
amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro.

A preferred group of compounds within Group F, designated Group FA, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^2$ is hydrogen;

$R^3$ is



;

k is 0;

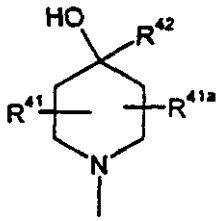
$Y^1$ is a covalent bond; and

$R^{43}$ is 4-pyrimidinyl substituted at the 2-position with 1-hydroxymethyl.

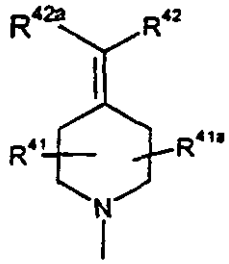
A preferred group of compounds within Group FA, designated Group FB, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, which is 1R-(4-{1'-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-[4,4']bipiperidinyl-1-yl}-pyrimidin-2-yl)-ethanol.

Another preferred group of compounds of formula I, designated Group G, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

$R^3$ is



or



$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3\text{-}C_7)$cycloalkyl, $Ar^6\text{-}(C_0\text{-}C_3)$alkylenyl, $Ar^6\text{-}(C_2\text{-}C_4)$alkenyl, $Ar^6$-carbonyl or $(C_1\text{-}C_6)$alkyl optionally substituted with up to five fluoro; and

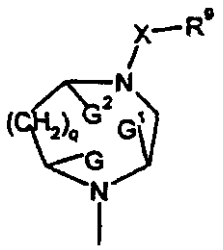
$R^{41}$ and $R^{41a}$ are independently hydrogen or $(C_1\text{-}C_4)$alkyl.

Still another preferred group of compounds of formula I, designated Group H, are those compounds of formula I, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

$R^1$ is $C(OH)R^4R^5$, where $R^4$ and $R^5$ are each independently hydrogen or methyl;

$R^2$ is hydrogen;

$R^3$ is



wherein said $R^3$ is substituted by $R^6$, $R^7$ or $R^8$;

G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen or ($C_1$-$C_4$)alkyl; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or
G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or
$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;
q is 0 or 1;
X is a covalent bond, oxycarbonyl,vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl or vinylenylsulfonyl; said vinylenylcarbonyl and said vinylenylsulfonyl in the definition of X are optionally substituted on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; said oxy($C_1$-$C_4$)alkylenylcarbonyl and said thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are optionally substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar;
$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_4$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro;
$Ar^1$ is phenyl, naphthyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, furopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, furopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; and
said $Ar^1$ is optionally substituted as set forth above.

A preferred group of compounds within Group H, designated Group HA, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

X is a covalent bond, oxycarbonyl or vinylenylcarbonyl optionally substituted on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar;

$R^9$ is $Ar^1$-($C_0$-$C_4$)alkylenyl;

$Ar^1$ is phenyl, naphthyl, pyridyl, pyrimidyl, pyrazinyl, triazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, furanyl, thienyl, indolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, furopyridyl, oxazolopyridyl, thiazolopyridyl, thienopyridyl, furopyrimidyl, thienopyrimidyl, oxazolopyrimidyl or thiazolopyrimidyl; and

said $Ar^1$ is optionally substituted as set forth in claim 1.

A preferred group of compounds within Group HA, designated Group HB, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs, wherein:

$R^2$ is hydrogen;

$R^4$ is hydrogen or methyl;

$R^5$ is methyl;

G, $G^1$ and $G^2$ are hydrogen;

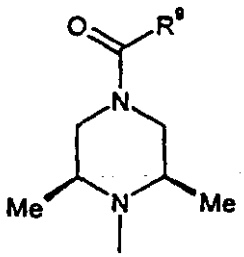
$R^6$ and $R^7$ are each independently hydrogen or methyl;

$R^8$ is hydrogen.

A preferred group of compounds within Group HB, designated Group HC, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is



A preferred compound within Group HC is the compound wherein $R^9$ is 2-furo[3,2-c]pyridyl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within Group HC is the compound wherein $R^9$ is 2-(4-chloro-furo[3,2-c]pyridyl), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within Group HC is the compound wherein $R^9$ is 2-(4-pyrrolidin-1-yl-furo[3,2-c]pyridyl), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within Group HC is the compound wherein $R^9$ is 2-(4-morpholin-4-yl-furo[3,2-c]pyridyl), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

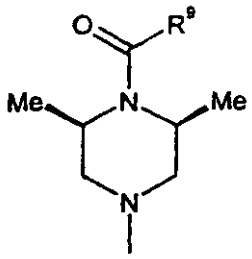
Another preferred compound within Group HC is the compound wherein $R^9$ is 2-imidazo[1,2-a]pyridyl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Preferred compounds within Group HC are furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone; (4-chloro-furo[3,2-c]pyridin-2-yl)-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-pyrrolidin-1-yl-furo[3,2-c]pyridin-2-yl)-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-morpholin-4-yl-furo[3,2-c]pyridin-2-yl)-methanone; and {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-imidazo[1,2-a]pyridin-2-yl-methanone.

Another preferred group of compounds within Group HB, designated Group HD, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is



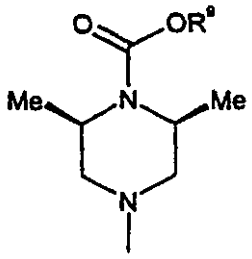
A preferred compound within Group HD is the compound wherein $R^9$ is 2-furo[3,2-c]pyridyl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

An especially preferred compound within Group HD is furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-methanone.

Another preferred group of compounds within Group HB, designated Group HE, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is



A preferred compound within Group HE is the compound wherein $R^9$ is 3-pyridyl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within Group HE is the compound wherein $R^9$ is 3-(2-methylpyridyl), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within Group HE is the compound wherein $R^9$ is 3-(5-chloropyridyl), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

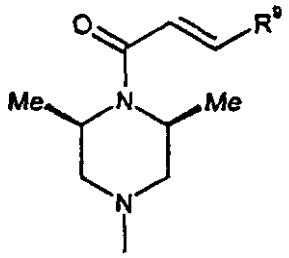
Another preferred compound within Group HE is the compound wherein $R^9$ is 3-(6-methylpyridyl), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Preferred compounds within Group HE are 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid pyridin-3-yl ester; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 2-methyl-pyridin-3-yl ester; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 5-chloro-pyridin-3-yl ester; and 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 6-methyl-pyridin-3-yl ester.

Another preferred group of compounds within Group HB, designated Group HF, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is



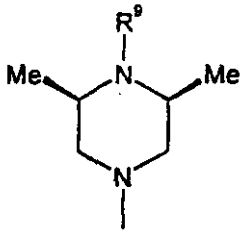

A preferred compound within the Group HF is the compound wherein $R^9$ is 2-thienyl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

An especially preferred compound within Group HF is (E)-1-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-3-thiophen-2-yl-propenone.

Another preferred group of compounds within Group HB, designated Group HG, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is



; and

$R^9$ is pyrimidyl or triazinyl; said pyrimidyl or triazinyl is optionally substituted with up to two hydroxy, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_4)$alkoxy, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkylenyl, phenyl, piperazinyl optionally substituted with $(C_1$-$C_4)$alkyl, or imidazolyl optionally substituted with up to two $(C_1$-$C_4)$alkyl.

A preferred group of compounds within Group HG, designated Group HH, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein: $R^9$ is pyrimid-2-yl optionally substituted with up to two $(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl.

A preferred compound within the Group HH is the compound wherein $R^9$ is 4,6-dimethylpyrimid-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HH is the compound wherein $R^9$ is 4-methoxymethyl-6-methylpyrimid-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HH is the compound wherein $R^9$ is 4-hydroxymethyl-6-methylpyrimid-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

A preferred group of compounds within the Group HH are 1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; and 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.

Another preferred group of compounds within the Group HG, designated HI, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein: $R^9$ is pyrimid-4-yl optionally substituted with up to two $(C_1$-$C_4)$alkylpiperazin-1-yl or imidazolyl; and said imidazolyl is optionally substituted with up to two $(C_1$-$C_4)$alkyl.

A preferred compound within the Group HI is the compound wherein $R^9$ is 2-(4-methylpiperazin-1-yl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HI is the compound wherein $R^9$ is 2-(4-ethylpiperazin-1-yl)- pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HI is the compound wherein $R^9$ is 2-(4-methylimidazol-1-yl)- pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein.

Another preferred compound within the Group HI is the compound wherein $R^9$ is 2-(2-methylimidazol-1-yl)- pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein.

Another preferred compound within the Group HI is the compound wherein $R^9$ is 2-(2,4-dimethylimidazol-1-yl)- pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HI is the compound wherein $R^9$ is 2-(4-isopropylpiperazin-1-yl)- pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Preferred compounds within Group HI are 1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(4-ethyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{3R,5S-dimethyl-4-[2-(2-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; and 1R-(4-{4-[2-(4-isopropyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.

Another preferred group of compounds within Group HG, designated Group HJ, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein: $R^9$ is [1,3,5]-triazin-2-yl optionally substituted with up to two hydroxy, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_4)$alkoxy, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkylpiperazin-1-yl or phenyl.

A preferred compound within the Group HJ is the compound wherein $R^9$ is 4-methyl-6-(4-methylpiperazin-1-yl)-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-methoxy-6-methyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4,6-dimethyoxy-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-ethoxy-6-methyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-isopropoxy-6-methyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-phenyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-hydroxymethyl-6-methoxy-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-isopropoxy-6-methoxy-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-isopropyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-ethyl-6-methoxy-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-cyclopropyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4,6-dimethyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

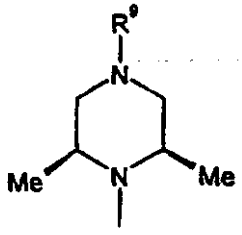
Another preferred compound within the Group HJ is the compound wherein $R^9$ is 4-methyl-6-phenyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Preferred compounds within the Group HJ are 1R-(4-{3R,5S-dimethyl-4-[4-methyl-6-(4-methyl-piperazin-1-yl)-[1,3,5]triazin-2-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-ethoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[3R,5S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropoxy-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl)-ethanol; 1R-{4-[3R,5S-dimethyl-4-(4-methyl-6-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; and 1R-{4-[4-(4-ethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.

Another group of preferred compounds within the Group HB, designated Group HK, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is




; and

$R^9$ is pyrimidyl or triazinyl, said pyrimidyl and triazinyl optionally substituted with up to two hydroxy, ($C_1$-$C_4$)alkyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkoxy, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, triazolyl, acetyl, morpholinyl, ($C_1$-$C_4$)alkylpiperazinyl, phenyl or imidazolyl optionally substituted with up to two ($C_1$-$C_4$)alkyl.

A preferred group of compounds within the Group HK, designated HL, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein: $R^9$ is pyrimid-2-yl optionally substituted with up to two ($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or triazolyl.

A preferred compound within the Group HL is the compound wherein $R^9$ is 4,6-dimethyl-pyrimid-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HL is the compound wherein $R^9$ is 4-hydroxymethyl-6-methylpyrimid-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HL is the compound wherein $R^9$ is 4-[1,2,4]-triazol-1-yl-pyrimid-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Preferred compounds within the Group HL are 1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]- pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; and 1R-{4-[2R,6S-dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.

Another preferred group of compounds within the Group HK, designated Group HM, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein: $R^9$ is pyrimid-4-yl optionally substituted with up to two ($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl, acetyl, morpholinyl, ($C_1$-$C_4$)alkylpiperazinyl, triazolyl or imidazolyl optionally substituted with up to two ($C_1$-$C_4$)alkyl.

A preferred compound within the Group HM is the compound wherein $R^9$ is 2,6-dimethyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-hydroxymethyl-6-methyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-acetyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-morpholin-4-yl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-(4-methylpiperazin-1-yl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-[1,2,4]-triazol-1-yl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-(1S-hydroxyethyl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-(1R-hydroxyethyl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-(4-ethylpiperazin-1-yl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

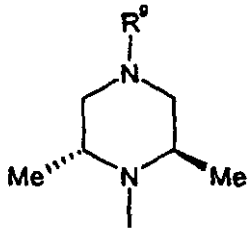
Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-(4-methylimidazol-1-yl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HM is the compound wherein $R^9$ is 2-(2,4-dimethylimidazol-1-yl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Preferred compounds within the HB Group are 1R-{4-[4-(2,6-dimethyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1S-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; (4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone; 1R-{4-[2R,6S-dimethyl-4-(2-morpholin-4-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[2R,6S-dimethyl-4-(2-[1,2,4]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6R-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(4-ethyl-piperazin-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; and 1R-(4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.

Another preferred compound within the Group HB is the compound wherein $R^1$ is (R)-1-hydroxyethyl; $R^3$ is




; and

$R^9$ is 2-(1R-hydroxyethyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

A preferred group of compounds within the Group HK, designated Group HN, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds and said prodrugs, wherein $R^9$ is [1,3,5]-triazin-2-yl optionally substituted with up to two hydroxy, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, morpholinyl or phenyl.

A preferred compound within the Group HN is the compound wherein $R^9$ is 4-morpholin-4-yl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4-methoxy-6-methyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4,6-dimethoxy-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4-phenyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4-cyclopropyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4,6-dimethyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4-hydroxymethyl-6-phenyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4-methoxy-6-methoxymethyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4-methyl-[1,3,5]-triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HN is the compound wherein $R^9$ is 4-methoxymethyl-6-phenyl-[1,3,5]triazin-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

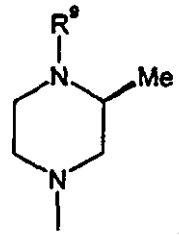
Preferred compounds within the Group HN are 1R-{4-[2R,6S-dimethyl-4-(4-morpholin-4-yl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxy-6-methoxymethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-

pyrimidin-2-yl}-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-methyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl-ethanol; 1R-{4-[4-(4-methoxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; and 1R-{4-[2R,6S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.

Another preferred group of compounds within the Group HB, designated Group HO, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is




; and

$R^9$ is pyrimidyl, quinoxalyl or oxazolopyridyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy or hydroxy-($C_1$-$C_4$)alkyl.

A preferred compound within the Group HO is the compound wherein $R^9$ is 4-hydroxymethyl-6-methyl-pyrimid-2-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HO is the compound wherein $R^9$ is 2-hydroxymethyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HO is the compound wherein $R^9$ is 2-hydroxymethyl-6-methyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HO is the compound wherein $R^9$ is 2-(oxazolo[5,4-b]pyridyl), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Another preferred compound within the Group HO is the compound wherein $R^9$ is 2-(oxazolo[4,5-b]pyridyl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

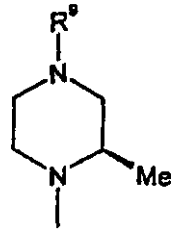
Another preferred compound within the Group HO is the compound wherein $R^9$ is 2-quinoxalyl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Preferred compounds within the Group HO are 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2-hydroxymethyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-py-rimidin-2-yl}-ethanol; 1R-[4-(3S-methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; 1R-[4-(3S-methyl-4-oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; and 1R-[4-(3S-methyl-4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.

Another preferred group of compounds within the Group HB, designated Group HP, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is




; and

$R^9$ is pyrimidyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, hydroxy-($C_1$-$C_4$)alkyl.

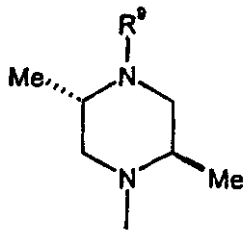
A preferred compound within the Group HP is the compound wherein $R^9$ is 2-(1R-hydroxyethyl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

A preferred compound within the Group HP is 1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R-methyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.

Another preferred group of compounds within the Group HB, designated HQ, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is



; and

$R^9$ is pyrimidyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, hydroxy-($C_1$-$C_4$)alkyl.

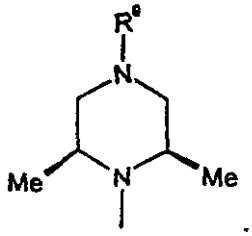
A preferred compound within the Group HQ is the compound wherein $R^9$ is 2-(1R-hydroxyethyl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

An especially preferred compound within the Group HQ is (4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.

Another preferred group of compounds within the Group HB, designated Group HR, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is (S)-1-hydroxy-ethyl;

$R^3$ is



; and

$R^9$ is pyrimidyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy or hydroxy-($C_1$-$C_4$)alkyl.

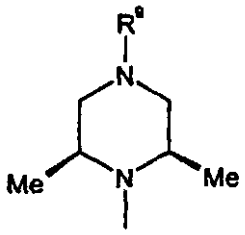
A preferred compound within the Group HR is the compound wherein $R^9$ is 2-(1R-hydroxy-ethyl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

An especially preferred compound within the Group HR is 1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.

Yet another preferred group of compounds within the Group HB, designated Group HS, are those compounds, prodrugs thereof and pharmaceutically acceptable salts of said compounds or said prodrugs wherein:

$R^1$ is acetyl;

$R^3$ is




; and

$R^9$ is pyrimidyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, acetyl or hydroxy-($C_1$-$C_4$)alkyl.

A preferred compound within the Group HS is the compound wherein $R^9$ is 2-acetyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

A preferred compound within the Group HS is the compound wherein $R^9$ is 2-(1R-hydroxyethyl)-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

Especially preferred compounds within the Group HS are 1-{4-[4-(2-acetyl-pyrimidin-4-yl)-2R*,6S*-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanone or 1-(-4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone.

A pharmaceutical composition, designated Composition A, comprising a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

A method of inhibiting sorbitol dehydrogenase in a mammal in need of such inhibition comprising administering to said mammal a sorbitol dehydrogenase inhibiting amount of a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

A method of treating diabetes in a mammal suffering from diabetes comprising administering to said mammal an effective amount of a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

A method, designated Method A, of treating or preventing diabetic complications in a mammal comprising administering to said mammal an effective

amount of a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

A method of Method A wherein said mammal is suffering from diabetes.

A method of Method A wherein said diabetic complication is diabetic neuropathy.

A method of Method A wherein said diabetic complication is diabetic nephropathy.

A method of Method A wherein said diabetic complication is diabetic retinopathy.

A method of Method A wherein said diabetic complication is foot ulcers.

A method of Method A wherein said diabetic complication is a cardiovascular condition.

A pharmaceutical composition, designated Composition B, comprising a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and an aldose reductase inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said aldose reductase inhibitor or said prodrug.

A composition of Composition B additionally comprising a pharmaceutically acceptable carrier or diluent.

A method of treating diabetes in a mammal suffering from diabetes comprising administering to said mammal an effective amount of a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and an aldose reductase inhibitor, a prodrug of said aldose reductase inhibitor or a pharmaceutically acceptable salt of said aldose reductase inhibitor or said prodrug.

*** A method, designated Method B, of treating or preventing diabetic complications in a mammal comprising administering to said mammal an effective amount of a compound of formula I, a prodrug thereof or a pharmaceutically acceptable of said compound or said prodrug and an aldose reductase inhibitor, a prodrug of said aldose reductase inhibitor or a pharmaceutically acceptable salt of said aldose reductase inhibitor or said prodrug thereof.

A method of Method B wherein said mammal is suffering from diabetes.

A method of Method B wherein said diabetic complication is diabetic neuropathy.

A method of Method B wherein said diabetic complication is diabetic nephropathy.

A method of Method B wherein said diabetic complication is diabetic retinopathy.

A method of Method B wherein said diabetic complication is foot ulcers.

A method of Method B wherein said diabetic complication is a cardiovascular condition.

A pharmaceutical composition, designated Composition C, comprising a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug of said NHE-1 inhibitor or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug thereof.

A method, designated Method C, of treating ischemia in a mammal suffering from ischemia comprising administering to said mammal an effective amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug of said NHE-1 inhibitor or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug.

A method of Method C wherein said ischemia is perioperative myocardial ischemia.

A method of treating or preventing diabetic complications in a mammal, designated Method D, comprising administering to said mammal an effective amount of a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug of said NHE-1 inhibitor or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug.

A method of Method D wherein said mammal is suffering from diabetes.

A method of Method D wherein said diabetic complication is diabetic neuropathy.

A method of Method D wherein said diabetic complication is diabetic nephropathy.

A method of Method D wherein said diabetic complication is diabetic retinopathy.

A method of Method D wherein said diabetic complication is foot ulcers.

A method of Method D wherein said diabetic complication is a cardiovascular condition.

A method of treating diabetes in a mammal suffering from diabetes comprising administering to said mammal an effective amount of a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, and a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug of said NHE-1 inhibitor or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug.

A kit comprising:

a. a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug in a first unit dosage form;

b. an aldose reductase inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said prodrug or said aldose reductase inhibitor in a second unit dosage form; and

c. a container.

A kit comprising:

a. a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug in a first unit dosage form;

b. a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said prodrug or said NHE-1 inhibitor in a second unit dosage form; and

c. a container.

A method, designated Method E, of inhibiting sorbitol dehydrogenase in a mammal in need thereof comprising administering to said mammal Composition A.

A method of Method E wherein said ischemia is perioperative myocardial ischemia.

A method of treating ischemia in a mammal suffering from ischemia comprising administering to said mammal Composition C.

A method, designated Method F, of treating or preventing diabetic complications in a mammal comprising administering to said mammal Composition A.

A method of Method F wherein said mammal is suffering from diabetes.

A method, designated Method G, of treating or preventing diabetic complications in a mammal comprising administering to said mammal Composition B.

A method of Method G wherein said mammal is suffering from diabetes.

A method, designated Method H, of treating or preventing diabetic complications in a mammal comprising administering to said mammal Composition C.

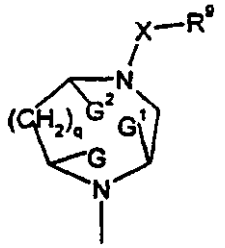
A method of Method H wherein said mammal is suffering from diabetes.

A compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

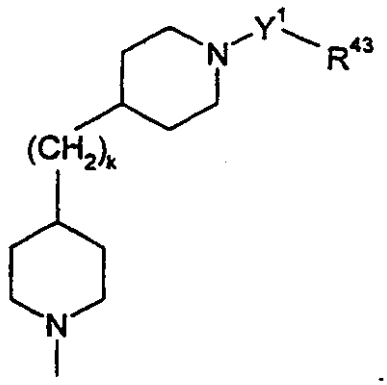
$R^1$ is $C(OH)R^4R^5$, where $R^4$ and $R^5$ are each independently hydrogen or methyl;

$R^2$ is hydrogen;

$R^3$ is



or



;

wherein said piperazinyl $R^3$ is substituted by $R^6$, $R^7$ or $R^8$;

G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen or ($C_1$-$C_4$)alkyl; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or

G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or

$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;

q is 0 or 1;

X is a covalent bond, oxycarbonyl,vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl or vinylenylsulfonyl; said vinylenylcarbonyl and said vinylenylsulfonyl in the definition of X are optionally substituted on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; said oxy($C_1$-$C_4$)alkylenylcarbonyl and said

thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are optionally substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar;

$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_4$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro;

$Ar^1$ is phenyl, naphthyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, furopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, furopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; and

said $Ar^1$ is optionally substituted as set forth above;

k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is ($C_3$-$C_7$)cycloalkyl, $Ar^5$-($C_0$-$C_4$)alkylenyl, $NR^{47}R^{48}$ or ($C_1$-$C_6$)alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, ($C_1$-$C_6$)alkyl and $Ar^5$-($C_0$-$C_4$)alkylenyl; or

$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy,

amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;
$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;
$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above.

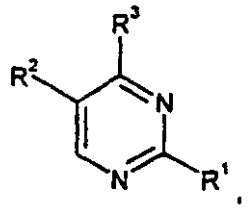
A compound selected from 1R-(4-{1'-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-[4,4']bipiperidinyl-1-yl}-pyrimidin-2-yl)-ethanol; furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone; (4-chloro-furo[3,2-c]pyridin-2-yl)-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-pyrrolidin-1-yl-furo[3,2-c]pyridin-2-yl)-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-morpholin-4-yl-furo[3,2-c]pyridin-2-yl)-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-imidazo[1,2-a]pyridin-2-yl-methanone; furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-methanone; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid pyridin-3-yl ester; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 2-methyl-pyridin-3-yl ester; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1- carboxylic acid 5-chloro-pyridin-3-yl ester; 4-[2-(1R-hydroxy-

ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 6-methyl-pyridin-3-yl ester; (E)-1-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-3-thiophen-2-yl-propenone; 1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-{4-[2-(4-ethyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{3R,5S-dimethyl-4-[2-(2-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(4-isopropyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{3R,5S-dimethyl-4-[4-methyl-6-(4-methyl-piperazin-1-yl)-[1,3,5]triazin-2-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-ethoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[3R,5S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropoxy-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-ethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]- pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2,6-dimethyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-

4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1S-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1-{4-[4-(2-acetyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanone; 1RS-(4-{4-[2-(1RS-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; (4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone; 1R-{4-[2R,6S-dimethyl-4-(2-morpholin-4-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[2R,6S-dimethyl-4-(2-[1,2,4]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6R-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(4-ethyl-piperazin-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-morpholin-4-yl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2-hydroxymethyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-py-rimidin-2-yl}-ethanol; 1R-[4-(3S-methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; 1R-[4-(3S-methyl-4-oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; 1R-[4-(3S-methyl-4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; (4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[3R,5S-dimethyl-4-(4-methyl-6-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-

2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxy-6-methoxymethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-methyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl-ethanol; 1-{4-[4-(2-acetyl-pyrimidin-4-yl)-2R*,6S*-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanone; 1-(-4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone; 1R-{4-[4-(4-methoxymethyl-6-phenyl-[1,3,5]-triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; and 1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.

A compound of the formula $I^A$



$I^A$

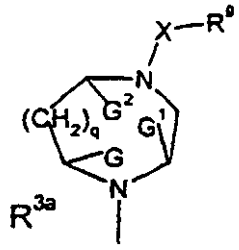
wherein:

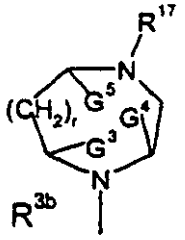
$R^1$ is C-($OR^{80}$)$R^4R^5$, where $R^{80}$ is independently ($C_1$-$C_4$)alkyl, benzyl, ($C_1$-$C_6$)alkylcarbonyl or phenylcarbonyl, where said benzyl and said phenyl are optionally substituted with up to three ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, halo or nitro;

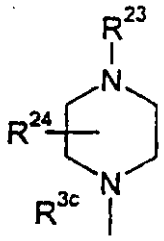
$R^4$ and $R^5$ are each independently hydrogen, methyl, ethyl or hydroxy-($C_1$-$C_3$)alkyl;

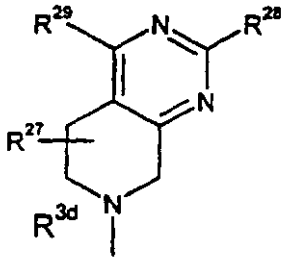
$R^2$ is hydrogen, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy;

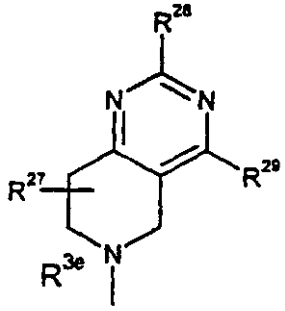
$R^3$ is a radical of the formula

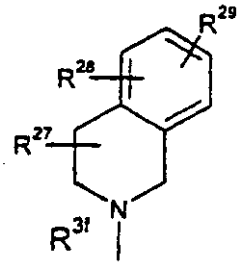


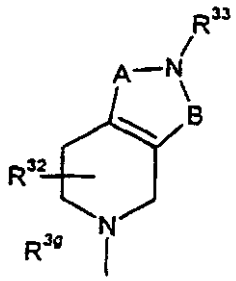


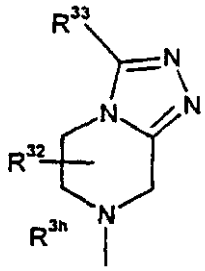


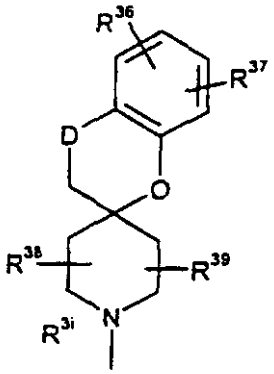


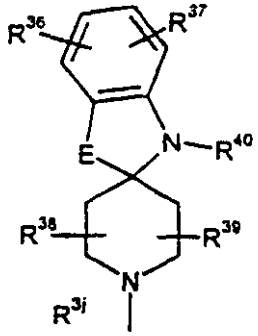


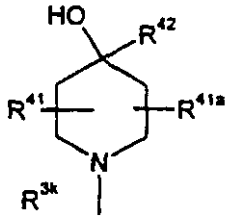


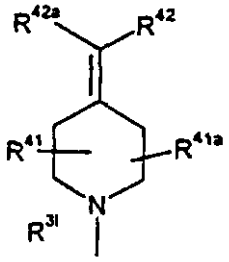


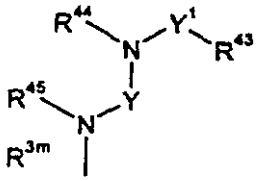


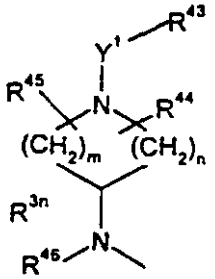


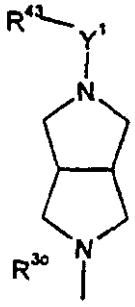


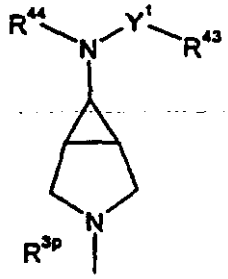




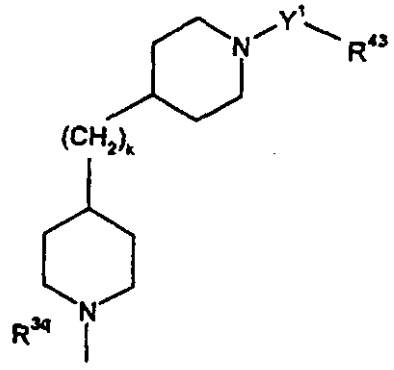








or



wherein said radical of formula $R^{3a}$ is substituted by $R^6$, $R^7$ and $R^8$;
said radical of formula $R^{3b}$ is substituted by $R^{18}$, $R^{19}$ and $R^{20}$;
G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or
G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or
$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;
q is 0 or 1;
X is a covalent bond, -(C=$NR^{10}$)-, oxycarbonyl, vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl, vinylenylsulfonyl, sulfinyl-($C_1$-$C_4$)alkylenylcarbonyl, sulfonyl-($C_1$-$C_4$)alkylenylcarbonyl or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl and thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar; said vinylenylsulfonyl and said vinylenylcarbonyl in the definition of X are optionally substituted independently on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; and said carbonyl($C_0$-$C_4$)alkylenylcarbonyl in the definition of X is optionally substituted indepedently with up to three ($C_1$-$C_4$)alkyl, benzyl or Ar;
$R^{10}$ is hydrogen or ($C_1$-$C_4$)alkyl;
$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_3$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro; provided that when q = 0 and X is a covalent bond, oxycarbonyl or ($C_1$-$C_4$)alkylenylcarbonyl, then $R^9$ is not ($C_1$-$C_6$)alkyl;
Ar and $Ar^1$ are independently a fully saturated, partially saturated or fully unsaturated five- to eight-membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two

fused independently partially saturated, fully saturated or fully unsaturated five- to seven-membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five to seven membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially saturated, fully saturated ring or fully unsaturated monocyclic ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

Ar and $Ar^1$ are optionally independently substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to a total of four substituents independently selected from $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$; wherein $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are each taken separately and are each independently halo, formyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)alkylenyloxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, $C(OH)R^{15}R^{16}$, naphthyl, phenyl, imidazolyl, pyridyl, triazolyl, morpholinyl, ($C_0$-$C_4$)alkylsulfamoyl, N-($C_0$-$C_4$)alkylcarbamoyl, N,N-di-($C_1$-$C_4$)alkylcarbamoyl, N-phenylcarbamoyl, N-($C_1$-$C_4$)alkyl-N-phenylcarbamoyl, N,N-diphenyl carbamoyl, ($C_1$-$C_4$)alkylcarbonylamido, ($C_3$-$C_7$)cycloalkylcarbonylamido, phenylcarbonylamido, piperidinyl, pyrrolidinyl, piperazinyl, cyano, benzimidazolyl, amino, anilino, pyrimidyl, oxazolyl, isoxazolyl, tetrazolyl, thienyl, thiazolyl, benzothiazolyl, pyrrolyl, pyrazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, 8-($C_1$-$C_4$)alkyl-3,8-diaza[3.2.1]bicyclooctyl, 3,5-dioxo-1,2,4-triazinyl, phenoxy, thiophenoxy, ($C_1$-$C_4$)alkylsulfanyl, ($C_1$-$C_4$)alkylsulfonyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said naphthyl, phenyl, pyridyl, piperidinyl, benzimidazolyl, pyrimidyl, thienyl, benzothiazolyl, pyrrolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, thiophenoxy, anilino and phenoxy in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of

$R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from ($C_1$-$C_4$)alkyl; said pyrrolidinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from hydroxy, hydroxy-($C_1$-$C_3$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to three substituents independently selected from ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, ($C_0$-$C_4$)alkylsulfamoyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said triazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said tetrazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy-($C_2$-$C_3$)alkyl or ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; and said phenyl and pyridyl which are optionally substituted on piperazine in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

$R^{11}$ and $R^{12}$ are taken together on adjacent carbon atoms and are $-CH_2OC(CH_3)_2OCH_2-$ or $-O-(CH_2)_p-O-$, and $R^{13}$ and $R^{14}$ are taken separately and are each independently hydrogen or ($C_1$-$C_4$)alkyl;

p is 1, 2 or 3;

$R^{15}$ and $R^{16}$ are taken separately and are each independently hydrogen, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; or $R^{15}$ and $R^{16}$ are taken separately and $R^{15}$ is hydrogen and $R^{16}$ is ($C_3$-$C_6$)cycloalkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, imidazolyl, benzothiazolyl or benzoxazolyl; or $R^{15}$ and $R^{16}$ are taken together and are ($C_3$-$C_6$)alkylene;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 0; $R^{18}$ is hydrogen, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, hydroxy-$(C_1-C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl or $(C_1-C_4)$alkoxy, wherein said $(C_1-C_4)$alkyl in the definition of $R^6$ and said $(C_1-C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently $(C_1-C_4)$alkyl; or

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; $R^{18}$ is hydrogen, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, hydroxy-$(C_1-C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl or $(C_1-C_4)$alkoxy, wherein said $(C_1-C_4)$alkyl in the definition of $R^6$ and said $(C_1-C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1-C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1-C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1-C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1-C_6)$alkoxycarbonyl, $(C_1-C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1-C_6)$alkylsulfonyl, $(C_1-C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1-C_6)$alkyl;

$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1-C_6)$alkyl, $(C_3-C_7)$cycloalkyl and $Ar^2$-$(C_0-C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy,

amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, pyrimidyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$Ar^2$ is independently defined as set forth for Ar and $Ar^1$ above;

said $Ar^2$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{23}$ is $CONR^{25}R^{26}$ or $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen ($C_1$-$C_4$)alkyl or $Ar^3$-($C_0$-$C_4$)alkylenyl and $R^{26}$ is $Ar^3$-($C_0$-$C_4$)alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

$R^{24}$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro;

$Ar^3$ is independently defined as set forth for Ar and $Ar^1$ above;
said $Ar^3$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;
$R^{27}$ is hydrogen or $(C_1$-$C_4)$alkyl;
$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro, $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$; said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and thiophenoxy in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{30}$ and $R^{31}$ are each independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or
$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
A is N optionally substituted with hydrogen or $(C_1$-$C_4)$alkyl and B is carbonyl; or

A is carbonyl and B is N optionally substituted with hydrogen or $(C_1-C_4)$alkyl;

$R^{32}$ is hydrogen or $(C_1-C_4)$alkyl;

$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl; said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl in the definition of $R^{33}$ are optionally substituted with up to three phenyl, phenoxy, $NR^{34}R^{35}$, halo, hydroxy, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{34}$ and $R^{35}$ are each independently hydrogen, $(C_1-C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;

D is CO, CHOH or $CH_2$;

E is O, NH or S;

$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, $(C_1-C_6)$alkylamino, di-$(C_1-C_6)$alkylamino, pyrrolidino, piperidino, morpholino, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, hydroxy-$(C_1-C_4)$alkyl, $Ar^4$, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or $(C_1-C_4)$-alkyl;

$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; or

$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are -O-$(CH_2)_k$-O-;

t is 1, 2 or 3;

Y is $(C_2-C_6)$alkylene;

$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or $(C_1-C_4)$alkyl;

m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;

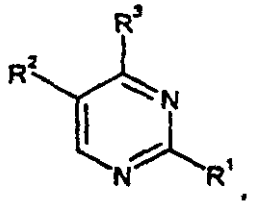
k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;
$R^{43}$ is $(C_3-C_7)$cycloalkyl, $Ar^5$-$(C_0-C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1-C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;
$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1-C_6)$alkyl and $Ar^5$-$(C_0-C_4)$alkylenyl; or
$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;
$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;
$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3-C_7)$cycloalkyl, $Ar^6$-$(C_0-C_3)$alkylenyl, $Ar^6$-$(C_2-C_4)$alkenyl, $Ar^6$-carbonyl or $(C_1-C_6)$alkyl optionally substituted with up to five fluoro;
$Ar^6$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^6$ is optionally independently substituted as set forth for Ar and $Ar^1$ above; and $R^{41}$ and $R^{41a}$ are each independently hydrogen or ($C_1$-$C_4$)alkyl.

A compound of formula $1^A$ selected from 1R-(4-{4-[2-(1R-butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; 1R-(4-{4-[2-(1S-butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; 1S-(4-{4-[2-(1R-butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; (E)-1R-{4-[4-(2-methyl-32-phenyl-acryloyl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl acetate; (R)-1-[4-(4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate; 1R-(4-{4-[2-(1RS-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; 1RS-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; 1R-[4-(3S-methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate; 1R-{4-[3R,5S-dimethyl-4-(4-methyl-6-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-hydroxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-methoxy-6-methoxymethyl-[1,3,5]triazin-2-yl)-R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; and 1R-{4-[2R,6S-dimethyl-4-(4-methyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate.

This invention is also directed to a mutual prodrug of the formula $I^B$,



$I^B$

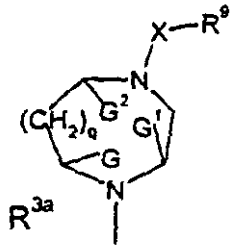
wherein:

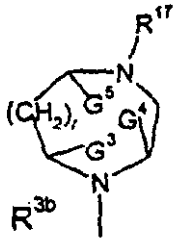
$R^1$ is C-($OR^{81}$)$R^4R^5$, where $R^{81}$ is independently an acyl radical of a carboxylic acid aldose reductase inhibitor;

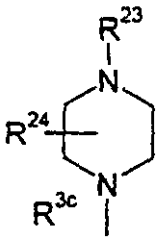
$R^4$ and $R^5$ are each independently hydrogen, methyl, ethyl or hydroxy-($C_1$-$C_3$)alkyl;

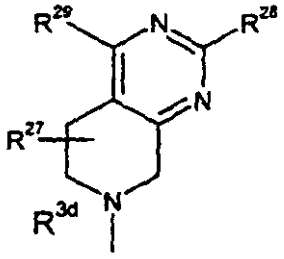
$R^2$ is hydrogen, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy;

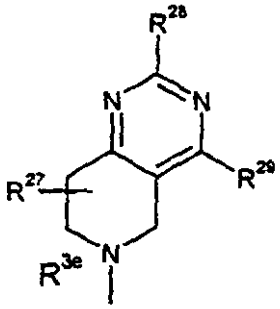
$R^3$ is a radical of the formula

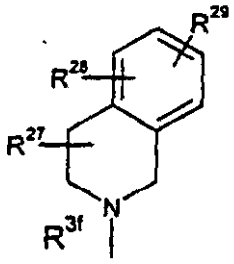


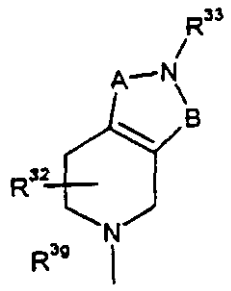


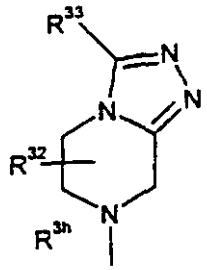


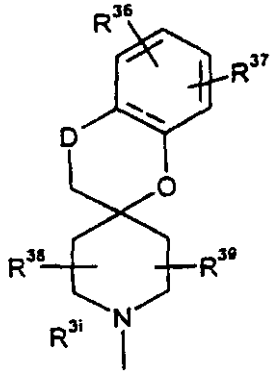


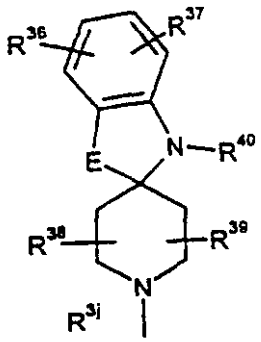


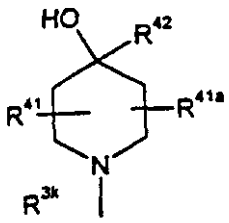


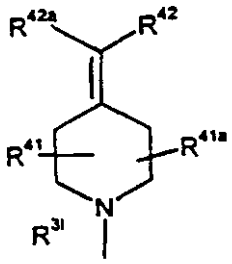


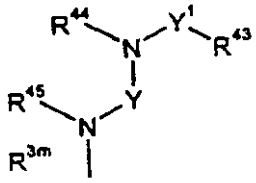


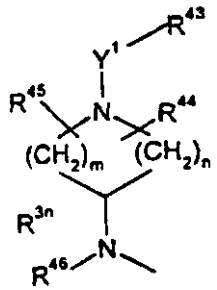


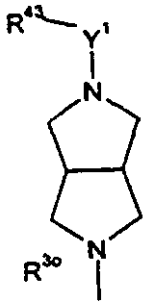


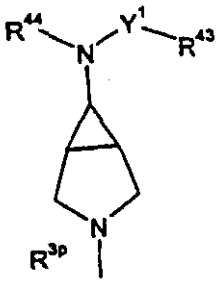




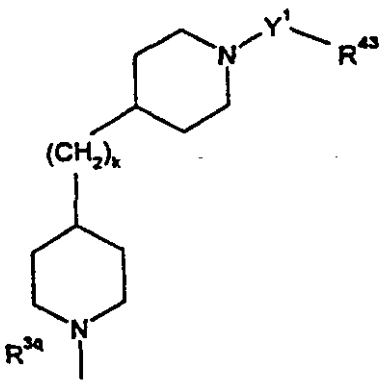








or



wherein said radical of formula $R^{3a}$ is substituted by $R^6$, $R^7$ and $R^8$;
said radical of formula $R^{3b}$ is substituted by $R^{18}$, $R^{19}$ and $R^{20}$;
G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or
G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or
$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;
q is 0 or 1;
X is a covalent bond, -(C=$NR^{10}$)-, oxycarbonyl, vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl, vinylenylsulfonyl, sulfinyl-($C_1$-$C_4$)alkylenylcarbonyl, sulfonyl-($C_1$-$C_4$)alkylenylcarbonyl or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl and thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar; said vinylenylsulfonyl and said vinylenylcarbonyl in the definition of X are optionally substituted independently on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; and said carbonyl($C_0$-$C_4$)alkylenylcarbonyl in the definition of X is optionally substituted indepedently with up to three ($C_1$-$C_4$)alkyl, benzyl or Ar;
$R^{10}$ is hydrogen or ($C_1$-$C_4$)alkyl;
$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_3$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro; provided that when q = 0 and X is a covalent bond, oxycarbonyl or ($C_1$-$C_4$)alkylenylcarbonyl, then $R^9$ is not ($C_1$-$C_6$)alkyl;
Ar and $Ar^1$ are independently a fully saturated, partially saturated or fully unsaturated five- to eight-membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two

fused independently partially saturated, fully saturated or fully unsaturated five- to seven-membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five to seven membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially saturated, fully saturated ring or fully unsaturated monocyclic ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

Ar and $Ar^1$ are optionally independently substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to a total of four substituents independently selected from $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$; wherein $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are each taken separately and are each independently halo, formyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)alkylenyloxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, $C(OH)R^{15}R^{16}$, naphthyl, phenyl, imidazolyl, pyridyl, triazolyl, morpholinyl, ($C_0$-$C_4$)alkylsulfamoyl, N-($C_0$-$C_4$)alkylcarbamoyl, N,N-di-($C_1$-$C_4$)alkylcarbamoyl, N-phenylcarbamoyl, N-($C_1$-$C_4$)alkyl-N-phenylcarbamoyl, N,N-diphenyl carbamoyl, ($C_1$-$C_4$)alkylcarbonylamido, ($C_3$-$C_7$)cycloalkylcarbonylamido, phenylcarbonylamido, piperidinyl, pyrrolidinyl, piperazinyl, cyano, benzimidazolyl, amino, anilino, pyrimidyl, oxazolyl, isoxazolyl, tetrazolyl, thienyl, thiazolyl, benzothiazolyl, pyrrolyl, pyrazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, 8-($C_1$-$C_4$)alkyl-3,8-diaza[3.2.1]bicyclooctyl, 3,5-dioxo-1,2,4-triazinyl, phenoxy, thiophenoxy, ($C_1$-$C_4$)alkylsulfanyl, ($C_1$-$C_4$)alkylsulfonyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said naphthyl, phenyl, pyridyl, piperidinyl, benzimidazolyl, pyrimidyl, thienyl, benzothiazolyl, pyrrolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, thiophenoxy, anilino and phenoxy in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of

$R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from ($C_1$-$C_4$)alkyl; said pyrrolidinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from hydroxy, hydroxy-($C_1$-$C_3$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to three substituents independently selected from ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, ($C_0$-$C_4$)alkylsulfamoyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said triazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said tetrazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy-($C_2$-$C_3$)alkyl or ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; and said phenyl and pyridyl which are optionally substituted on piperazine in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

$R^{11}$ and $R^{12}$ are taken together on adjacent carbon atoms and are $-CH_2OC(CH_3)_2OCH_2-$ or $-O-(CH_2)_p-O-$, and $R^{13}$ and $R^{14}$ are taken separately and are each independently hydrogen or ($C_1$-$C_4$)alkyl;

p is 1, 2 or 3;

$R^{15}$ and $R^{16}$ are taken separately and are each independently hydrogen, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; or $R^{15}$ and $R^{16}$ are taken separately and $R^{15}$ is hydrogen and $R^{16}$ is ($C_3$-$C_6$)cycloalkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, imidazolyl, benzothiazolyl or benzoxazolyl; or $R^{15}$ and $R^{16}$ are taken together and are ($C_3$-$C_6$)alkylene;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 0; $R^{18}$ is hydrogen, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, hydroxy-$(C_1-C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl or $(C_1-C_4)$alkoxy, wherein said $(C_1-C_4)$alkyl in the definition of $R^6$ and said $(C_1-C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently $(C_1-C_4)$alkyl; or

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; $R^{18}$ is hydrogen, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, hydroxy-$(C_1-C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl or $(C_1-C_4)$alkoxy, wherein said $(C_1-C_4)$alkyl in the definition of $R^6$ and said $(C_1-C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1-C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1-C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1-C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1-C_6)$alkoxycarbonyl, $(C_1-C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1-C_6)$alkylsulfonyl, $(C_1-C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1-C_6)$alkyl;

$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1-C_6)$alkyl, $(C_3-C_7)$cycloalkyl and $Ar^2$-$(C_0-C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy,

amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, pyrimidyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$Ar^2$ is independently defined as set forth for Ar and $Ar^1$ above;

said $Ar^2$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{23}$ is $CONR^{25}R^{26}$ or $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen ($C_1$-$C_4$)alkyl or $Ar^3$-($C_0$-$C_4$)alkylenyl and $R^{26}$ is $Ar^3$-($C_0$-$C_4$)alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

$R^{24}$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro;

$Ar^3$ is independently defined as set forth for Ar and $Ar^1$ above;
said $Ar^3$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;
$R^{27}$ is hydrogen or $(C_1-C_4)$alkyl;
$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro, $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$; said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and thiophenoxy in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{30}$ and $R^{31}$ are each independently hydrogen, $(C_1-C_4)$alkyl, $(C_3-C_7)$cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; or
$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxycarbonyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
A is N optionally substituted with hydrogen or $(C_1-C_4)$alkyl and B is carbonyl; or

A is carbonyl and B is N optionally substituted with hydrogen or $(C_1$-$C_4)$alkyl;

$R^{32}$ is hydrogen or $(C_1$-$C_4)$alkyl;

$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl; said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl in the definition of $R^{33}$ are optionally substituted with up to three phenyl, phenoxy, $NR^{34}R^{35}$, halo, hydroxy, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{34}$ and $R^{35}$ are each independently hydrogen, $(C_1$-$C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

D is CO, CHOH or $CH_2$;

E is O, NH or S;

$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, $(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, pyrrolidino, piperidino, morpholino, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl, $Ar^4$, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or $(C_1$-$C_4)$-alkyl;

$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or

$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are -O-$(CH_2)_t$-O-;

t is 1, 2 or 3;

Y is $(C_2$-$C_6)$alkylene;

$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl;

m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;

k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is $(C_3-C_7)$cycloalkyl, $Ar^5-(C_0-C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1-C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1-C_6)$alkyl and $Ar^5-(C_0-C_4)$alkylenyl; or

$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;

$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3-C_7)$cycloalkyl, $Ar^6-(C_0-C_3)$alkylenyl, $Ar^6-(C_2-C_4)$alkenyl, $Ar^6$-carbonyl or $(C_1-C_6)$alkyl optionally substituted with up to five fluoro;

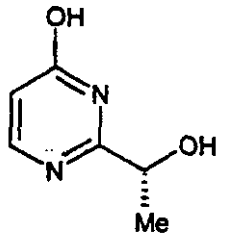
$Ar^6$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^6$ is optionally independently substituted as set forth for Ar and $Ar^1$ above; and $R^{41}$ and $R^{41a}$ are each independently hydrogen or $(C_1-C_4)$alkyl.

A preferred group of compounds within the compound of formula $I^B$ are those compounds wherein $R^{61}$ is the acyl radical of ponalrestat, tolrestat, zenarastat, zopolrestat, epalrestat, ZD5522 or sorbinil.

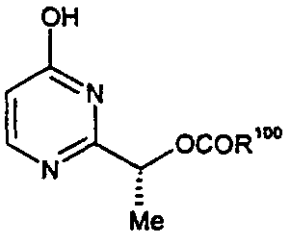
Especially preferred mutual prodrugs of this invention are selected from (E)-[4-oxo-3-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-3,4-dihydro-phthalazin-1-yl]-acetic acid 1R-[4-(4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl ester and (E)-[4-Oxo-3-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-3,4-dihydro-phthalazin-1-yl]-acetic acid 1R-{4-[4-(3-thiophen-2-yl-acryloyl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl ester.

This invetion is also directed to intermediate compounds of the formula Z




Z

This invention is still further directed to intermediate compounds, designated Group AA, of the formula ZZ,



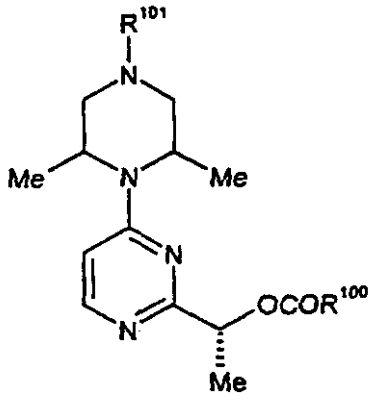

ZZ

wherein $R^{100}$ is $(C_1-C_8)$alkyl, benzyl or phenyl wherein said benzyl and phenyl are optionally substituted with up to three halo or $(C_1-C_4)$alkyl.

A preferred group of compounds within Group AA, designated Group AB, are those compounds wherein $R^{100}$ is $(C_1-C_4)$alkyl.

More preferred compounds within the Group AB are those compounds wherein $R^{100}$ is n-butyl or ethyl.

This invention is still further directed to a compound of the formula ZZZ,



ZZZ

wherein:

$R^{100}$ is ($C_1$-$C_8$)alkyl, benzyl or phenyl wherein said benzyl and phenyl are optionally substituted with up to three halo or ($C_1$-$C_4$)alkyl; and

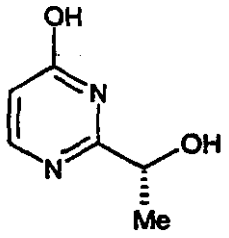
$R^{101}$ *is hydrogen or a suitable amine protecting group.*

A preferred group of compounds of formula ZZZ, designated Group AC, are those compounds wherein $R^{100}$ is ($C_1$-$C_4$)alkyl and $R^{101}$ is benzyl or tert-butyloxycarbonyl.

A preferred group of compounds within the Group AC are those compounds *wherein* $R^{100}$ *is n-butyl or ethyl and* $R^{101}$ *is benzyl.*

Another preferred group of compounds within the Group AC are those compuunds wherein $R^{100}$ is n-butyl or ethyl and $R^{101}$ is tert-butyloxycarbonyl.

This invention is also directed to a process for preparing a compound of the formula Z,



Z

comprising:

a) reacting R-(+)-2-hydroxy-propionamide with triethyloxonium tetrafluoroborate in a reaction inert solvent for 10 minutes to 24 hours at 0 °C to ambient temperature to form the corresponding imidate;

b) reacting said corresponding imidate with anhydrous ammonia in a reaction inert solvent for 2 hours to 24 hours at 0 °C to ambient temperature to form R-(+)-2-hydroxy-propionamidine hydrochloride; and

c) reacting said R-(+)-2-hydroxy-propionamidine hydrochloride with ethyl 3-hydroxy-acrylate sodium salt and a suitable base in a reaction inert solvent to form said compound of formula Z.

This invention is also directed to a pharmaceutical composition, designated Composition AA, comprising a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said prodrug or said compound, and a glycogen phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

This invention is also directed to a kit comprising:

a. a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said prodrug or said compound in a first unit dosage form;

b. a glycogen phosphorylase inhibitor (GPI), a prodrug thereof or a pharmaceutically acceptable salt of said prodrug or said GPI in a second unit dosage form; and

c. a container.

This invention is also directed to a method of treating or preventing diabetic complications in a mammal comprising administering to said mammal a pharmaceutical composition of Composition AA.

This invention is also directed to a method of treating hyperglycemia in a mammal comprising administering to said mammal a pharmaceutical composition of Composition AA.

This invention is also directed to a method of treating ischemia in a mammal suffering from ischemia comprising administering to said mammal a pharmaceutical composition of Composition AA.

This invention is also directed to a method of treating diabetes in a mammal comprising adminstering to said mammal a pharmaceutical composition of Composition AA.

This invention is also directed to a method of treating diabetic complications in a mammal comprising adminstering to said mammal a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a glycogen phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

This invention is also directed to a method of treating hyperglycemia in a mammal comprising administering to said mammal a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a glycogen phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

This invention is also directed to a method of treating ischemia in a mammal comprising adminstering to said mammal a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a glycogen phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

This invention is also directed to a method of treating diabetes in a mammal comprising administering to said mammal a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a glycogen phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

The subject invention also includes isotopically-labeled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}O$, $^{17}O$, $^{31}P$, $^{32}P$, $^{35}S$, $^{18}F$ and $^{36}Cl$, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain

isotopically-labeled compounds of the present invention, for example those into which racioactive isotopes such as $^{3}H$ and $^{14}C$ are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., $^{3}H$, and carbon-14, i.e., $^{14}C$, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., $^{2}H$, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and /or in the Examples and Preparations below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The term "reduction" is intended to include partial prevention or prevention which, although greater than that which would result from taking no compound or from taking a placebo, is less than 100% in addition to substantially total prevention.

The term "damage resulting from ischemia" as employed herein refers to conditions directly associated with reduced blood flow to tissue, for example due to a clot or obstruction of blood vessels which supply blood to the subject tissue and which result, *inter alia*, in lowered oxygen transport to such tissue, impaired tissue performance, tissue dysfunction and/or necrosis. Alternatively, where blood flow or organ perfusion may be quantitatively adequate, the oxygen carrying capacity of the blood or organ perfusion medium may be reduced, e.g., in hypoxic environment, such that oxygen supply to the tissue is lowered, and impaired tissue performance, tissue dysfunction, and/or tissue necrosis ensues.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

The expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

This invention is further directed to compounds which are mutual prodrugs of aldose reductase inhibitors and sorbitol dehydrogenase inhibitors. By mutual prodrug is meant a compound which contains two active components, in this case, an aldose reductase inhibitor and a sorbitol dehydrogenase inhibitor, which, following administration, is cleaved, releasing each individual active component. Such mutual prodrugs of an aldose reductase inhibitor and a sorbitol dehydrogenase inhibitor are formed under standard esterification conditions well known to those skilled in the art.

By alkylene is meant saturated hydrocarbon (straight chain or branched) wherein a hydrogen atom is removed from each of the terminal carbons. Exemplary of such groups (assuming the designated length encompasses the particular example) are methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene.

By halo is meant chloro, bromo, iodo, or fluoro.

By alkyl is meant straight chain saturated hydrocarbon or branched saturated hydrocarbon. Exemplary of such alkyl groups (assuming the designated length encompasses the particular example) are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, neopentyl, tertiary pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl, isohexyl, heptyl and octyl.

By alkoxy is meant straight chain saturated alkyl or branched saturated alkyl bonded through an oxygen. Exemplary of such alkoxy groups (assuming the designated length encompasses the particular example) are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, neopentoxy, tertiary pentoxy, hexoxy, isohexoxy, heptoxy and octoxy .

It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridyl" means 2-, 3-, or 4-pyridyl, the term "thienyl" means 2-, or 3-thienyl, and so forth.

The expression "pharmaceutically-acceptable salt" refers to nontoxic anionic salts containing anions such as (but not limited to) chloride, bromide, iodide, sulfate, bisulfate, phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate; methanesulfonate and 4-toluene-sulfonate. Where more than one basic moiety exists the expression includes multiple salts (e.g., di-salt). The expression also

refers to nontoxic cationic salts such as (but not limited to) sodium, potassium, calcium, magnesium, ammonium or protonated benzathine (N,N'-dibenzylethylenediamine), choline, ethanolamine, diethanolamine, ethylenediamine, meglamine (N-methyl-glucamine), benethamine (N-benzylphenethylamine), piperazine or tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol).

As used herein, the expressions "reaction inert solvent" and "inert solvent" refers to a solvent or mixture of solvents which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

The chemist of ordinary skill will recognize that certain compounds of formula I of this invention will contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers and configurational isomers. All such isomers and mixtures thereof are included in this invention. Compounds of formula I may be chiral. In such cases, the isomer wherein $R^1$ has the R configuration is preferred. Hydrates of the compounds of formula I of this invention are also included.

The chemist of ordinary skill in the art will also recognize that certain compounds of formula I of this invention can exist in tautomeric form, i.e., that an equilibrium exists between two isomers which are in rapid equilibrium with each other. A common example of tautomerism is keto-enol tautomerism, i.e.,

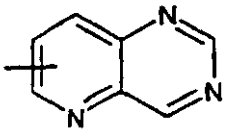



Examples of compounds which can exist as tautomers include hydroxypyridines, hydroxypyrmidines and hydroxyquinolines. Other examples will be recognized by those skilled in the art. All such tautomers and mixtures thereof are included in this invention.

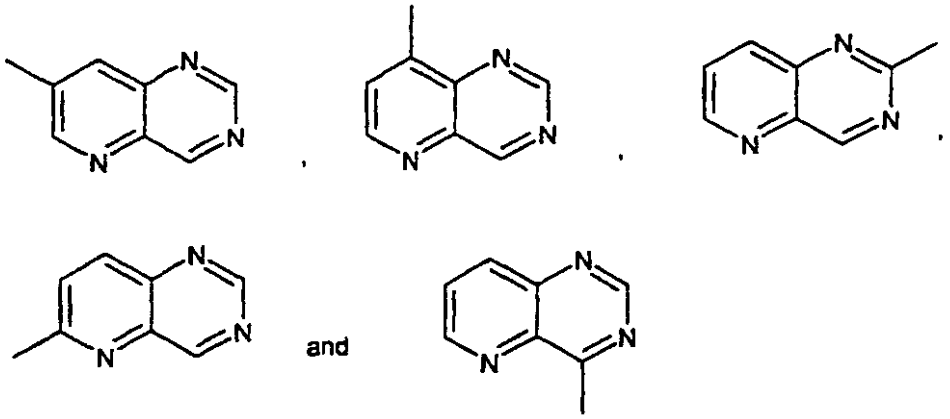
DMF means N,N-dimethylformamide. DMSO means dimethyl sulfoxide. THF means tetrahydrofuran.

Whenever the structure of a cyclic radical is shown with a bond drawn from outside the ring to inside the ring, it will be understood by those of ordinary skill in the

art to mean that the bond may be attached to any atom on the ring with an available site for bonding. If the cyclic radical is a bicyclic or tricyclic radical, then the bond may be attached to any atom on any of the rings with an available site for bonding. For example,



represents any or all of the following radicals:

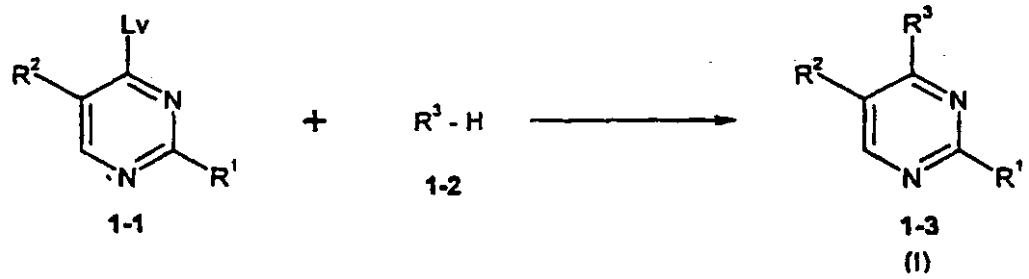


Other features and advantages will be apparent from the specification and claims which describe the invention.

## DETAILED DESCRIPTION OF THE INVENTION

In general the compounds of formula I of this invention can be made by processes which include processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of formula I of this invention are provided as further features of the invention and are illustrated by the following reaction schemes. Other processes are described in the experimental section.

**Scheme 1**




1-1 1-2 1-3 (I)

Compounds of formula 1-3 (i.e., formula I) are prepared as set forth in Scheme 1, particularly as described below.

Compounds of formula 1-3 are prepared by the displacement reaction of a pyrimidine of the formula 1-1 where $R^1$ and $R^2$ are defined herein. Lv is a leaving group preferably selected from fluoro, chloro, bromo, iodo, thiomethyl, methylsulfone, or $OSO_2J$ wherein J is $(C_1$-$C_6)$-lower alkyl, trifluoromethyl, pentafluoroethyl, phenyl optionally substituted with up to three $(C_1$-$C_4)$alkyl, nitro or halo. The leaving group Lv is displaced by an amine of the formula 1-2 where $R^3$ is defined above. The reaction is conducted in the presence of a non-aqueous base, preferably an organic amine or an inorganic base. Preferred organic amines include triethylamine, pyridine, dimethylaminopyridine and N,N'-diisopropylethylamine (Hunig's base). Preferred inorganic bases include alkaline metal carbonates and bicarbonates such as sodium or potassium carbonate and sodium or potassium bicarbonate. An especially preferred inorganic base is potassium carbonate. An especially preferred organic amine is triethylamine. Alternatively, an excess of the reacting amine 1-2 can be used as the base for this reaction. The reaction can be conducted in the absence of solvent or in a reaction inert solvent. Where used herein, "reaction inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product. Preferred reaction inert solvents include aqueous media, pyridine, $(C_1$-$C_4)$alcohol, $(C_2$-$C_6)$glycol, halocarbon, aliphatic/aromatic hydrocarbon, ethereal solvent, polar aprotic solvent, ketonic solvent, or combinations thereof. The reaction time ranges from 15 minutes to 3 days and the reaction temperature ranges from 0 °C to 180 °C. Conveniently, the reaction may be conducted at the reflux temperature of the solvent being used. The reaction is preferably conducted at ambient pressure. The term ambient pressure, where used herein, refers to the pressure of the room in which the reaction is being conducted. The term ambient temperature, where used herein, refers to the temperature of the room in which the reaction is being conducted.

When $R^1$ contains a hydroxy group, the hydroxyl group may or may not be protected. When the hydroxyl group is protected, the protecting group may be any suitable hydroxyl protecting group. The conditions used to remove such optional hydroxyl protecting groups contained in $R^1$ in compounds of formula 1-3 are as

follows. When the protecting group is an ester, removal of such ester protecting groups is conducted under basic conditions using inorganic hydroxides or carbonates, preferably lithium hydroxide, sodium hydroxide, potassium hydroxide or potassium carbonate. The reaction is carried out in a reaction inert solvent, preferably an alcoholic solvent. Especially preferred is methanol or methanol in combination with co-solvents such as water, tetrahydrofuran, or dioxane. The reaction time ranges from 15 minutes to 24 hours and the reaction temperature ranges from 0 °C to 100 °C or to the reflux temperature of the solvent(s) of use. Alternatively, ester cleavage may be accomplished under acidic conditions. It is preferred to utilize aqueous hydrochloric acid, generally 2 N to concentrated, with or without a co-solvent. When a co-solvent is used, dioxane or methanol are preferred. The reaction time ranges from 4 hours to 3 days and the reaction temperature ranges from 0 °C to 60 °C.

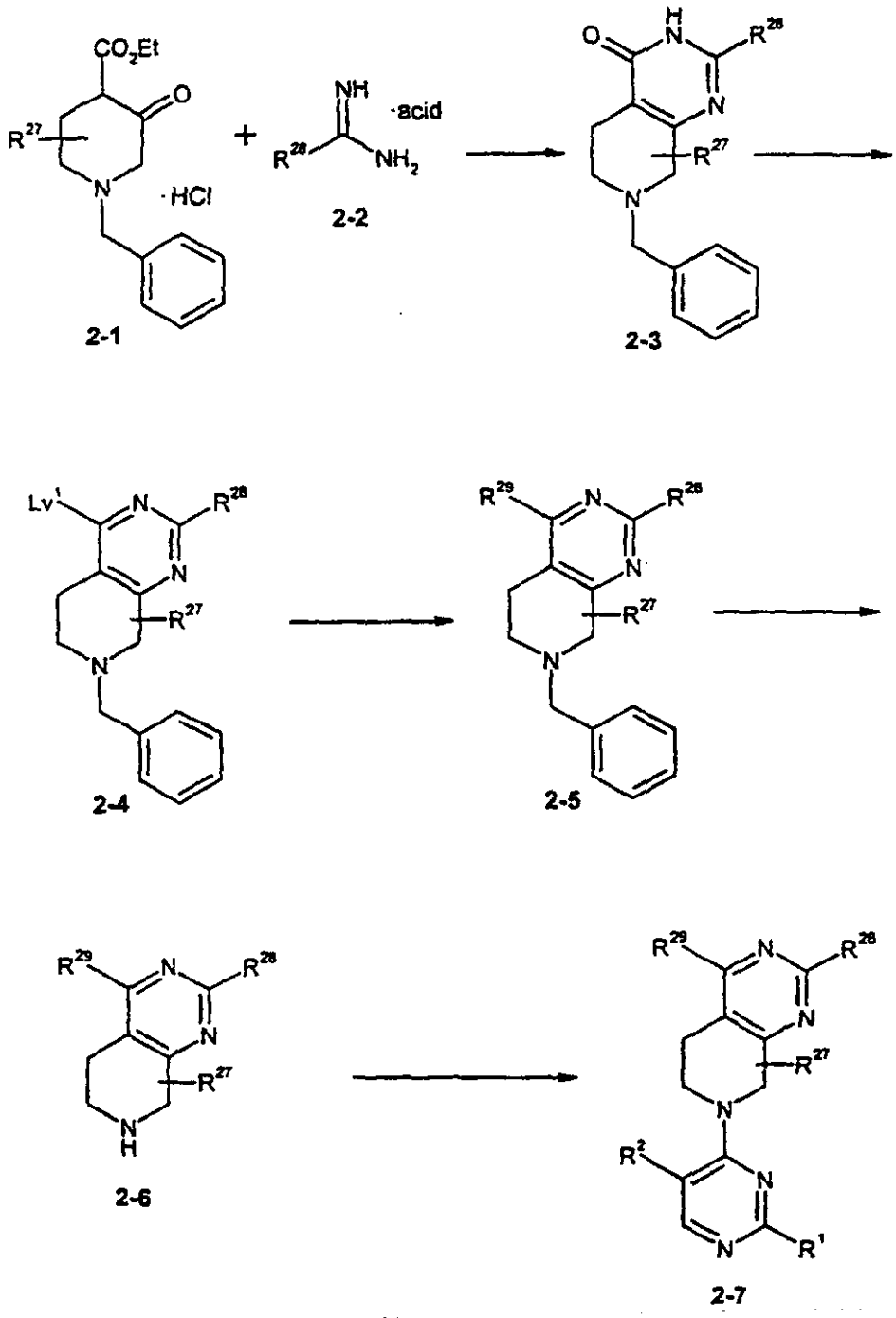
When the protecting group is an alkyl ether, removal of such alkyl ether protecting groups is conducted using well known dealkylative conditions. For example, the alkyl ether may be cleaved by reaction with boron tribromide or diethylboron bromide in a reaction inert solvent, preferably a halocarbon solvent. It will be recognized by those skilled in the art that a buffer such as triethylamine may facilitate the reaction. The reaction times range from 15 minutes to 24 hours and the reaction temperature ranges from 0 °C to 60 °C. In addition, a benzyl ether protecting group can be removed via standard or transfer hydrogenolysis using a palladium catalyst such as palladium on carbon. The hydrogenolysis reaction is conducted under a hydrogen atmosphere at ambient pressure to 50 psi in a reaction inert solvent, preferably methanol. The hydrogen source may be hydrogen gas, ammonium formate or trialkylammonium formate or cyclohexene. The reaction temperature ranges from room temperature to the reflux temperature of the solvent employed. The reaction time ranges from 15 minutes to 24 hours.

When a silyl ether protecting group is employed, removal of such silyl ether protecting groups is conducted under acidic conditions, preferably with aqueous hydrochloric acid such as 1 N to 6 N hydrochloric acid. The de-protection may be carried out in the presence of a co-solvent such as methanol or tetrahydrofuran. The reaction time ranges from 2 hours to 48 hours and the reaction temperature ranges from 0 °C to 100 °C. Alternatively, the silyl ether protecting group may be removed via fluoride-mediated deprotection. In this case, deprotection is conducted using

tetrabutylammonium fluoride or one of a variety of hydrofluoric acid sources in a reaction inert solvent. It is preferred to use ethereal solvents such as diethyl ether, dioxane or tetrahydrofuran, with tetrahydrofuran being especially preferred. The reaction time ranges from 2 hours to 48 hours and the reaction temperatures range from 0°C to the reflux temperature of the solvent being used. Other methods for removal of the aforementioned protecting groups are well known to those skilled in the art or can be found in Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons Inc.: New York, 1991. Other suitable hydroxyl protecting groups and methods for their removal may be found also be found therein.

The method of Scheme I is preferred when $R^3$ is $R^{3k, l, m, n, o, p \text{ and } q}$. Thus, compounds of formula 1-2 are reacted with compounds of formula 1-1. Compounds of formula 1-2 where $R^3$ is $R^{3k, l, m, n, o, p \text{ or } q}$ are commercially available or can be prepared by methods well known to those skilled in the art.

Scheme 2




Compounds of formula 2-7 are prepared as set forth in Scheme 2, particularly as described below.

Where $R^{27}$ is H, ethyl 1-benzyl-3-oxo-4-piperidine-carboxylate hydrochloride, the compound of formula 2-1, which is available from Aldrich, is condensed with compounds of formula 2-2 to give compounds of formula 2-3. The compounds of formula 2-1 where $R^{27}$ is not H can be prepared according to methods well known to those skilled in the art. The reaction is conducted in the presence of excess base including non-aqueous bases, organic amines and inorganic bases. Preferred organic amines include triethylamine and pyridine. Preferred non-aqueous bases include alkaline metal ($C_1$-$C_4$)alkoxides. Preferred inorganic bases include potassium carbonate. The reaction is conducted in a reaction inert solvent. Preferred such solvents include ($C_1$-$C_4$)alcohols, aromatic or aliphatic hydrocarbons, polar aprotic solvents, halocarbons, and ethereal solvents. ($C_1$-$C_4$)Alcohols are especially preferred. The reaction time ranges from 2 hours to 3 days. The reaction temperature ranges from ambient temperature to the reflux temperature of the solvent being employed. The reaction is preferably run at ambient pressure but may be conducted at pressures up to 250 psi.

Compounds of formula 2-4 are prepared from compounds of formula 2-3 by converting a compound of formula 2-3 into an activated compound of formula 2-4 where $Lv^1$ is selected from fluoro, chloro, bromo, iodo, trifluoromethanesulfonate, ($C_1$-$C_6$)alkylsulfonate, or phenylsulfonate, wherein said phenyl is optionally substituted with up to three ($C_1$-$C_4$)alkyl, halo or nitro. This reaction is accomplished by reacting compounds of formula 2-3 with a chlorinating agent such as phosphorus oxychloride and/or phosphorus pentachloride to provide compounds of formula 2-4 where $Lv^1$ is chloro. This reaction is conducted at ambient pressure in the absence of solvent or in a reaction inert solvent, preferably a halocarbon solvent at temperatures ranging from ambient temperature to 180 °C. Treatment of the chloro compound thus formed with the requisite mineral acid provides a compound of formula 2-4 where $Lv^1$ is bromo or iodo. A sulfonate of formula 2-4 is prepared by reaction of a compound of formula 2-3 with a sulfonic acid chloride or anhydride in the presence of an organic amine base, preferably triethylamine or pyridine. In certain cases recognized by those skilled in the art, it may be necessary to add a catalyst to the reaction. In those cases, a preferred catalyst is 4-dimethylaminopyridine. This reaction is conducted at ambient pressure in a reaction inert solvent, preferably pyridine, a halocarbon such as chloroform, dichloromethane or carbon tetrachloride, an aromatic or aliphatic hydrocarbon, an

ethereal solvent, or combinations thereof. The reaction temperature ranges from -20° C to 100 °C and the reaction time ranges from 15 minutes to 1 day.

Compounds of formula 2-5 wherein $R^{29}$ is defined above are prepared from compounds of formula 2-4 by a reduction reaction or by displacement of $Lv^1$ with a nucleophile. The reduction is conducted with a reducing agent, preferably ammonium formate or hydrogen gas, in a reaction inert solvent. The reduction is conducted in the presence of a palladium catalyst at ambient pressure or under a hydrogen pressure of up to 50 psi. Preferred solvents include ($C_1$-$C_4$)alcohols such as methanol and ethanol, and ether solvents such as diethyl ether, dioxane and tetrahydrofuran. The nucleophilic displacement reaction may be conducted by adding the nucleophile directly or by pre-forming the nucleophile separately or in situ from a nucleophile precursor. Preferred nucleophiles include organoaluminum, organoboron, organocopper, organotin, organozinc or Grignard reagent; $R^{29}$-H; or, where $R^{29}$ contains a hydroxyl or thiol group, the anion of $R^{29}$. The term "organo" in the terms organoaluminum, organoboron, organocopper, organotin and organozinc refers to an organic radical selected from $R^{29}$. It will be recognized by those skilled in the art that transition-metal catalysts may be required to effect reaction in certain displacement reactions. When required, such transition metal catalysts may include palladium(0), palladium(II), nickel(0), and nickel(II) complexes. Palladium(II) bis(diphenylphosphinobutane) dichloride is a preferred such catalyst. Additionally, an aqueous or non-aqueous base may be required in the displacement reaction. Preferred such bases include sodium carbonate, sodium hydride, triethylamine and sodium tert-butoxide. The reaction is conducted at ambient pressure in a reaction inert solvent such as a halocarbon, an aromatic or aliphatic hydrocarbon, an ether or a polar aprotic solvent or a combination thereof. In certain cases, a ($C_1$-$C_4$)alcohol is used as a solvent or co-solvent. The reaction temperature ranges from –20 °C to the reflux temperature of the solvent employed. The reaction time ranges from 1 hour to 3 days.

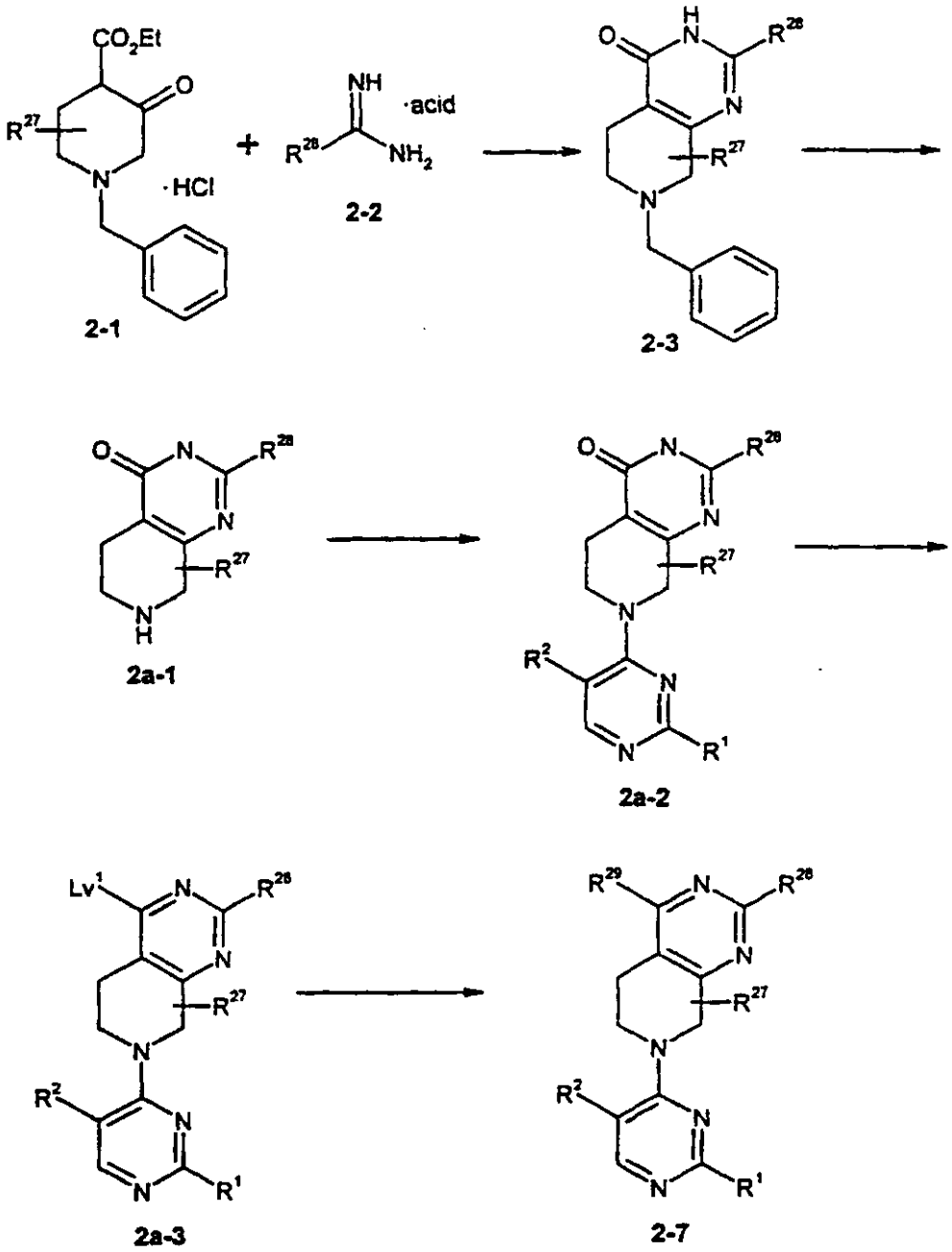
Compounds of formula 2-6 are prepared by removal of the benzyl protecting group from compounds of formula 2-3 or 2-5. This transformation is accomplished using the freebase, or preferably the pre-formed hydrochloride or similar salt, under standard or transfer hydrogenolysis conditions. The catalysts which may be used in the hydrogenolysis reaction include, but are not limited to, palladium on carbon,

palladium hydroxide on carbon and platinum(IV) oxide. The reaction is conducted in a reaction inert solvent, preferably methanol or ethanol and the reaction temperature ranges from room temperature to the reflux temperature of the solvent being employed. The hydrogen source is hydrogen gas, ammonium formate, trialkylammonium formate, or cyclohexene. The reaction time ranges from 15 minutes to 3 days. Generally the reaction is conducted at ambient pressure but pressures of up to 50 psi of hydrogen may be employed. Alternatively, if appropriate, the benzyl protecting group is removed in two steps via chloroformate-induced acylative dealkylation. This involves reaction with a chloroformate derivative to form a carbamate followed by cleavage of the carbamate. While this reaction is preferably conducted with 1-chloroethyl chloroformate and sodium iodide catalysis, it will be recognized by those skilled in the art that catalysis may not be required in certain cases. The reaction is conducted at ambient temperature in a reaction inert solvent such as a halocarbon, an aromatic or aliphatic hydrocarbon, a ketone, an ether or a polar aprotic solvent. The reaction temperature ranges from –78 °C to the reflux temperature of the solvent being employed and the reaction time ranges from 15 minutes to 1 day. Cleavage of the carbamate formed by reaction with 1-chloroethyl chloroformate is accomplished upon exposure to methanol or ethanol at ambient pressure to give compounds of formula 2-6 as a hydrochloride salt. The reaction proceeds at temperatures from room temperature to the reflux temperature of the solvent being employed and the reaction time ranges from 15 minutes to 1 day. Deprotection conditions for other carbamates can be found in Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons Inc.: New York, 1991, pp 315-348.

Compounds of formula 2-7 are prepared from the displacement reaction of amine 2-6 as described in Scheme 1, where the amine 2-6 is equivalent to $R^3$-NH.

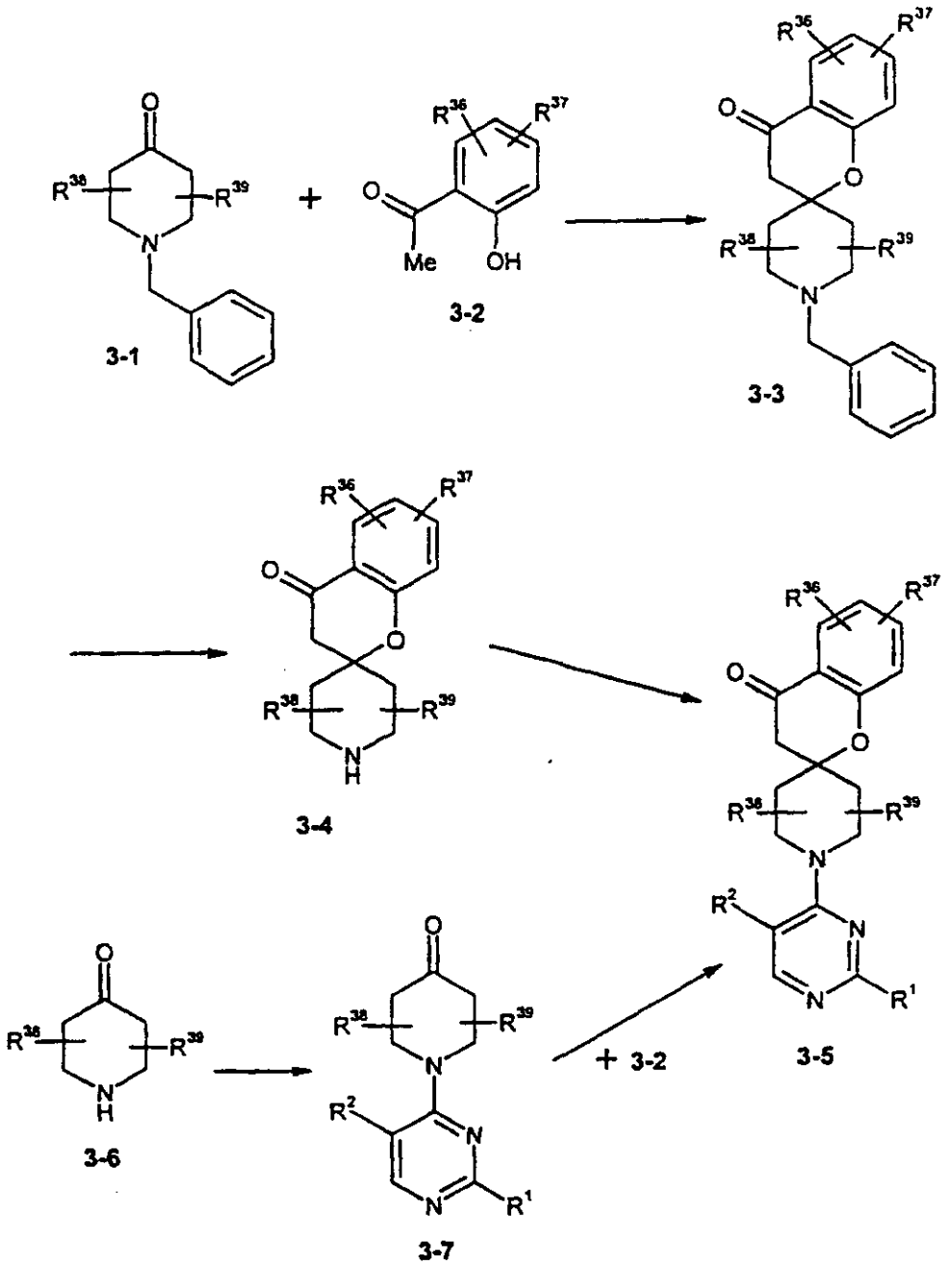
Alternatively, compounds of formula 2-7 where $R^{29}$ is as defined above are prepared from compounds of formula 2-3 wherein $R^{29}$ is OH according to the sequence outlined in Scheme 2a below, wherein the conditions are as set forth as described for Scheme 2.

**Scheme 2a**




Compounds of formula 2-2 which are used in Schemes 2 and 2a above are commercially available or are prepared according to methods well known to those skilled in the art, such as those described in March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons.: New York, 1985, p 359, 374.

Scheme 3




Compounds of formula 3-5 are prepared as set forth in Scheme 3 above and more particularly as described below.

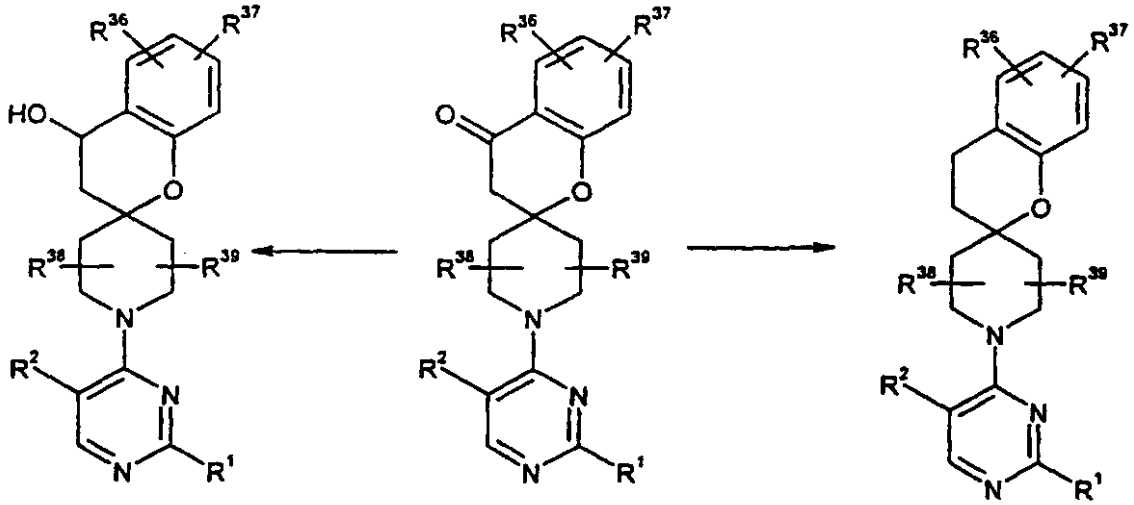
Compounds of formula 3-3 are prepared by condensing a compound of formula 3-1 with a compound of formula 3-2. Where $R^{38}$ and $R^{39}$ are each H, the compound of formula 3-1 is 1-benzyl-4-piperidone, which is commercially available

from Aldrich. Compounds of formula 3-2 are either commercially available or can be prepared according to methods well known to those skilled in the art, particularly according to methods set forth in March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons Inc.: New York, 1985, pp 499-500. The reaction is conducted at ambient pressure in the presence of a secondary amine. Generally an excess of the secondary amine, preferably pyrrolidine, piperidine, morpholine or diethylamine, is used. An especially preferred secondary amine is pyrrolidine. The reaction is conducted in a reaction inert solvent, preferably a ($C_1$-$C_4$)alcohol, an aromatic or aliphatic hydrocarbon, a polar aprotic solvent, a halocarbon or an ether. An especially preferred solvent is ethanol. The reaction time ranges from 2 hours to 3 days and the reaction temperature ranges from ambient temperature to the reflux temperature of the solvent being employed.

Compounds of the formula 3-4 are prepared by removal of the benzyl protecting group from compounds of formula 3-3. This transformation is conducted in a manner analogous to the procedure set forth for the preparation of compounds of formula 2-6 above.

Compounds of formula 3-5 are prepared from the displacement reaction of amine 3-4 as described in Scheme 1, where the amine 3-4 is equivalent to $R^3$-NH.

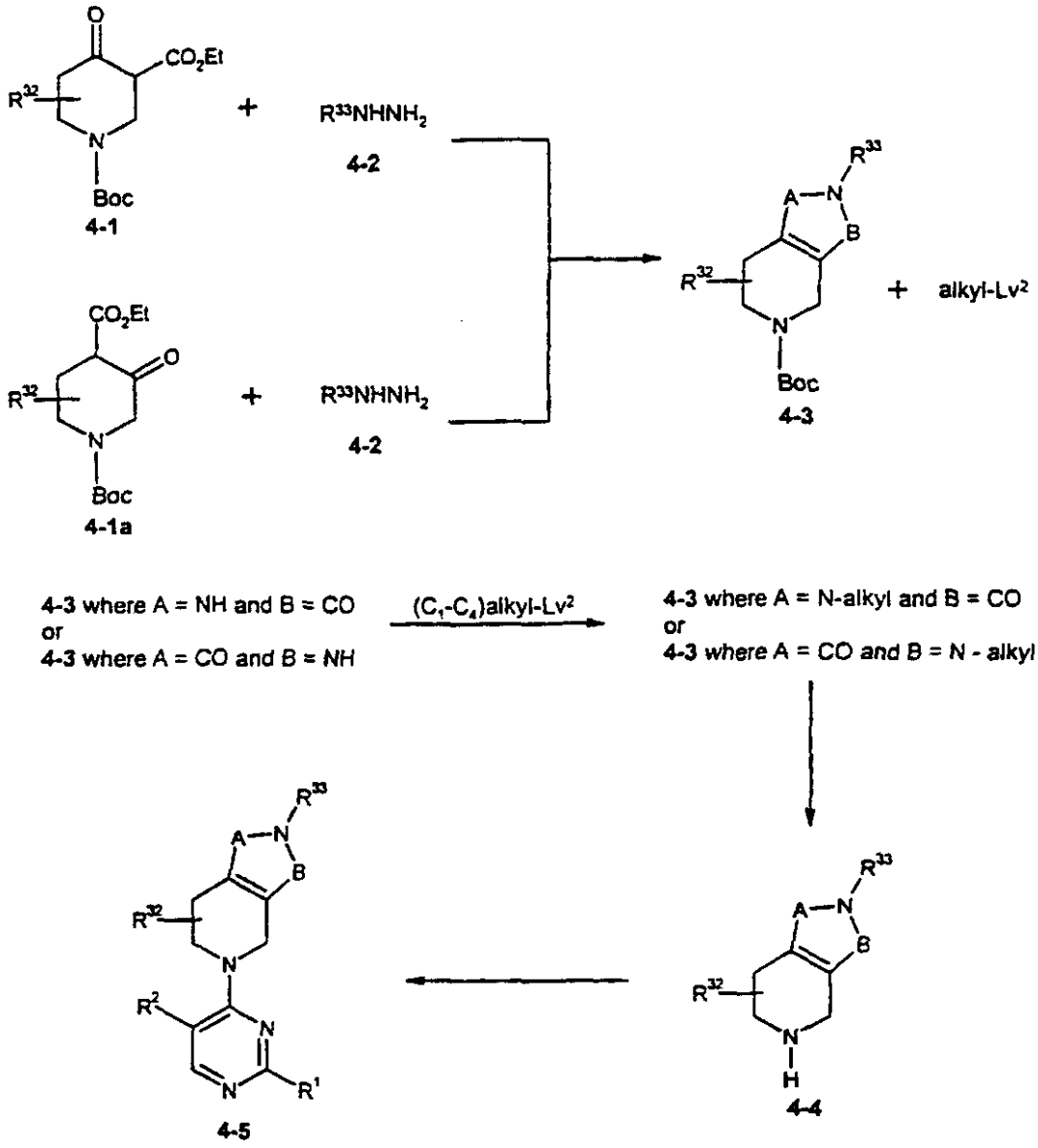
**Scheme 3a**



Compounds of formulas 3a-1 and 3a-2 are prepared as shown in Scheme 3a from compounds of formula 3-5. Thus, to prepare a compound of 3a-1, a compound of formula 3-5 is reduced with a common reducing agent, such as, for example, sodium borohydride, lithium aluminum hydride or diisobutylaluminum hydride. Other reducing agents capable of effecting the reduction of a ketone to an alcohol are well known to those skilled in the art (e.g., Larock, R. D. *Comprehensive Organic Transformations*, VCH Publishers, Inc.: New York, 1989, pp 527-547). Likewise, compounds of formula 3a-2 are prepared from compounds of formula 3-5 by reduction with reducing agents capable of reducing a ketone completely to a methylene group. A preferred such reducing agent is aluminum trichloride/borane-tert-butylamine complex. Other such reducing agents are well known to those skilled in the art (e.g., *J. Org. Chem.* **1989**, *54*, 4350; Larock, R. D. *Comprehensive Organic Transformations*, VCH Publishers, Inc.: New York, 1989, pp 35-37). It will be recognized by those skilled in the art that the transformation of 3-5 to 3a-1 or 3a-2 can be conducted at different points in Scheme 3, depending upon the dynamics of the particular system.

Alternatively, compounds of formula 3-5 wherein $R^{38}$ and $R^{39}$ are hydrogen can be prepared from 4-piperidone monohydrate monochloride in a manner analogous to the procedure described in Scheme 1, where the amine 3-6 is equivalent to $R^3$-NH to give compounds of formula 3-7. Compounds of formula 3-7 can be reacted with compounds of formula 3-2 in a manner analogous to the procedure set forth for the synthesis of compounds of formula 3-3 to afford compounds of formula 3-5.

**Scheme 4**




Compounds of formula 4-5 are prepared according to Scheme 4 and more particularly as described below.

Compounds of formula 4-3 are prepared by reacting a compound of formula 4-2 with a compound of formula 4-1 or 4-1a. Compounds of formula 4-1 and 4-1a are prepared according to methods well known to those skilled in the art. Where $R^{32}$ is hydrogen, 4-oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester is condensed with a compound of formula 4-2 to afford a compound of formula 4-3. Said

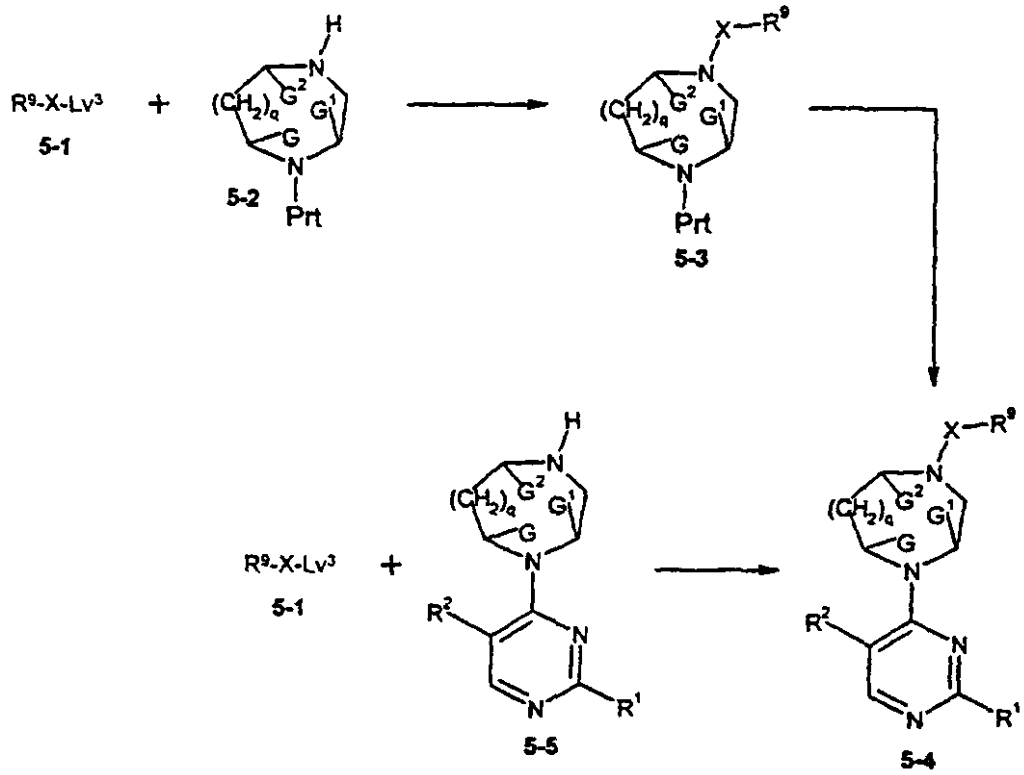
compounds of formula 4-2 are readily available from well known commercial vendors, known in the literature, or are synthesized under standard conditions well known to those skilled in the art. Preferred conditions to prepare compounds of formula 4-3 from a compound of formula 4-1 where A is CO and B is NH or from a compound of formula 4-1a where A is NH and B is CO can be found in March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons Inc.: New York, 1985, p 1163. The reaction is conducted at ambient pressure in a reaction inert solvent. Preferred such solvents include aqueous media, a ($C_1$-$C_4$)alcohol, glacial acetic acid, an aromatic or aliphatic hydrocarbon, a polar aprotic solvent, a halocarbon and ethers or combinations thereof. The reaction time ranges from 2 hours to 3 days and the reaction temperature ranges from ambient temperature to the reflux temperature of the solvent being used. An optional second step using aqueous or non-aqueous base may be employed in certain cases which will be recognized by those skilled in the art. This second step is conducted at ambient pressure in a reaction inert solvent. Preferred such solvents include aqueous media, a ($C_1$-$C_4$)alcohol, glacial acetic acid, an aromatic or aliphatic hydrocarbon, a polar aprotic solvent, a halocarbon and ethers or combinations thereof. The reaction time ranges from 2 hours to 3 days and the reaction temperature ranges from ambient temperature to the reflux temperature of the solvent being used.

Compounds of formula 4-3 wherein B is CO and A is N-alkyl or wherein B is N-alkyl and A is CO are prepared by alkylation of compounds of formula 4-3 where B is CO and A is NH or wherein B is NH and A is CO, respectively. The anion of those compounds of formula 4-3 is formed by reaction with an appropriate base. Preferred such bases include sodium hydride and sodium hexamethyldisilazide, although other bases may be used where conditions warrant, as determined by the skilled person. The reaction is conducted in a reaction inert solvent, preferably an ether such as tetrahydrofuran, diethyl ether, dioxane or diglyme or polar aprotic solvent such as dimethylformamide. The reaction proceeds at ambient pressure and at temperatures ranging from –100 °C to ambient temperature. The reaction times are from 10 minutes to 2 hours. Addition of ($C_1$-$C_4$)alkyl halides or ($C_1$-$C_4$)alkylsulfonates such as mesylate, tosylate or nosylate to the anion of 4-3 proceeds at ambient pressure and at temperatures ranging from –20 °C to 50 °C. The reaction times range from 10 minutes to 1 day.

Compounds of formula 4-4 are prepared form compounds of formula 4-3 wherein A is N-alkyl and B is CO or A is CO and B is N-alkyl via acid-catalyzed deprotection of the Boc carbamate under standard conditions, for example, hydrochloric acid or trifluoroacetic acid in a reaction inert solvent or in the absence of solvent. Such conditions are known to those skilled in the art. Exemplary conditions are disclosed in Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons Inc.: New York, 1991, pp 327-330.

Compounds of formula 4-5 are prepared by the displacement reaction of amine 4-4 as described in Scheme 1, where the amine 4-4 is equivalent to $R^3$-H.

**Scheme 5**




Compounds of formula 5-4 where X is a covalent bond and G, $G^1$, $G^2$, q, $R^1$, $R^2$, $R^6$, $R^7$ and $R^8$ are as defined above are prepared according to Scheme 5 above and particularly as described below.

Compounds of formula 5-3 are prepared by reaction of a compound of formula 5-1 with a compound of formula 5-2 where Prt is an optional amine protecting group selected from benzyl and $CO_2R^{90}$, where $R^{90}$ is selected from ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)allyl,

trichloroethyl and benzyl substitutedby up to two ($C_1$-$C_4$)alkoxy. Compounds of formula 5-1 where $R^9$ is $Ar^1$ and $Lv^3$ is halo, ($C_1$-$C_4$)alkylsulfide, ($C_1$-$C_4$)alkylsulfone, trifluoromethanesulfonate, ($C_1$-$C_6$)alkylsulfonate or phenylsulfonate, where said phenyl is optionally substituted with up to three halo, nitro or ($C_1$-$C_4$)alkyl are commercially available or are readily prepared according to methods well known to those skilled in the art. For example, to prepare compounds of formula 5-1 wherein $Lv^3$ is chloro, a compound of formula $Ar^1$-OH, or the $Ar^1$-(=O) tautomer thereof, is reacted with a chlorinating agent such as phosphorus oxychloride and/or phosphorus pentachloride. This chlorinating reaction is conducted at ambient pressure in the absence of solvent or in a reaction inert solvent, preferably a halocarbon solvent, at temperatures ranging from ambient temperature to 180 °C. Treatment of the chloro compound with the requisite mineral acid provides compounds of formula 5-1 where $Lv^3$ is bromo or iodo. Compounds of formula 5-1 wherein $Lv^3$ is trifluoromethanesulfonate, ($C_1$-$C_6$)alkylsulfonate or phenylsulfonate are prepared from a compound of formula $Ar^1$-OH, or the $Ar^1$-(=O) tautomer thereof, by reaction with a sulfonic acid chloride or anhydride in the presence of a base, preferably an organic amine such as triethylamine, N,N'-diisopropylethylamine, dimethylaminopyridine or pyridine. In certain cases it will be recognized by those skilled in the art that a catalyst will be required to effect reaction. In those cases, a preferred catalyst is 4-dimethylaminopyridine. This reaction is conducted at ambient pressure in a reaction inert solvent such as pyridine, a halocarbon, an aromatic or aliphatic hydrocarbon, an ether, or a combination thereof. The reaction temperature ranges from –20 °C to 100 °C and the reaction time ranges from 15 minutes to 1 day. Compounds of formula 5-1 where $Lv^3$ is thiomethyl are prepared by reacting a compound of formula $Ar^1$-SH, or the $Ar^1$-(=S) tautomer thereof, with methyl iodide or dimethylsulfate in the presence of an inorganic base, preferably potassium carbonate. These reactions are conducted at ambient pressure in a reaction inert solvent, preferably an ether or a polar aprotic solvent. An especially preferred polar aprotic solvent is dimethylformamide at a temperature ranging from 0 °C to 100 °C. Compounds of formula 5-1 where $Lv^3$ is methylsulfone are prepared from a compound of formula 5-1 where $Lv^3$ is thiomethyl by oxidation thereof according to procedures well known to those skilled in the art, specifically as set forth in March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons.: New York, 1985, pp 1089-1090.

A representative set of compounds of formula 5-1 which are commercially available or which can be prepared according to methods analogous to a literature procedure include 4-chloropyridine (Aldrich, P.O. Box 355, Milwaukee, Wisconsin 53201, USA), 3-chloro-6-methyl-pyridazine (Maybridge, c/o Ryan Scientific, 443 Long Point Road, Suite D, Mount Pleasant, South Carolina 29464, USA), 2-chloro-pyrazine (Aldrich), 2,6-dichloro-pyrazine (Aldrich), 3-chloro-2,5-dimethylpyrazine (Aldrich), 2,4-dichloro-pyrimidine (Aldrich), 4,6-dichloro-pyrimidine (Aldrich), 4-chloro-2-methyl-pyrimidine (*Chem. Ber.* **1904**, *37*, 3641), 4-chloro-6-methyl-pyrimidine (*Chem. Ber.* **1899**, *32*, 2931), 4-chloro-2,6-dimethyl-pyrimidine (*J. Am. Chem. Soc.* **1946**, *68*, 1299), 4-chloro-2,6-bis(trifluoromethyl)-pyrimidine (*J. Org. Chem.* **1961**, *26*, 4504), 4-chloro-2-methylsulfanyl-pyrimidine (Aldrich), 4-chloro-2-methoxymethyl-pyrimidine (US Patent 5 215 990), 1-chloro-isoquinoline (*J. Am. Chem. Soc.* **1946**, *68*, 1299), 2-chloro-quinoline (Aldrich), 4-chloro-quinazoline (*J. Am. Chem. Soc.* **1909**, *31*, 509), 2-chloro-quinoxaline (US Patent 2 537 870), 2-chloro-3-methyl-quinoxaline (Aldrich), 2,6,7-trichloro-quinoxaline (*J. Chem. Soc., Chem. Commun.* **1956**, 4731), 4-chloro-pteridine (*J. Chem. Soc., Chem. Commun.* **1954**, 3832), 7-chloro-pteridine (*J. Chem. Soc., Chem. Commun.* **1954**, 3832), and 6-chloro-9H-purine (Aldrich). Other compounds of formula 5-1 can be prepared using methods well known to those skilled in the art or by using methods analogous to those described in the foregoing references.

Compounds of formula 5-3 are prepared by the displacement reaction of a compound of formula 5-1 with an amine of the formula 5-2. The reaction is conducted in the presence of a non-aqueous base, prefeably an organic amine such as pyridine, 4-dimethylaminopyridine, triethylamine or N,N'-diisopropylethylamine; an inorganic base such as potassium or sodium carbonate or bicarbonate; or an alkaline metal alkoxide such as potassium t-butoxide. Alternatively, an excess of the reacting amine 5-2 can be used in lieu of the added base. In cases where the leaving group $Lv^3$ is unactivated, or in specific cases which will be recognized by those skilled in the art, the use of a transition-metal catalyst such as palladium(0), palladium (II), nickel(0) or nickel(II), along with phosphine-based ligands, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), may be required to effect reaction. More specific details concerning this reaction are available in the following references: *J. Org. Chem.* **1997**, *62*, 1264; *J. Org. Chem.* **1997**, *62*, 1568; *SynLett* **1997**, 329. The reaction can be

conducted in the absence of solvent or in a reaction inert solvent. Preferable reaction inert solvents include aqueous media, ($C_1$-$C_4$)alcohol, ($C_2$-$C_6$)glycol, a halocarbon, an aliphatic or aromatic hydrocarbon, an ether, a polar aprotic solvent, a ketone, or combinations thereof. The reaction time ranges from 15 minutes to 3 days and the reaction temperature ranges from 0 °C to 180 °C or to the reflux temperature of the solvent being used. The reactions are preferably conducted at ambient pressure.

In certain cases which will be recognized by those skilled in the art, transformations of existing functionality in $Ar^1$ of compound 5-3 may be necessary to produce compounds of formula 5-4. This pertains in particular to those cases where, for example, $R^9$ in 5-3 contains an aromatic or heteroaromatic halide, ($C_1$-$C_4$)alkylsulfonate or triflate. Said compounds of formula 5-3 wherein $Ar^1$ contains up to two substituents selected from halide, ($C_1$-$C_4$)alkylsulfonate or triflate, may be converted to a compound of formula $Ar^1$ where said halide, ($C_1$-$C_4$)alkylsulfonate or triflate is transformed into another functional group by a reduction reaction or by a displacement reaction of said halide, ($C_1$-$C_4$)alkylsulfonate or triflate with a nucleophile. The reduction reaction is conducted with a reducing agent, preferably ammonium formate or hydrogen gas, in a reaction inert solvent. The reduction is conducted in the presence of a palladium catalyst at ambient pressure or under a hydrogen pressure of up to 50 psi. Preferred solvents include ($C_1$-$C_4$)alcohols such as methanol and ethanol, and ether solvents such as diethyl ether, dioxane and tetrahydrofuran. The nucleophilic displacement reaction may be conducted by adding the nucleophile directly or by pre-forming the nucleophile separately or in situ from a nucleophile precursor. Preferred nucleophiles include organoaluminum, organoboron, organocopper, organotin, organozinc or Grignard reagent; $R^{11}$-oxide or $R^{11}$-thioxide; or anilino where anilino is within the scope of $R^{11}$. It will be recognized by those skilled in the art that transition-metal catalysts may be required to effect reaction in certain displacement reactions. When required, such transition metal catalysts may include palladium(0), palladium(II), nickel(0), and nickel(II) complexes. Palladium(II) bis(diphenylphosphinobutane) dichloride is a preferred such catalyst. Additionally, an aqueous or non-aqueous base may be required in the displacement reaction. Preferred such bases include sodium carbonate, sodium hydride, triethylamine and sodium tert-butoxide. The reaction is conducted at ambient pressure in a reaction inert solvent such as a halocarbon, an aromatic or aliphatic hydrocarbon, an ether or a

polar aprotic solvent or a combination thereof. In certain cases, a ($C_1$-$C_4$)alcohol is used as a solvent or co-solvent. The reaction temperature ranges from –20 °C to the reflux temperature of the solvent employed. The reaction time ranges from 1 hour to 3 days.

Optional protecting groups which may be present in compounds of formula 5-3 are removed according to methods set forth above, or according to methods well known to those skilled in the art, particularly as set forth in: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons Inc.: New York, 1991.

Compounds of formula 5-4 are prepared from the displacement reaction of amine 5-3 as described in Scheme 1, where the amine 5-3 is equivalent to $R^3$-NH. A representative set of amines of formula 5-3 which are commercially available or which can be prepared by a literature procedure include 1-phenyl-piperazine (Aldrich), 1-pyridin-2-yl-piperazine (Aldrich), 3-piperazin-1-yl-benzo[d]isoxazole (*J. Med. Chem.* **1986**, *29*, 359), 3-piperazin-1-yl-benzo[d]isothiazole (*J. Med. Chem.* **1986**, *29*, 359), 2-piperazin-1-yl-quinoxaline (*J. Med. Chem.* **1981**, *24*, 93), 1-naphthalen-2-yl-piperazine (*cf. Tetrahedron Lett.* **1994**, 35, 7331), and 1-(3,5-dimethylphenyl)-piperazine (*cf. Tetrahedron Lett.* **1994**, 35, 7331). Other compounds of formula 5-3 can be prepared using methods well known to those skilled in the art or by using methods analogous to those described in the foregoing references.

Alternatively, compounds of formula 5-4 can be prepared from reaction with compounds of formula 5-1 with compounds of formula 5-5 using conditions set forth above to prepare 5-3. Compounds of formula 5-5 can be prepared in a manner analogous to the method used to prepare compounds of formula 1-3.

Compounds of formula 5-4 wherein X is oxycarbonyl, vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_1$-$C_4$)alkenylcarbonyl, vinylenylsulfonyl or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, and thio($C_3$-$C_4$)alkenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl, or Ar; said vinylenylsulfonyl and said vinylenylcarbonyl in the definition of X are each optionally and independently substituted with up to three ($C_1$-$C_4$)alkyl, benzyl, or Ar are also prepared according to Scheme 5 above and particularly as described below.

Compounds of formula 5-4 where X is as defined in the immediately preceding paragraph are prepared by reacting a compound of formula 5-5 with a compound of formula 5-1 where $R^9$ is described above, X is as defined in the immediately preceding paragraph and $Lv^3$ is chloro. The reaction is conducted under anhydrous conditions in the presence of a non-aqueous base, which includes organic amines such as triethylamine, N,N'-diisopropylethylamine and pyridine and derivatives thereof. The reaction is generally conducted in a reaction inert solvent. Preferred solvents include halocarbon, aliphatic or aromatic hydrocarbon, ethers, ethyl acetate, pyridine and combinations thereof. The reaction time ranges from 15 minutes to 24 hours and the reaction temperature ranges from 0 °C to 80 °C or to the reflux temperature of the solvent being used. The reactions are preferably conducted at from 0 °C to ambient temperature and at ambient pressure. Removal of optional protecting groups is carried out as described in Scheme I.

Compounds of formula 5-4 wherein X is vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_2$-$C_4$)alkenylcarbonyl, or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, and thio($C_2$-$C_4$)alkenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl, or Ar; and said vinylenylcarbonyl in the definition of X are each optionally and independently substituted with up to three ($C_1$-$C_4$)alkyl, benzyl, or Ar are also prepared according to Scheme 5 avove and particularly as described below.

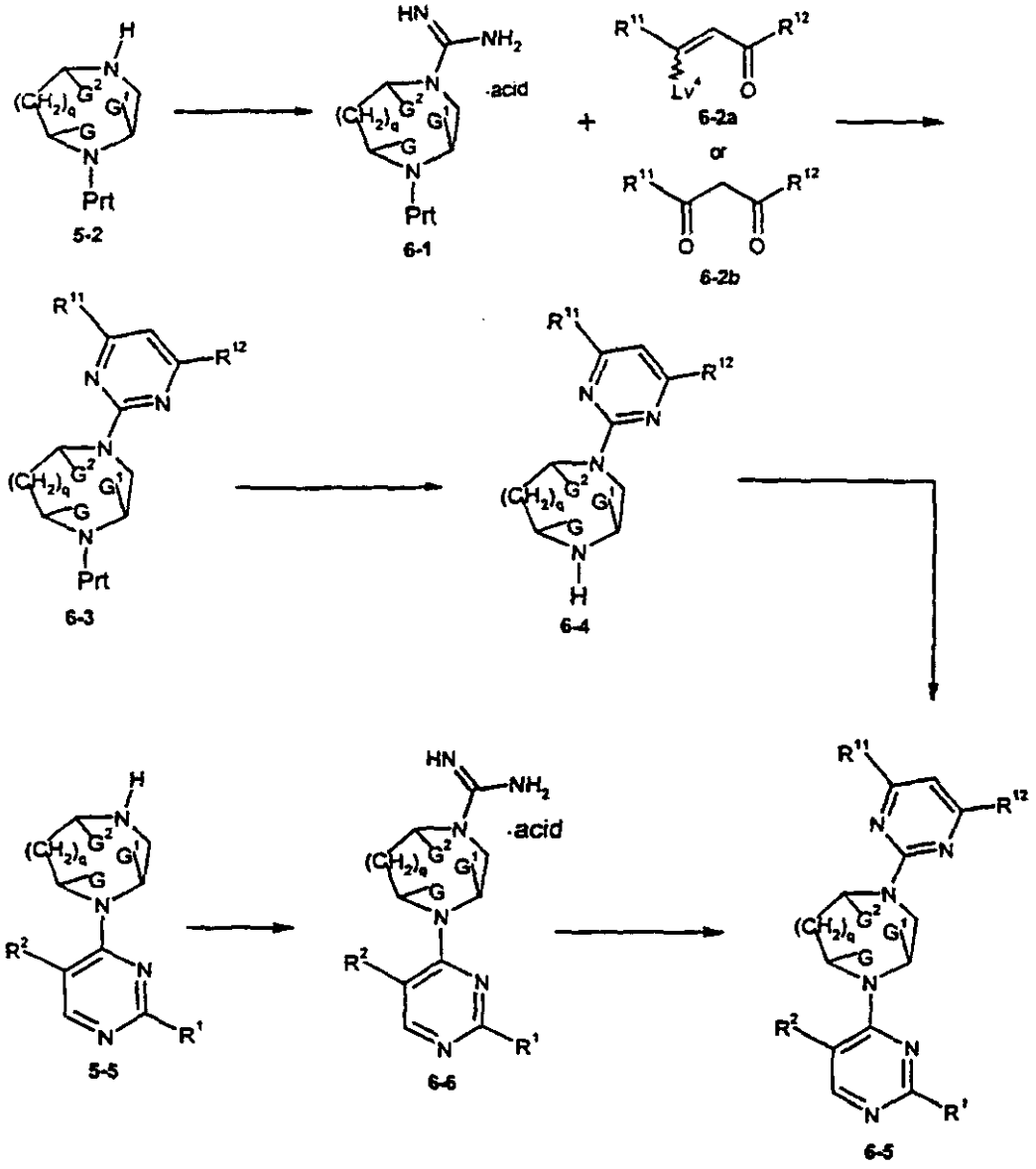
Compounds of formula 5-4 are prepared by reacting a compound of formula 5-5 with a compound of formula $R^9$-X-$Lv^3$ where $R^9$ is described above, X is as defined in the immediately preceding paragraph and $Lv^3$ is OH. The reaction is conducted in the presence of coupling agents, preferably dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride as described in *J. Amer. Chem. Soc.* **1996**, *118*, 4952. The reaction is conducted in a reaction inert solvent. Preferred solvents include halocarbon, aliphatic or aromatic hydrocarbon and ethers. Especially preferred solvents include dichloromethane and chloroform. Other coupling agents that can be used are well known to those skilled in the art and include, but are not limited to, various phosphine reagents, ethyl chloroformate, and N-hydroxysuccinimide. These reagents and procedures are described in "Compendium

of Organic Synthetic Methods" (Ed., I. T. Harrison and S. Harrison, John Wiley & Sons). Specific references include the following: *J. Org. Chem*, **1971**, *36*, 1305; *Bull. Soc. Chim. Fr.*, **1971**, 3034; *Bull. Chem. Soc. Japan*, **1971**, *44*, 1373; *Tetrahedron Lett.*, **1973**, *28*, 1595; *Tetrahedron Lett.*, **1971**, *26*, 2967, and *J. Med. Chem.*, **1968**, *11*, 534. Removal of optional protecting groups is carried out as described in Scheme I.

Compounds of formula 5-4 wherein X is a covalent bond and $R^9$ is ($C_3$-$C_7$)cycloalkyl or $Ar^1$-($C_1$-$C_3$)alkylenyl are also prepared according to Scheme 5 above and particularly as described below.

Compounds of formula 5-4 wherein X is a covalent bond and $R^9$ is ($C_3$-$C_7$)cycloalkyl or $Ar^1$-($C_1$-$C_3$)alkylenyl are prepared by reacting a compound of formula 5-1 wherein X is a covalent bond, $R^9$ is ($C_3$-$C_7$)cycloalkyl or $Ar^1$-($C_1$-$C_3$)alkylenyl and $Lv^3$ is halo, methanesulfonate, p-toluenesulfonate or trifluoromethanesulfonate. The reaction is conducted under anhydrous conditions in the presence of a non-aqueous base, which includes organic amines such as triethylamine, N,N'-diisopropylethylamine and pyridine and derivatives thereof. The reaction is conducted in a reaction inert solvent. Preferred solvents for the reaction include halocarbons, aliphatic or aromatic hydrocarbons, ethers, ethyl acetate, pyridine and combinations thereof. The reaction time ranges from 15 minutes to 24 hours and the reaction temperature ranges from –20 °C to 80 °C or to the reflux temperature of the solvent being used. The reactions are preferably conducted at ambient temperature of the solvent being used and at ambient pressure. Removal of optional protecting groups is conducted as set forth in Scheme I.

Scheme 6




Compounds of formula 6-5 wherein G, $G^1$, $G^2$, q, $R^1$, $R^2$, $R^6$, $R^7$ and $R^8$ are as defined above are prepared as set forth in Scheme 6 above and particularly as described below.

Compounds of formula 6-1 are prepared from an amine of the formula 5-2 where Prt is an optional amine protecting group selected from benzyl and $CO_2R^{90}$, where $R^{90}$ is selected from ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)allyl, trichloroethyl and benzyl substituted with up to two ($C_1$-$C_4$)alkoxy. The preferred procedure for preparing

compounds of formula 6-1 can be found in *Tetrahedron Lett.* **1993**, 48, 7767 or *J. Org. Chem* **1997**, 62, 1540.

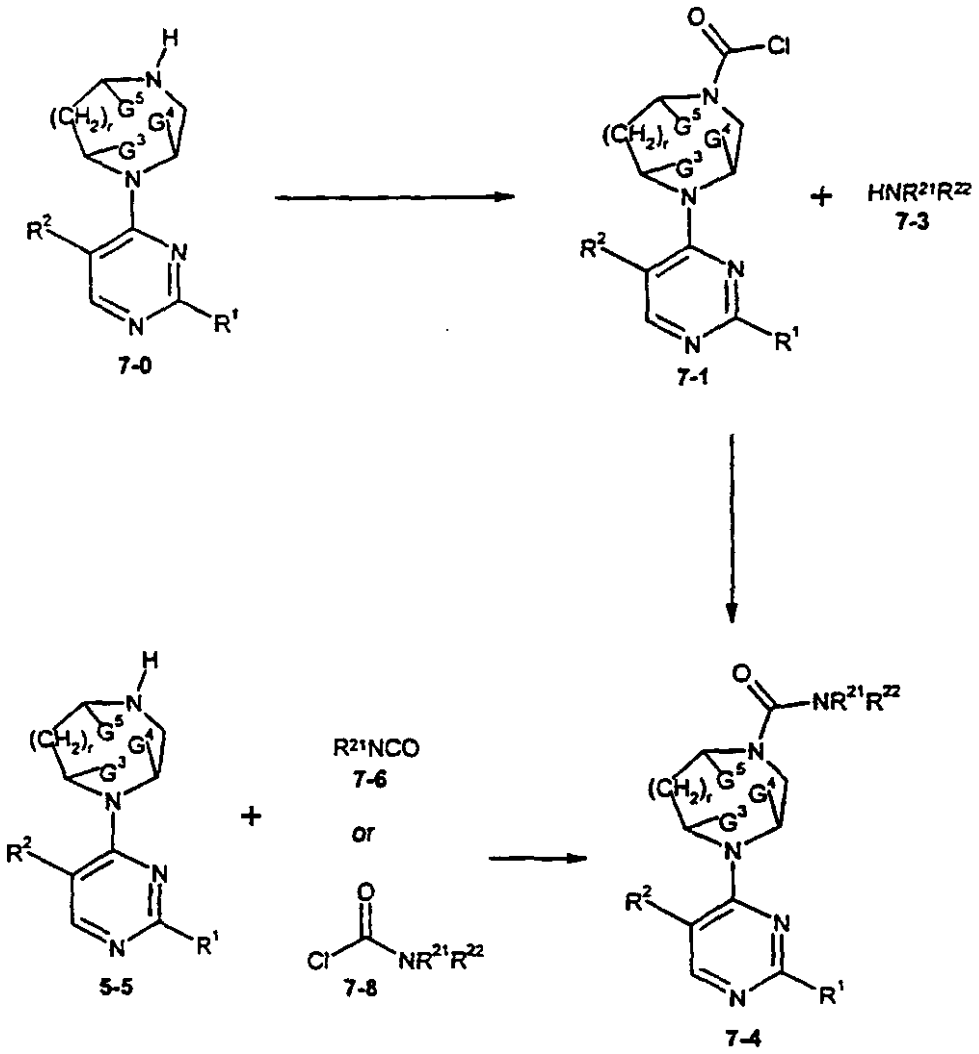
Compounds of formula 6-3 are prepared by condensation of β-diketones or β-ketoesters of the formula 6-2b, where $R^{11}$ and $R^{12}$ are independently substituted as set forth above, or compounds of the formula 6-2a where $Lv^4$ is, for example, hydroxy, chloro or dimethylamino with guanidines of the formula 6-1. The reaction is conducted in the presence of an aqueous or non-aqueous base, preferably potassium or sodium hydroxide, potassium or sodium ($C_1$-$C_4$)-alkoxide, triethylamine, pyridine, 4-dimethylaminopyridine, potassium or sodium carbonate or potassium or sodium bicarbonate. The reaction is conducted in a reaction inert solvent, preferably aqueous media, a ($C_1$-$C_4$)alcohol, a ($C_2$-$C_6$)dialcohol, an aromatic hydrocarbon, a polar aprotic solvent, or combinations thereof. The reaction time ranges from 2 hours to 3 days and the reaction temperature ranges from room temperature to reflux of the solvent employed. The reaction is preferably run at ambient pressure, but may be conducted at pressures up to 250 psi.

Removal of of optional protecting groups in compounds of formula 6-3 to afford compounds of formula 6-4 is accomplished as set forth above.

Compounds of formula 6-5 are prepared from the displacement reaction of amine 6-4 as described in Scheme 1, where the amine 6-4 is equivalent to $R^3$-NH.

Alternatively, compounds of formula 6-5 are prepared from compounds of formula 5-5 by formation of a compound of formula 6-6, or by reaction with compounds of formula 6-2a or 6-2b under the conditions outlined above in Scheme 6. Removal of optional protecting groups is conducted as described in Scheme 1. Compounds of formula 5-5 are prepared as set forth above.

**Scheme 7**




Compounds of formula 7-4 wherein $G^3$, $G^4$, $G^5$, r, $R^1$, $R^2$, $R^{18}$, $R^{19}$ and $R^{20}$ are defined as set forth above are prepared as set forth in Scheme 7 and particularly as described below.

Compounds of formula 7-1 are prepared by reaction of an amine of the formula 7-0 with phosgene or a phosgene equivalent such as triphosgene. Compounds of 7-1 wherein the chloro group is replaced by an imidazolyl group are also useful in this reaction. Such compounds are prepared by reaction of an amine of formula 7-0 with carbonyl diimidazole. The reaction is conducted under anhydrous conditions in the presence of a nonaqueous base. Preferred such bases include

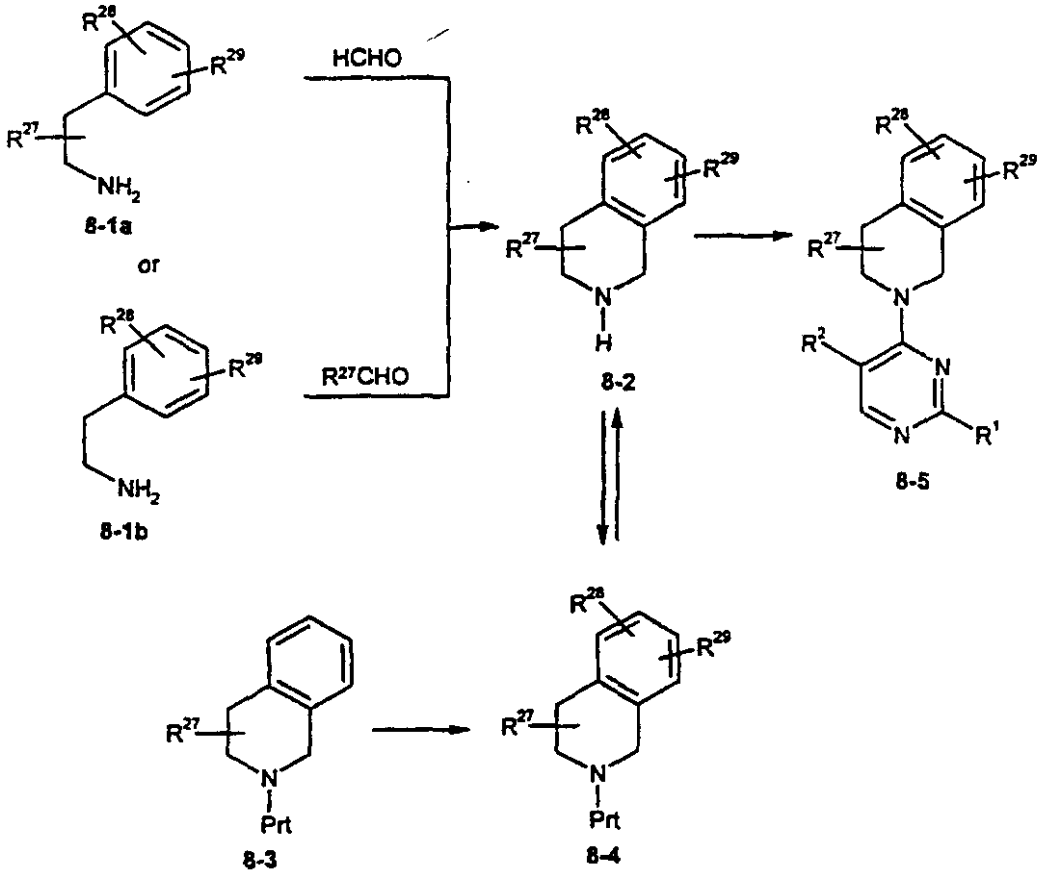
triethylamine and other tertiary amines and pyridine and derivatives thereof. The reaction is conducted in a reaction inert solvent at –78 °C to 80 °C or at the reflux temperature of the solvent being used for 15 minutes to 24 hours. Preferred solvents for this reaction include a halocarbon, an aliphatic or aromatic hydrocarbon, an ether, ethyl acetate, pyridine and combinations thereof. The reactions are preferably conducted at from 0 °C to ambient temperature and at ambient pressure.

Compounds of formula 7-4 are prepared by reaction of carbamoyl chlorides of the formula 7-1 with amines of the formula 7-3, where $R^{21}$ and $R^{22}$ are defined above. The reaction can be conducted in the absence of solvent, or in a reaction inert solvent. Preferred such solvents include aqueous media, a ($C_1$-$C_4$)alcohol, a ($C_2$-$C_6$)dialcohol, an aromatic or aliphatic hydrocarbon, a halocarbon, an ether, a polar aprotic solvent, a ketone, pyridine or combinations thereof. The reaction time ranges from 15 minutes to 3 days and the reaction temperature ranges from 0 °C to the reflux temperature of the solvent being used. The reaction is preferably conducted at ambient pressure. It will be recognized by those skilled in the art that addition of a base may be required to effect reaction. In those cases, preferred bases include potassium or sodium hydroxide, triethylamine and other tertiary amines, pyridine and its derivatives and inorganic bases such as sodium or potassium carbonate and sodium or potassium bicarbonate. Removal of optional hydroxyl protecting groups contained in $R^1$ is carried out according to methods set forth in Scheme 1.

Alternatively, compounds of formula 7-4 are prepared from compounds of formula 7-0 by reaction with isocyanates of the formula 7-6 or with carbamoyl chlorides of the formula 7-8. Said isocyanates are commercially available, known in the literature, or synthesized under standard conditions known to those skilled in the art, particularly as described in March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons Inc.: New York, 1985, p 1166. A preferred method of forming such isocyanates is the Curtius rearrangement of a suitable acyl azide. Said carbamoyl chlorides are synthesized using methods analogous to that described for the preparation of compounds of formula 7-1 in Scheme 7. Removal of optional hydroxyl protecting groups contained in $R^1$ is carried out according to methods set forth in Scheme 1.

Compounds of formula I containing the radical $R^{3c}$ are prepared according to the procedures set forth in Scheme 7 using the corresponding starting materials and reagents.

**Scheme 8**




Compounds of formula 8-5 are prepared as set forth in Scheme 8 and particularly as described below.

Compounds of formula 8-2 are readily prepared from commercially available phenethylamines of formula 8-1a and formaldehyde or an aldehyde of the formula $R^{27}$-CHO under Pictet-Spengler conditions. The Pictet-Spengler reaction is reviewed in *Chem. Rev.* **1995**, *95*, 1797. A similar route route to 1,2,3,4-tetrahydroisoquinolines using the Bischler-Napieralski reaction, as disclosed in March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons.: New York, 1985, 495, followed by standard reduction of the imine formed may also be employed.

Compounds of formula 8-4 are prepared from compounds of formula 8-3 by aromatic electrophilic substitution using the appropriate electrophile. A general reference for this type of reaction can be found in March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons.: New York, 1985, 447-511.

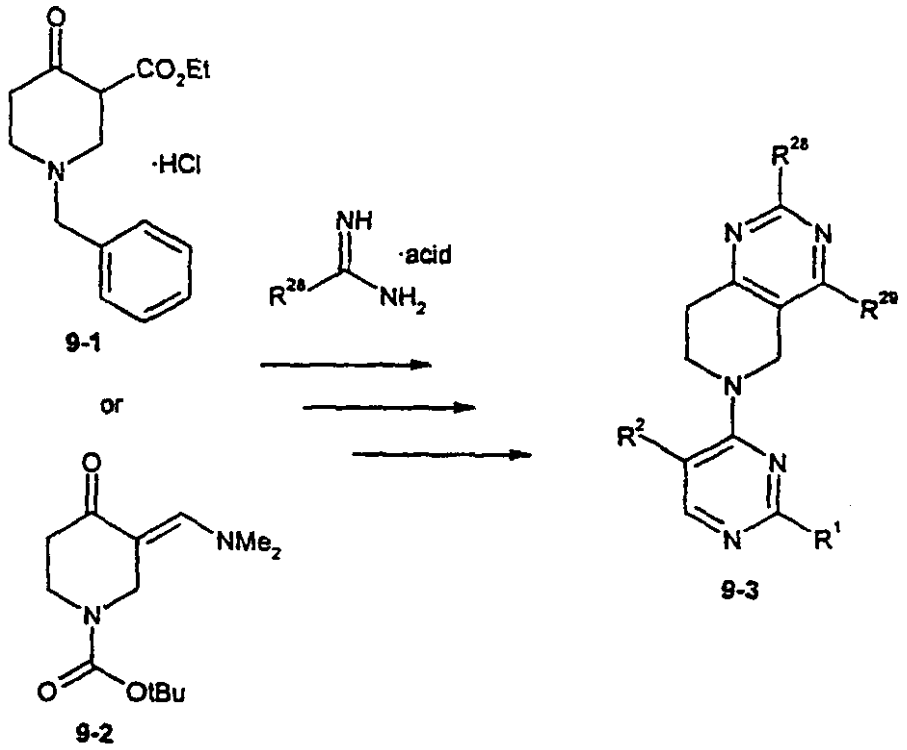
Compounds of formula 8-2 are also prepared by removal of the protecting group from a compound of formula 8-4. Preferably the protecting group is trifluoroacetamide which may be removed under basic conditions using inorganic hydroxides or carbonates in a reaction inert solvent. Suitable such solvents include ($C_1$-$C_4$)alcohols and preferably methanol. Optionally, one or more co-solvents, preferably selected from water, tetrahydrofuran and dioxane may be employed. The reaction time ranges from 15 minutes to 24 hours and the reaction temperature ranges from 0 °C to 100 °C or to the reflux temperature of the solvent or solvent system being used. The reaction is preferably conducted at ambient temperature. Other conditions for deprotection of trifluoroacetamides and deprotection conditions for other suitable protecting groups can be found in Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons Inc.: New York, 1991.

Compounds of formula 8-4 are prepared by adding a protecting group to compounds of formula 8-2. Preferably the protecting group is trifluoroacetamide or tert-butoxycarbonyl (BOC). The protecting group is attached by reaction of a compound of formula 8-2 with trifluoroacetyl chloride or di-tert-butyl dicarbonate or an equivalent thereof in the presence of a base, preferably triethylamine or pyridine. The reaction is conducted in a reaction inert solvent. Preferred such solvents include ethers such as tetrahydrofuran, diethyl ether, dioxane or dimethoxyethane; a halocarbon such as dichloromethane, chloroform or carbon tetrachloride; and aromatic or aliphatic hydrocarbons such as benzene, toluene or hexanes. The reaction time ranges from 15 minutes to 3 days and the reaction temperature ranges from 0 °C to the reflux temperature of the solvent being used. The reaction is preferably conducted at ambient pressure. Other conditions for protection of amines with trifluoroacetamides or tert-butoxycarbonyl groups as well as other suitable protecting groups can be found in Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons Inc.: New York, 1991.

Manipulation of the substituents $R^{28}$ and $R^{29}$ is carried out to provide isoquinolines with altered substitution. Preferably, transition metal-catalyzed cross-coupling of a compound of formula 8-4 where $R^{28}$ or $R^{29}$ is bromide or triflate is employed to afford compounds of formula 8-4 wherein $R^{28}$ or $R^{29}$ are as set forth above. This reaction is conducted according to methods well known to those skilled in the art, particularly as set forth in *Tetrahedron*, **1998**, *54*, 263 for Stille and Suzuki Reactions and in *Acc. Chem. Res.* **1998**, *31*, 805 for Buchwald Amination Reactions.

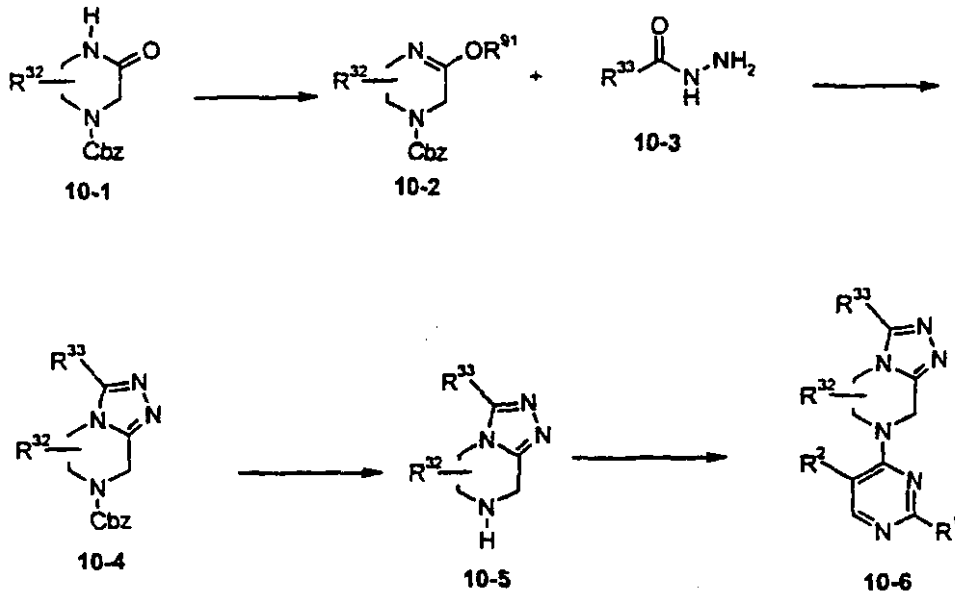
Compounds of formula 8-5 are prepared from the displacement reaction of amine 8-2 as described in Scheme 1, where the amine 8-2 is equivalent to $R^3$-NH.

**Scheme 9**




Compounds of formula 9-3 are prepared according to the general procedures set forth in Scheme 2 starting from ethyl 1-benzyl-4-oxo-3-piperidine carboxylate hydrochloride (9-1). In certain cases, where $R^{29}$ is H, N-tertbutoxycarbonyl-3-(dimethylaminomethylene)-4-piperidone (9-2, Chemical Abstracts 121:157661) is used as the starting material.

**Scheme 10**




Compounds of formula 10-6 wherein $R^1$, $R^2$, $R^{32}$ and $R^{33}$ are as defined above are prepared as set forth in Scheme 10 and more particularly as described below.

Compounds of formula 10-2 where $R^{91}$ is ($C_1$-$C_4$)alkyl are prepared by reacting a compound of formula 10-1, where Cbz is benzyloxycarbonyl, with an O-alkylating agent. A preferred compound of formula 10-1 is 3-oxo-piperazine-1-carboxylic acid benzyl ester. A preferred O-alkylating agent is triethyloxonium tetrafluoroborate. The reaction is conducted at ambient pressure in a reaction inert solvent. Preferred solvents include an aromatic or aliphatic hydrocarbons, halocarbons and ethers. Dichloromethane is especially preferred. The reaction time ranges from 2 hours to 3 days and the reaction temperature ranges from –100 °C to ambient temperature.

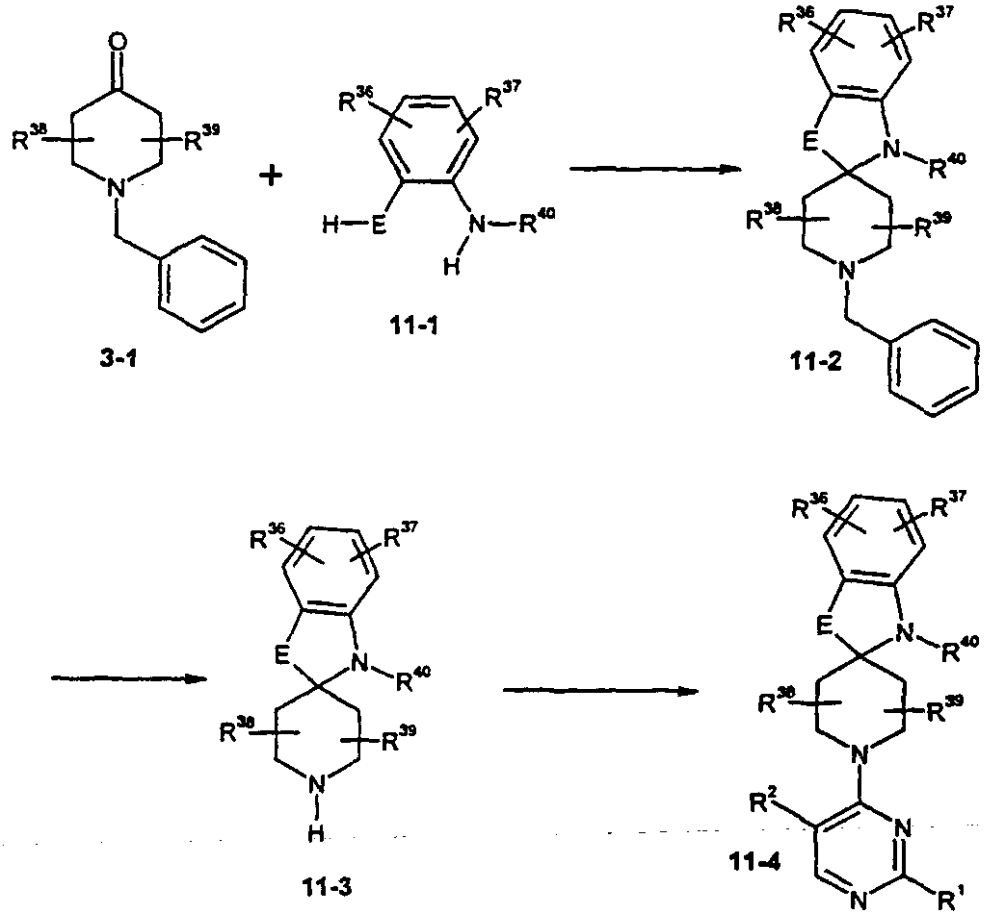
Compounds of formula 10-4 are prepared by condensation of a compound of formula 10-2 with a compound of formula 10-3. Said compounds of formula 10-3 are commercially available, are known in the literature, or are readily prepared via standard amidation of hydrazine and an activated carboxylic acid, such as a carboxylic acid chloride. Such reactions are well known by those skilled in the art. The condensation reaction is preferably run at ambient pressure, although higher pressures up to 250 psi may be employed if necessary. The reaction is conducted in a reaction inert solvent, preferably selected from ($C_1$-$C_4$)alcohols, aromatic or aliphatic

hydrocarbons, polar aprotic media, halocarbons and ethers, or combinations thereof. The reaction is conducted at temperatures ranging from ambient temperature to 180 °C. The reaction times are from 2 hours to 3 days.

Compounds of formula 10-5 are prepared form compounds of formula 10-4 via Lewis acid-catalyzed cleavage or hydrogenolysis of the Cbz carbamate under standard conditions which are well known to those skilled in the art, particularly as set forth in Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons Inc.: New York, 1991, pp 335-338.

Compounds of formula 10-6 are prepared from the displacement reaction of an amine of the formula 10-5 as described in Scheme 1, where the amine 10-5 is equivalent to $R^3$-NH.

**Scheme 11**



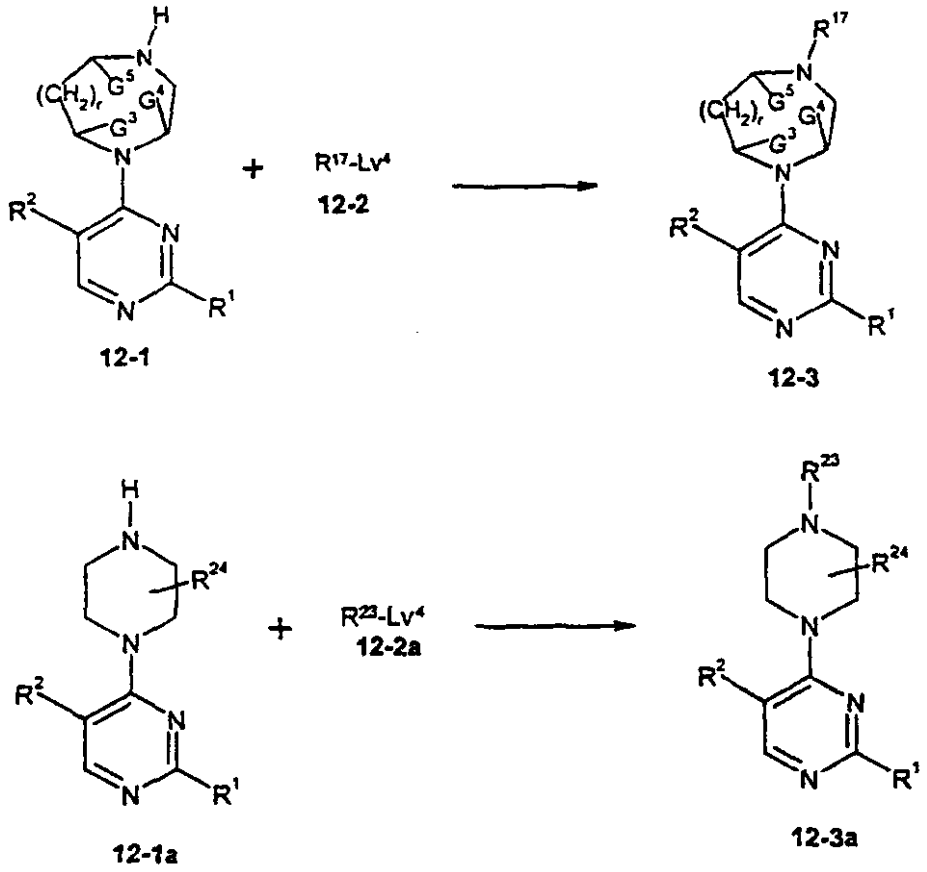
Compounds of formula 11-4, wherein $R^1$, $R^2$, $R^{36}$, $R^{37}$, $R^{38}$, $R^{39}$ and $R^{40}$ are as defined above are prepared as set forth in Scheme 11 and more particularly as described below.

Where $R^{38}$ and $R^{39}$ are hydrogen, 1-benzyl-4-piperidone (3-1), available from Aldrich, is condensed with a compound of formula 11-1, which are either commercially available or well known to those skilled in the art, to give compounds of formula 11-2. Where $R^{38}$ and $R^{39}$ are not hydrogen, compounds of formula 3-1 can be prepared according to methods well known to those skilled in the art. The reaction is conducted at ambient pressure in the absence of solvent or in a reaction inert solvent. Preferred solvents include ($C_1$-$C_4$)alcohols, aromatic or aliphatic hydrocarbons, polar aprotic solvents, halocarbons and ethers. The reaction time ranges from 2 hours to 3 days and the reaction temperature ranges from ambient temperature to the reflux temperature of the solvent being employed. More specific conditions can be found in *Indian J. Chem.* **1976**, *14B*, 984 and *J. Chem. Soc., Perkin Trans. 1* **1984**, 2465.

Compounds of formula 11-3 are prepared by removal of the benzyl protecting group from a compound of formula 11-2 in a manner analogous to the method employed for the preparation of compounds of 2-6 described above.

Compounds of formula 11-4 are prepared by the displacement reaction of an amine of the formula 11-3 as described in Scheme 1, where the amine 11-3 is equivalent to $R^3$-H.

**Scheme 12**




Compounds of formula 12-3 and 12-3a where $R^{17}$ and $R^{23}$ are ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)alkylcarbonyl, $Ar^2$-carbonyl, ($C_1$-$C_6$)alkylsulfonyl, $Ar^2$-sulfonyl, or $Ar^2$-sulfinyl are prepared according to Scheme 12 above and particularly as set forth below.

*Compounds of formula 12-3 and 12-3a where $R^{17}$ and $R^{23}$ are as defined in* the immediately preceding paragraph are prepared by condensation with a compound of formula 12-2 and 12-2a, wherein $Lv^4$ is chloro, respectively. Examples of compounds of formula 12-2 and 12-2a include ($C_1$-$C_6$)alkoxyCOCl, ($C_1$-$C_6$)alkylCOCl, $Ar^2$-COCl, ($C_1$-$C_6$)alkyl$SO_2$Cl, $Ar^2$-$SO_2$Cl, or $Ar^2$-SOCl. The reaction is conducted under *anhydrous conditions in the presence of a non-aqueous base, which includes organic* amines such as triethylamine, N,N'-diisopropylethylamine and pyridine and derivatives thereof. The reaction is conducted in a reaction inert solvent. Preferred solvents for the reaction include halocarbon, aliphatic or aromatic hydrocarbon, ethers, ethyl

acetate, pyridine and combinations thereof. The reaction time ranges from 15 minutes to 24 hours and the reaction temperature ranges from 0 °C to 80 °C or to the reflux temperature of the solvent being used. The reactions are preferably conducted at from 0 °C to ambient temperature and at ambient pressure. Removal of optional protecting groups is carried out as described in Scheme I.

Compounds of formula 12-3 and 12-3a wherein $R^{17}$ and $R^{23}$ are ($C_1$-$C_6$)alkylcarbonyl or $Ar^2$-carbonyl are also prepared according to Scheme 12 above and particularly as described below.

Compounds of formula 12-3 and 12-3a wherein $R^{17}$ and $R^{23}$ are ($C_1$-$C_6$)alkylcarbonyl or $Ar^2$-carbonyl are prepared by a condensation reaction with a compound of formula 12-2 or 12-2a, respectively, wherein $Lv^4$ is hydroxy in the presence of coupling agents such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reaction is conducted in a reaction inert solvent. Preferred solvents include halocarbon, aliphatic/aromatic hydrocarbons and ethers. Especially preferred solvents include dichloromethane and chloroform. Other coupling agents that can be used are well known to those skilled in the art and include, but are not limited to, various phosphine reagents, ethyl chloroformate, and N-hydroxysuccinimide. Removal of optional protecting groups is carried out as described in Scheme I.

Compounds of formula 12-3 where $R^{17}$ is ($C_1$-$C_6$)alkyyl are also prepared according to Scheme 12 and particularly as described below.

Compounds of formula 12-3 where $R^{17}$ is ($C_1$-$C_6$)alkyl are prepared by reacting a compound of formula 12-1 with a compound of formula 12-2 where $R^{17}$ is ($C_1$-$C_4$)alkyl and $Lv^4$ is Cl, Br, I, methanesulfonyloxy, p-toluenesulfonyloxy or trifluoromethanesulfonyloxy. The reaction is conducted under anhydrous conditions in the presence of a nonaqueous base, which includes organic amines such as triethylamine, Hunig's base and pyridine and derivatives thereof. The reaction is conducted in a reaction inert solvent. Preferred solvents for the reaction include halocarbons, aliphatic or aromatic hydrocarbons, ethers, ethyl acetate, pyridine and combinations thereof. The reaction time ranges from 15 minutes to 24 hours and the reaction temperature ranges from ambient temperature to 80 °C or to the reflux temperature of the solvent being used. The reactions are preferably conducted at ambient temperature and pressure.

The starting materials and reagents for the above described compounds are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, many of the compounds used herein are related to, or are derived from, compounds found in nature, in which there is a large scientific interest and commercial need, and accordingly many such compounds are commercially available or are reported in the literature or are easily prepared from other commonly available substances by methods which are reported in the literature.

The compounds of the instant invention inhibit the formation of sorbitol dehydrogenase and as such have utility in the treatment of diabetic complications including but not limited to such complications as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic microangiopathy and diabetic macroangiopathy and diabetic cardiomyopathy. The utility of the compounds of the present invention as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.g., humans) for example, diabetic complications such as diabetic cardiomyopathy, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic microangiopathy and diabetic macroangiopathy is demonstrated by the activity of the compounds of formula I of this invention in conventional assays. Such assays also provide a means whereby the activities of the compounds of formula I of this invention can be compared with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

**Measurement of SDH Activity**

Male Sprague-Dawley rats (350-400 g) are used for these experiments. Diabetes is induced in some of the rats by a tail vein injection of streptozocin, 85 mg/kg. Twenty-four hours later, 4 groups of diabetic rats are given a single dose of the test compound of formula I of this invention (0.001 to 100 mg/kg) by oral gavage. Animals are sacrificed 4-6 hours after dosing and blood and sciatic nerves are harvested. Tissues and cells are extracted with 6% perchloric acid.

Sorbitol in erythrocytes and nerves is measured by a modification of the method of R. S. Clements et al. (Science, 166: 1007-8, 1969). Aliquots of tissue extracts are added to an assay system which has final concentrations of reagents of 0.033 M glycine, pH 9.4, 800 mM ß-nicotine adenine dinucleotide, and 4 units/ml of

sorbitol dehydrogenase. After incubation for 30 minutes at room temperature, sample fluorescence is determined on a fluorescence spectrophotometer with excitation at 366 nm and emission at 452 nm. After subtracting appropriate blanks, the amount of sorbitol in each sample is determined from a linear regression of sorbitol standards processed in the same manner as the tissue extracts.

Fructose is determined by a modification of the method described by M. Ameyama, Methods in Enzymology, 89: 20-25 (1982). Resazurin is substituted for ferricyanide. Aliquots of tissue extracts are added to the assay system, which has final concentrations of reagents of 1.2 M citric acid, pH 4.5, 13 mM resazurin, 3.3 units/ml of fructose dehydrogenase and 0.068% Triton X-100. After incubation for 60 minutes at room temperature, sample fluorescence is determined on a fluorescence spectrophotometer with excitation at 560 nm and emission at 580 nm. After subtracting appropriate blanks, the amount of fructose in each sample is determined from a linear regression of fructose standards processed in the same manner as the tissue extracts.

SDH activity is measured by a modification of the method described by U. Gerlach, Methodology of Enzymatic Analyses, edited by H. U. Bergmeyer, 3, 112-117 (1983). Aliquots of sera or urine are added to the assay system, which has final concentrations of reagents of 0.1 M potassium phosphate buffer, pH 7.4, 5 mM NAD, 20 mM sorbitol, and 0.7 units/ml of sorbitol dehydrogenase. After incubation for 10 minutes at room temperature, the average change in sample absorbance is determined at 340 nm. SDH activity was presented as milli$OD_{340}$ units/minute ($OD_{340}$ = optical density at 340 nm).

Any aldose reductase inhibitor may be used as the second compound (active agent) of this invention for combination therapies. The term aldose reductase inhibitor refers to compounds which inhibit the bioconversion of glucose to sorbitol catalyzed by the enzyme aldose reductase. Such inhibition is readily determined by those skilled in the art according to standard assays (J. Malone, Diabetes, 29:861-864, 1980. "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are described and referenced below, however, other aldose reductase inhibitors will be known to those skilled in the art. The disclosures of U.S. patents listed below are hereby incorporated by reference. Also, common chemical USAN names or other designation are in parentheses

where applicable, together with reference to appropriate patent literature disclosing the compound.

The activity of an aldose reductase inhibitor in a tissue can be determined by testing the amount of aldose reductase inhibitor that is required to lower tissue sorbitol (i.e., by inhibiting the further production of sorbitol consequent to blocking aldose reductase) or lower tissue fructose (by inhibiting the production of sorbitol consequent to blocking aldose reductase and consequently the production of fructose). While not wishing to be bound by any particular theory or mechanism, it is believed that an aldose reductase inhibitor, by inhibiting aldose reductase, prevents or reduces ischemic damage as described hereinafter.

Accordingly, examples of aldose reductase inhibitors useful in the compositions and methods of this invention include:

1. 3-(4-bromo-2-fluorobenzyl)-3,4-dihydro-4-oxo-1-phthalazineacetic acid (ponalrestat, US 4,251,528);

2. N[[(5-trifluoromethyl)-6-methoxy-1-naphthalenyl]thioxomethyl}-N-methylglycine (tolrestat, US 4,600,724);

3. 5-[(Z,E)-β-methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolideneacetic acid (epalrestat, US 4,464,382, US 4,791,126, US 4,831,045);

4. 3-(4-bromo-2-fluorobenzyl)-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazolineacetic acid (zenarestat, US 4,734,419, and 4,883,800);

5. 2R,4R-6,7-dichloro-4-hydroxy-2-methylchroman-4-acetic acid (US 4,883,410);

6. 2R,4R-6,7-dichloro-6-fluoro-4-hydroxy-2-methylchroman-4-acetic acid (US 4,883,410);

7. 3,4-dihydro-2,8-diisopropyl-3-oxo-2H-1,4-benzoxazine-4-acetic acid (US 4,771,050);

8. 3,4-dihydro-3-oxo-4-[(4,5,7-trifluoro-2-benzothiazolyl)methyl]-2H-1,4-benzothiazine-2-acetic acid (SPR-210, U.S. 5,252,572);

9. N-[3,5-dimethyl-4-[(nitromethyl)sulfonyl]phenyl]-2-methyl-benzeneacetamide (ZD5522, U.S. 5,270,342 and U.S. 5,430,060);

10. (S)-6-fluorospiro[chroman-4,4'-imidazolidine]-2,5'-dione (sorbinil, US 4,130,714);

11. d-2-methyl-6-fluoro-spiro(chroman-4',4'-imidazolidine)-2',5'-dione (US 4,540,704);

12. 2-fluoro-spiro(9H-fluorene-9,4'–imidazolidine)-2',5'-dione (US 4,438,272);

13. 2,7-di-fluoro-spiro(9H-fluorene-9,4'–imidazolidine)-2',5'-dione (US 4,436,745, US 4,438,272);

14. 2,7-di-fluoro-5-methoxy-spiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (US 4,436,745, US 4,438,272);

15. 7-fluoro-spiro(5H-indenol[1,2-b]pyridine-5,3'-pyrrolidine)-2,5'-dione (US 4,436,745, US 4,438,272);

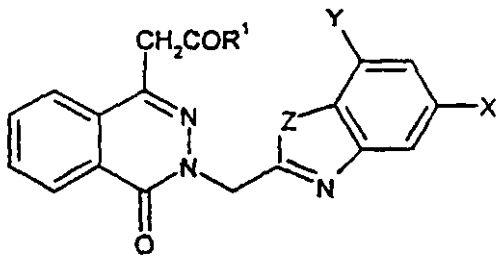
16. d-cis-6'-chloro-2',3'-dihydro-2'-methyl-spiro-(imidazolidine-4,4'-4'H-pyrano(2,3-b)pyridine)-2,5-dione (US 4,980,357);

17. spiro[imidazolidine-4,5'(6H)-quinoline]-2,5-dione-3'-chloro-7,'8'-dihydro-7'-methyl-(5'-cis) (US 5,066,659);

18. (2S,4S)-6-fluoro-2',5'-dioxospiro(chroman-4,4'-imidazolidine)-2-carboxamide (US 5,447,946); and

19. 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (ARI-509, US 5,037,831).

Other aldose reductase inhibitors include compounds having formula ARI,




ARI

or a pharmaceutically acceptable salt thereof, wherein

Z in the compound of formula ARI is O or S;

$R^1$ in the compound of formula ARI is hydroxy or a group capable of being removed *in vivo* to produce a compound of formula ARI wherein $R^1$ is OH; and

X and Y in the compound of formula ARI are the same or different and are selected from hydrogen, trifluoromethyl, fluoro, and chloro.

A preferred subgroup within the above group of aldose reductase inhibitors includes numbered compounds 1, 2, 3, 4, 5, 6, 9, 10, and 17, and the following compounds of Formula ARI:

20. 3,4-dihydro-3-(5-fluorobenzothiazol-2-ylmethyl)-4-oxophthalazin-1-yl-acetic acid [$R^1$=hydroxy; X=F; Y=H];

21. 3-(5,7-difluorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [$R^1$=hydroxy; X=Y=F];

22. 3-(5-chlorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [$R^1$=hydroxy; X=Cl; Y=H];

23. 3-(5,7-dichlorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [$R^1$=hydroxy; X=Y=Cl];

24. 3,4-dihydro-4-oxo-3-(5-trifluoromethylbenzoxazol-2-ylmethyl)phthalazin-1-ylacetic acid [$R^1$=hydroxy; X=$CF_3$; Y=H];

25. 3,4-dihydro-3-(5-fluorobenzoxazol-2-ylmethyl)-4-oxophthalazin-1-yl-acetic acid [$R^1$=hydroxy; X=F; Y=H];

26. 3-(5,7-difluorobenzoxazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [$R^1$=hydroxy; X=Y=F];

27. 3-(5-chlorobenzoxazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [$R^1$=hydroxy; X=Cl; Y=H];

28. 3-(5,7-dichlorobenzoxazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid [$R^1$=hydroxy; X=Y=Cl]; and

29. zopolrestat; 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]- [$R^1$=hydroxy; X=trifluoromethyl; Y=H].

In compounds 20-23, and 29 Z is S. In compounds 24-28, Z is O.

Of the above subgroup, compounds 20-29 are more preferred with 29 especially preferred.

An especially preferred aldose reductase inhibitor is 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl)-2-benzothiazolyl]methyl]-.

The term "acyl radical of a carboxylic acid aldose reductase inhibitor" refers to any of the above-mentioned aldose reductase inhibitors which contains a carboxylic acid group in which the carboxylic acid group is replaced with a carbonyl radical.

The aldose reductase inhibitor compounds of this invention are readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis, particularly in view of the pertinent patent specification descriptions.

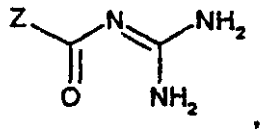
An amount of the aldose reductase inhibitor of this invention that is effective for the activities of this invention may be used. Typically, an effective dosage for the aldose reductase inhibitors of this invention is in the range of about 0.1 mg/kg/day to 100 mg/kg/day in single or divided doses, preferably 0.1 mg/kg/day to 20 mg/kg/day in single or divided doses.

Any sodium hydrogen ion exchange (NHE-1) inhibitor may be used as the second compound (active agent) of this invention for combination therapies. The term NHE-1 inhibitor refers to compounds which inhibit the sodium/proton ($Na^+/H^+$) exchange transport system and hence are useful as a therapeutic or prophylactic agent for diseases caused or aggravated by the acceleration of the sodium/proton ($Na^+/H^+$) exchange transport system, for example, cardiovascular diseases [e.g., arteriosclerosis, hypertension, arrhythmia (e.g. ischemic arrhythmia, arrhythmia due to myocardial infarction, myocardial stunning, myocardial dysfunction, arrhythmia after PTCA or after thrombolysis, etc.), angina pectoris, cardiac hypertrophy, myocardial infarction, heart failure (e.g. congestive heart failure, acute heart failure, cardiac hypertrophy, etc.), restenosis after PTCA, PTCI, shock (e.g. hemorrhagic shock, endotoxin shock, etc.)], renal diseases (e.g. diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.) organ disorders associated with ischemia or ischemic reperfusion [e.g. heart muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) surgeries, vascular surgeries, organ transplantation, non-cardiac surgeries or percutaneous transluminal coronary angioplasty (PTCA)], cerebrovascular diseases (e.g. ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e.g. disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema. NHE-1 inhibitors can also be used as an agent for myocardial protection during coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary angioplasty (PTCA), PTCI, organ transplantation, or non-cardiac surgeries. The utility of NHE-1 inhibitors as medical agents in the treatment of diseases, such as are

detailed herein in mammals (e.g. humans) for example, myocardial protection during surgery or mycardial protection in patients presenting with ongoing cardiac or cerebral ischemic events or chronic cardioprotection in patients with diagnosed coronary heart disease, or at risk for coronary heart disease, cardiac dysfunction or myocardial stunning is demonstrated by the activity of the compounds of formula I of this invention in conventional preclinical cardioprotection assays [see the *in vivo* assay in Klein, H. et al., Circulation 92:912-917 (1995); the isolated heart assay in Scholz, W. et al., Cardiovascular Research 29:260-268 (1995); the antiarrhythmic assay in Yasutake M. et al., Am. J. Physiol., 36:H2430-H2440 (1994); the NMR assay in Kolke et al., J. Thorac. Cardiovasc. Surg. 112: 765-775 (1996)] and the additional *in vitro* and *in vivo* assays described below. Such assays also provide a means whereby the activities of the compounds of formula I of this invention can be compared with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

NHE-1 inhibitors are disclosed in U.S. Pat. No. 5,698,581, European Patent Application Publication No. EP 803 501 A1, International Patent Application Publication Nos. WO 94/26709 and PCT/JP97/04650, each of which is incorporated herein by reference. The NHE-1 inhibitors disclosed therein have utility in the combination of this invention. Said NHE-1 inhibitors can be prepared as disclosed therein.

Preferred NHE-1 inhibitors include compounds of the formula NHE,



NHE

a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug, wherein

Z in the compound of formula NHE is carbon connected and is a five-membered, diaza, diunsaturated ring having two contiguous nitrogens, said ring optiortally mono-, di-, or tri-substituted with up to three substituents independently selected from $R^1$, $R^2$ and $R^3$;

or

Z in the compound of formula NHE carbon connected and is a five-membered, triaza, diunsaturated ring, said ring optionally mono- or di-substituted with up to two substituents independently selected from $R^4$ and $R^5$;

wherein $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ in the compound of formula NHE are each independently hydrogen, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkylthio, ($C_3$-$C_4$)cycloalkyl, ($C_3$-$C_7$)cycloalkyl($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkoxy($C_1$-$C_4$)alkyl, mono-N- or di-N,N-($C_1$-$C_4$)alkylcarbamoyl, M or M($C_1$-$C_4$)alkyl, any of said previous ($C_1$-$C_4$)alkyl moieties optionally having from one to nine fluorines; said ($C_1$-$C_4$)alkyl or ($C_3$-$C_4$)cycloalkyl optionally mono-or di-substituted independently with hydroxy, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkylthio, ($C_1$-$C_4$)alkylsulfinyl, ($C_1$-$C_4$)alkylsulfonyl, ($C_1$-$C_4$)alkyl, mono-N- or di-N,N-($C_1$-$C_4$)alkylcarbamoyl or mono-N- or di-N,N-($C_1$-$C_4$)alkylaminosulfonyl; and said ($C_3$-$C_4$)cycloalkyl optionally having from one to seven fluorines;

wherein M in the compound of formula NHE is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

said M in the compound of formula NHE is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from $R^6$, $R^7$ and $R^8$, wherein one of $R^6$, $R^7$ and $R^8$ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with ($C_1$-$C_4$)alkyl and additionally $R^6$, $R^7$ and $R^8$ are optionally hydroxy, nitro, halo, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkyl, formyl, ($C_1$-$C_4$)alkanoyl, ($C_1$-$C_4$)alkanoyloxy, ($C_1$-$C_4$)alkanoylamino, ($C_1$-$C_4$)alkoxycarbonylamino, sulfonamido, ($C_1$-$C_4$)alkylsulfonamido, amino, mono-N- or di-N,N-($C_1$-$C_4$)alkylamino, carbamoyl, mono-N- or di-N,N-($C_1$-$C_4$)alkylcarbamoyl, cyano,

thiol, ($C_1$-$C_4$)alkylthio, ($C_1$-$C_4$)alkylsulfinyl, ($C_1$-$C_4$)alkylsulfonyl, mono-N- or di-N,N-($C_1$-$C_4$)alkylaminosulfonyl, ($C_2$-$C_4$)alkenyl, ($C_2$-$C_4$)alkynyl or ($C_5$-$C_7$)cycloalkenyl,

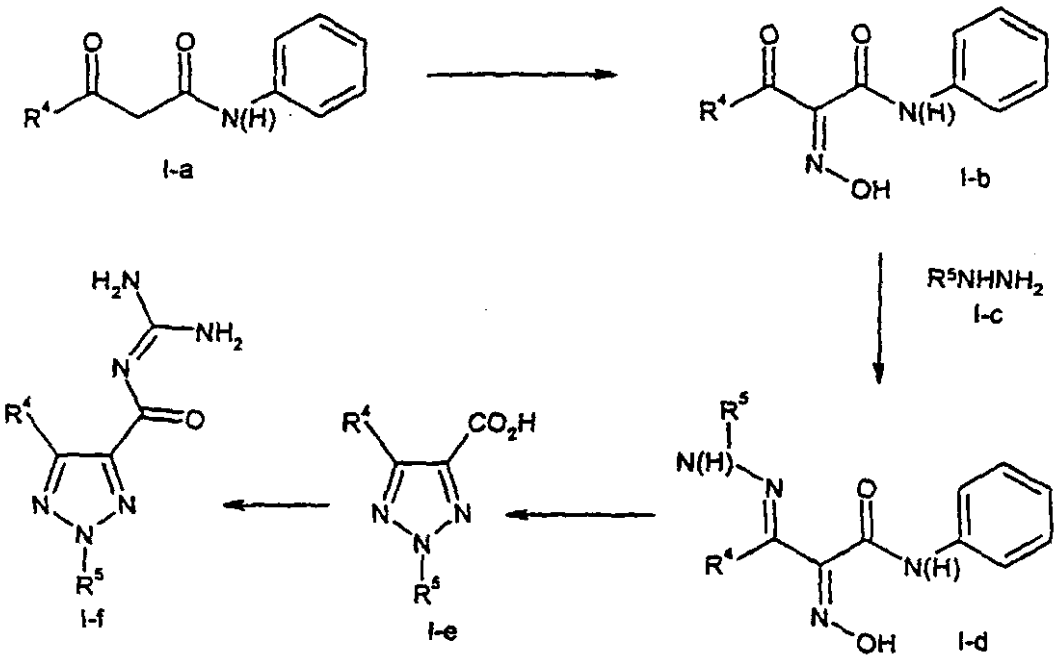
wherein said ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkyl, ($C_1$-$C_7$)alkanoyl, ($C_1$-$C_4$)alkylthio, mono-N- or di-N,N-($C_1$-$C_4$)alkylamino or ($C_3$-$C_7$)cycloalkyl $R^6$, $R^7$ and $R^8$ substituents are optionally mono- substituted independently with hydroxy, ($C_1$-$C_4$)alkoxycarbonyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkanoyl, ($C_1$-$C_4$)alkanoylamino, ($C_1$-$C_4$)alkanoyloxy, ($C_1$-$C_4$)alkoxycarbonylamino, sulfonamido, ($C_1$-$C_4$)alkylsulfonamido, amino, mono-N- or di-N,N-($C_1$-$C_4$)alkylamino, carbamoyl, mono-N- or di-N,N-($C_1$-$C_4$)alkylcarbamoyl, cyano, thiol, nitro, ($C_1$-$C_4$)alkylthio, ($C_1$-$C_4$)alkylsulfinyl, ($C_1$-$C_4$)alkylsulfonyl or mono-N- or di-N,N-($C_1$-$C_4$)alkylaminosulfonyl or optionally substituted with one to nine fluorines.

Especially preferred NHE-1 inhibitors include [1-(8-bromoquinolin-5-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(6-chloroquinolin-5-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(indazol-7-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(benzimidazol-5-yl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(1-isoquinolyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-(4-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-(quinolin-5-yl)-1H-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-(quinolin-8-yl)-1H-pyrazole-4-carbonyl]guanidine; [1-(indazol-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(indazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(benzimidazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(1-methylbenzimidazol-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; 1-(5-quinolinyl)-5-*n*-propyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(5-quinolinyl)-5-isopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [5-ethyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-methylbenzimidazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(1,4-benzodioxan-6-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(benzotriazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(3-chloroindazol-5-yl)-5-ethyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(5-quinolinyl)-5-butyl-1*H*-pyrazole-4-carbonyl]guanidine; [5-propyl-1-(6-quinolinyl)-1*H*-pyrazole-4-carbonyl]guanidine; [5-isopropyl-1-(6-quinolinyl)-1*H*-pyrazole-4-

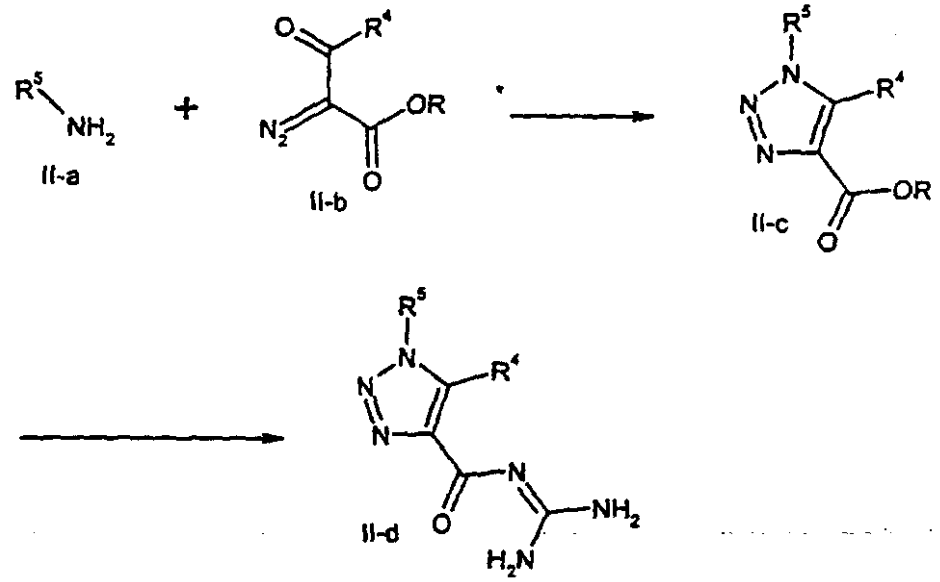
carbonyl]guanidine; [1-(2-chloro-4-methylsulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-trifluoromethyl-4-fluorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-bromophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-fluorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chloro-5-methoxyphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chloro-4-methylaminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2,5-dichlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2,3-dichlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chloro-5-aminocarbonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chloro-5-aminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-fluoro-6-trifluoromethylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chloro-5-methylsulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chloro-5-dimethylaminosulfonylphenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-trifluoromethyl-4-chlorophenyl)-5-cyclopropyl-1*H*-pyrazole-4-carbonyl]guanidine; [1-(2-chlorophenyl)-5-methyl-1H-pyrazole-4-carbonyl]guanidine; [5-methyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine; [5-ethyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-(2-trifluoromethylphenyl)-1H-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-phenyl-1H-pyrazole-4-carbonyl]guanidine; [5-cyclopropyl-1-(2,6-dichlorophenyl)-1H-pyrazole-4-carbonyl]guanidine or or a pharmaceutically acceptable salt thereof.

The preferred and especially preferred NHE-1 inhibitors disclosed in the above two paragraphs can be prepared according to methods set forth in International Patent Application No. PCT/IB99/00206 or as set forth below, where the variables in the following schemes and description refer only to the NHE-1 compounds.

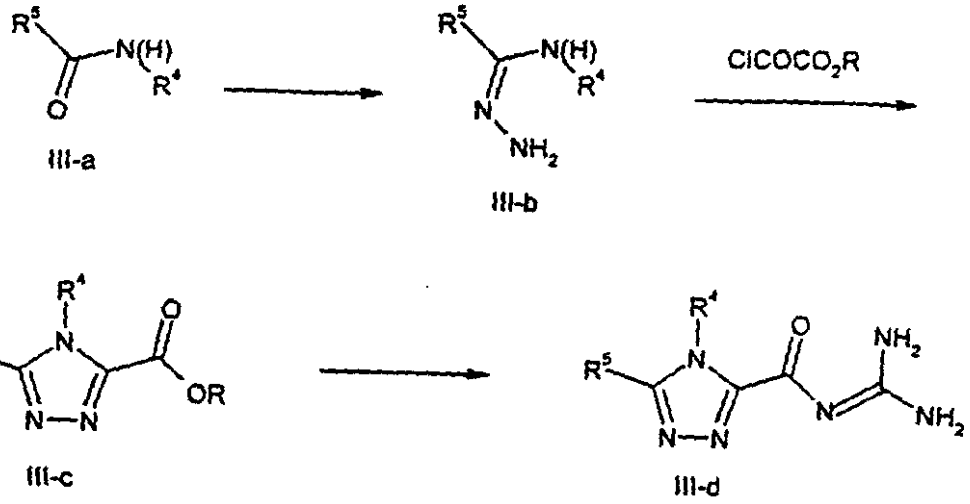
SCHEME I



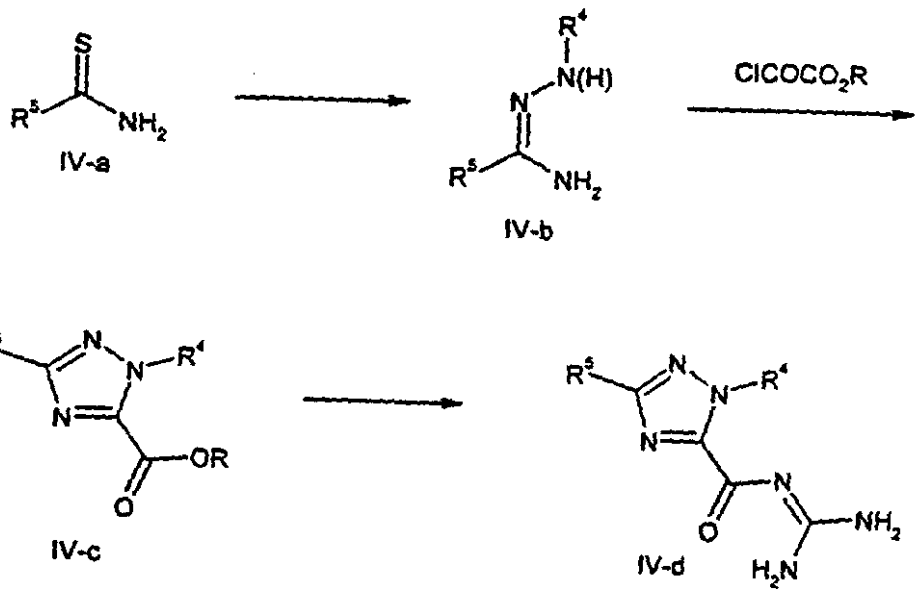

SCHEME II



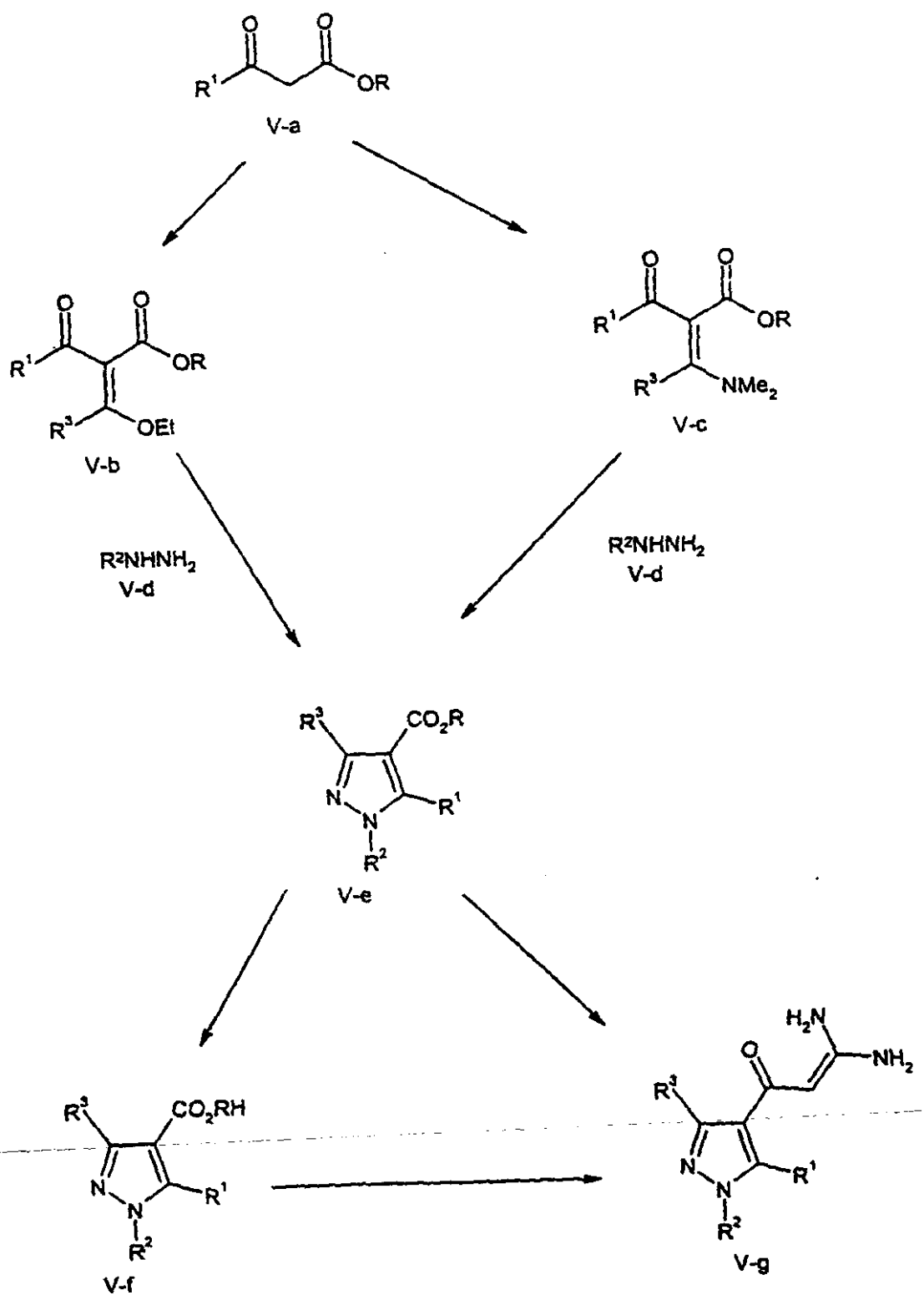
SCHEME III



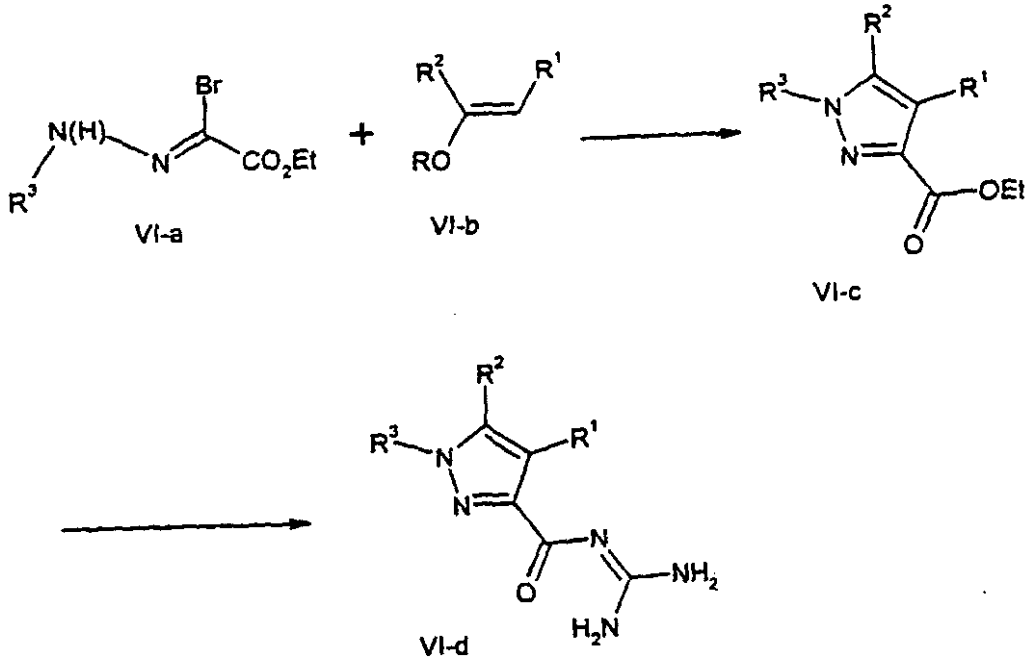

SCHEME IV



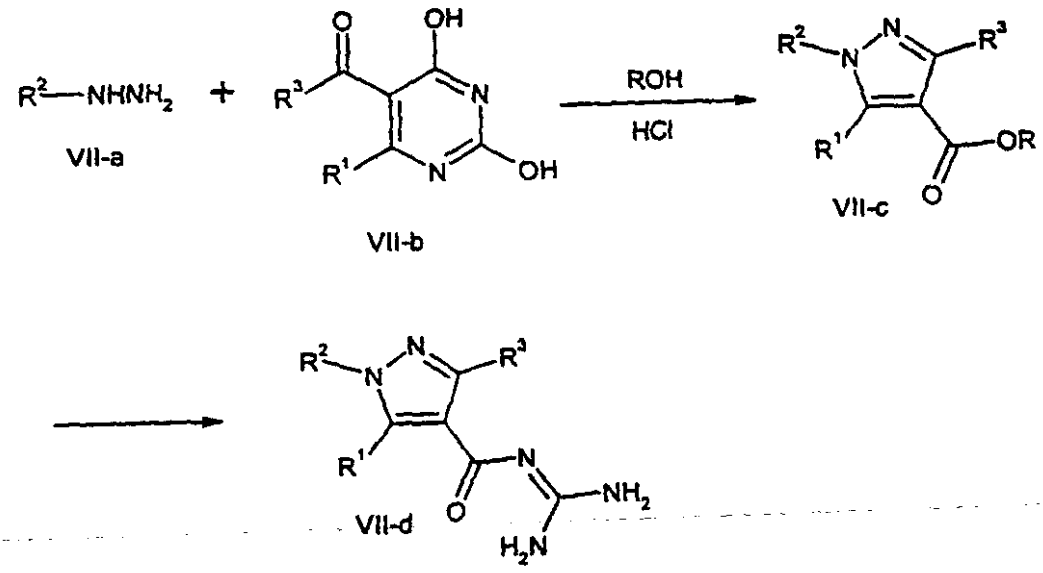
SCHEME V



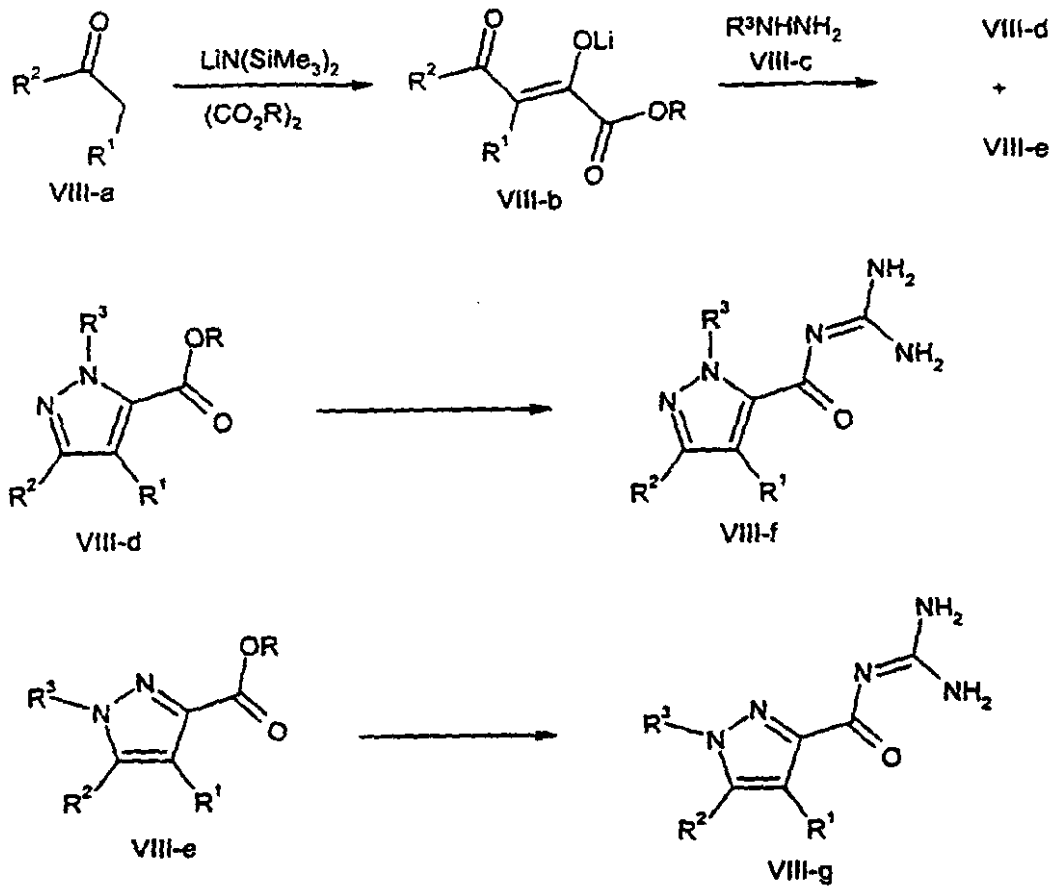
SCHEME VI




SCHEME VII



SCHEME VIII




According to Scheme I, the Formula I-a compound, wherein $R^4$ is as described above for the compound of formula NHE, is dissolved or suspended in an aqueous alkali metal hydroxide solution (e.g. 1 N sodium hydroxide) along with sodium nitrite and the mixture is added to an aqueous acidic solution (e.g. 10% v/v sulfuric acid) at a pH of about 0 at a temperature of about 0°C to about 5°C for about 30 min to about 1 hour. The resulting mixture is filtered to yield the Formula I-b oxime. Alternatively, the Formula I-a compound is dissolved in 1:1 acetic acid/propionic acid and solid sodium nitrite is added at about 0°C. The reaction mixture is stirred at about 0°C for about 2 hours, then poured into ice water and the Formula I-b oxime is obtained by filtration.

The Formula I-b compound is reacted with a Formula I-c compound, wherein $R^5$ is as described above for the compound of formula NHE in a protic solvent such as

ethanol at a temperature of about 50°C to about 110°C for about 10 min to about 1 hour to form the Formula I-d hydrazone.

The Formula I-d hydrazone is cyclized and hydrolyzed to the Formula I-e triazole in an alcoholic solvent such as 2-ethoxyethanol under basic conditions (e.g., potassium hydroxide) at a temperature of about 100 °C to about 175°C for about 1/2 hour to about 2 hours followed by acidification to yield the Formula I-e triazole acid.

The Formula I-e acid is coupled with guanidine in the presence of a suitable coupling agent. A suitable coupling agent is one which transforms a carboxylic acid into a reactive species which forms an amide linkage on reaction with an amine.

The coupling agent may be a reagent which effects this condensation in a one pot process when mixed together with the carboxylic acid and guanidine. Exemplary coupling reagents are 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride-hydroxybenzotriazole (EDC/HBT), dicyclohexylcarbodiimide/hydroxybenzotriazole(HBT), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), and diethylphosphorylcyanide. The coupling is performed in an inert solvent, preferably an aprotic solvent at a temperature of about -20°C to about 50°C for about 1 to about 48 hours, in the presence of excess guanidine as base. Exemplary solvents include acetonitrile, dichloromethane, dimethylformamide and chloroform or mixtures thereof.

The coupling agent may also be that agent which converts the carboxylic acid to an activated intermediate which is isolated and/or formed in a first step and allowed to react with guanidine in a second step. Examples of such coupling agents and activated intermediates are thionyl chloride or oxalyl chloride to form the acid chloride, cyanuric fluoride to form an acid fluoride or an alkyl chloroformate such as isobutyl or isopropenyl chloroformate or propanephosphonic anhydride (propanephosphonic acid anhydride, PPA) (with a tertiary amine base) to form a mixed anhydride of the carboxylic acid, or carbonyldiimidazole to form an acylimidazole. If the coupling agent is oxalyl chloride, it is advantageous to employ a small amount of dimethylformamide as cosolvent with another solvent (such as dichloromethane) to catalyze the formation of the acid chloride. This activated acid derivative may be coupled by mixing with excess guanidine in an appropriate solvent together with an appropriate base. Appropriate solvent/base combinations are for example, dichloromethane, dimethylformamide or acetonitrile or mixtures thereof in the presence of excess

guanidine as base. Other appropriate solvent/base combinations include water or a ($C_1$-$C_5$)alcohol or a mixture thereof together with a cosolvent such as dichloromethane, tetrahydrofuran or dioxane and a base such as sodium, potassium or lithium hydroxide in sufficient quantity to consume the acid liberated in the reaction. Use of these coupling agents and appropriate selection of solvents and temperatures are known to those skilled in the art or can be readily determined from the literature. These and other exemplary conditions useful for coupling carboxylic acids are described in Houben-Weyl, Vol XV, part II, E. Wunsch, Ed., G. Theime Verlag, 1974, Stuttgart; M. Bodansky, Principles of Peptide Synthesis, Springer-Verlag, Berlin 1984; and The Peptides, Analysis, Synthesis and Biology (ed. E. Gross and J. Meienhofer), vols 1-5 (Academic Press, NY 1979-1983).

According to Scheme II, the Formula II-a primary amine wherein $R^5$ is as described above for the compound of formula NHE is reacted with a Formula II-b α-diazo-β-keto-ester wherein $R^4$ is as described above for the compound of formula NHE, and R is lower alkyl, in the presence of titanium tetrachloride analogously to the method described in Eguchi S. *et al. Synthesis 1993*, 793 to form the Formula II-c triazole carboxylic acid ester. The Formula II-c ester is converted directly to the acylguanidine II-d by reaction with guanidine in an alcoholic solvent at a temperature of about 60 to about 110°C, preferably refluxing methanol, for a period of 8 to 20 hours.

According to Scheme III, the Formula III-a compound wherein $R^4$ and $R^5$ are as described above for the compound of formula NHE is treated with Lawesson's reagent (i.e., 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in an aprotic solvent such as dimethoxyethane at a temperature of about 20°C to about 120°C for about one to eight hours. The resulting thioamide is treated with an alkylating agent such as methyl iodide in a polar, inert solvent such as acetone, conveniently at ambient temperature for about eight hours to about forty-eight hours. The resulting compound is reacted with anhydrous hydrazine in an alcoholic solvent at a temperature of about 0°C to about 25°C for about one to eight hours to provide the Formula III-b compound (analogously as described in Doyle and Kurzer, *Synthesis 1974*, 583).

The Formula III-b compound is treated with a monoalkyloxalyl chloride in an aprotic solvent at a temperature of about 25°C to about 50°C for about one to eight

hours to provide the Formula III-c carboxylic ester compound wherein R is lower alkyl. The Formula III-c ester is directly coupled with guanidine in an alcoholic solvent at a temperature of about 60°C to about 110 °C, preferably refluxing methanol, for a period of eight to twenty hours, to prepare the Formula III-d triazole carbonyl guanidines.

According to Scheme IV the Formula IV-a compound wherein $R^5$ is as described above for the compound of formula NHE is treated with methyl iodide in an inert solvent, conveniently at ambient temperature for about four to twenty-four hours. The resulting compound is reacted with anhydrous $R^4$-hydrazine (wherein $R^4$ is as described above for the compound of formula NHE) in an alcoholic solvent at a temperature of about 0°C to about 25°C for about one to eight hours to provide the Formula IV-b amidrazone compound (analogously as described in Doyle and Kurzer, *Synthesis 1974*, 583).

The Formula IV-b compound is treated with a monoalkyloxalyl chloride in an aprotic solvent at a temperature of about 25°C to about 50°C for about one to eight hours to provide the Formula IV-c carboxylic ester compound wherein R is lower alkyl. The Formula IV-c ester is directly coupled with guanidine in an alcoholic solvent at a temperature of about 60°C to about 110°C, preferably refluxing methanol, for a period of eight to twenty hours to prepare the Formula IV-d triazole carbonyl guanidines.

According to Scheme V the Formula V-a compound wherein $R^1$ is as described above for the compound of formula NHE is combined with excess $(CH_3O)_2C(R^3)N(CH_3)_2$ (N,N-dimethyl amide dimethyl acetal) wherein $R^3$ is as described above for the compound of formula NHE, optionally in the presence of an acid catalyst such as *p*-toluenesulfonic acid at a temperature of about 90°C to about 110°C for about one to about two hours to prepare the Formula V-c compound above.

The Formula V-c compound is cyclized with a Formula V-d compound, wherein $R^2$ is as described above for the compound of formula NHE, in an inert solvent such as ethanol at a temperature of about 20°C to about 30°C for about 5 minutes to about one hour followed by heating to a temperature of about 70°C to about 110°C for about two hours to about four hours to form the Formula V-f pyrazole.

Alternatively, according to Scheme V the Formula V-a compound, wherein $R^1$ is as described above for the compound of formula NHE, is combined with a

triethylorthoester (i.e., $R^3C(OEt)_3$ wherein $R^3$ is as described above for the compound of formula NHE) and acetic anhydride at a temperature of about 120°C to about 150 °C for about two to about five hours to prepare the Formula V-b compound.

The Formula V-b compound is cyclized with a Formula V-d compound, wherein $R^2$ is as described above for the compound of formula NHE, to form the Formula V-c pyrazole.

The Formula V-c pyrazole is hydrolyzed with a base such as sodium hydroxide or lithium hydroxide in a solvent such as water and/or methanol and/or THF conveniently at ambient temperature or at elevated temperature (e.g., reflux) for about one hour to about five hours to prepare the Formula V-f acid.

The Formula V-f acid is coupled with guanidine in the presence of a suitable coupling agent as described for the above coupling of the Formula I-e acid and guanidine. In one embodiment, the Formula V-f acid is activated with thionyl chloride at a temperature of about 60°C to about 90°C for about fifteen minutes to about two hours. The resulting activated acid chloride is combined with guanidine hydrochloride and an inorganic base (e.g., sodium hydroxide) in anhydrous tetrahydrofuran and optionally methanol and/or water. The solution is heated, conveniently at reflux, for about one hour to about eight hours to prepare the Formula V-g compound.

Alternatively according to Scheme V the Formula V-e compound can be directly converted to the Formula V-g compound by several methods. For example, the Formula V-e compound can be heated in the presence of excess guanidine, in a polar protic solvent for example, methanol or isopropanol at a suitable temperature conveniently, at reflux for about one to about seventy-two hours. This transformation may also be performed by repeatedly removing the solvent, for example removing ethanol or toluene about four times, from a mixture of the Formula V-e compound and excess guanidine at a pressure of about one to about 100 mmHg and at a temperature of about 25°C to about 95°C. This reaction may also be performed in the absence of solvent by heating the mixture of the Formula V-e compound and excess guanidine at a temperature of about 100°C to about 180°C, optionally at about a pressure of about 1 to about 100 mmHg for about five minutes to about eight hours.

According to Scheme VI, the Formula VI-a compound, wherein $R^3$ is as described above for the compound of formula NHE, is reacted with the Formula VI-b compound, wherein $R^1$ and $R^2$ are as described above for the compound of formula

NHE, in an aprotic solvent at a temperature of about 0°C to about 25°C for about two hours to about twenty-four hours in the presence of an appropriate amine base, such as triethylamine, to form the Formula VI-c compound.

The resulting Formula VI-c compound is hydrolyzed and coupled with guanidine using one of the methods described in earlier Schemes, such as the method employing carbonyldiimidazole, to form the Formula VI-d compound.

According to Scheme VII, the Formula VII-a hydrazine, wherein $R^2$ is as described above for the compound of formula NHE, is reacted with the appropriate Formula VII-b compound to form the Formula VII-c pyrazole ester wherein R is lower alkyl according to the method of Bajnati, A. and Hubert-Habart, M. *Bull. Soc. Chim. France 1988*, 540. The resulting pyrazole ester is converted to the Formula VII-d acyl guanidine using the hydrolysis and coupling methods described above.

According to Scheme VIII, the Formula VIII-a compound wherein $R^2$ and $R^1$ are as described above for the compound of formula NHE is transformed to the Formula VIII-b lithium salt where R is lower alkyl according to the method described in *J. Het. Chem. 1989*, 26, 1389. The Formula VIII-b lithium salt is combined with the Formula VIII-c hydrazine, wherein $R^3$ is as described above for the compound of formula NHE, in an inert solvent such as ethanol, in the presence of a mineral acid, at a temperature of about 20°C to about 30°C for about five minutes to about one hour followed by heating to a temperature of about 70°C to about 110°C for two hours to about four hours to form both the Formula VIII-d and VIII-e pyrazoles. The Formula VIII-d and VIII-e pyrazoles are converted to the Formula VIII-f and VIII-g acyl guanidines respectively using the hydrolysis and coupling methods described above. Some of the methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in Formula I precursors). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

The compounds of formula I of the present invention, when used in combination with NHE-1 inhibitors, inhibit the sodium/proton ($Na^+/H^+$) exchange

transport system and hence are useful as a therapeutic or prophylactic agent for diseases caused or aggravated by the acceleration of the sodium/proton ($Na^+/H^+$) exchange transport system, for example, cardiovascular diseases [e.g., arteriosclerosis, hypertension, arrhythmia (e.g. ischemic arrhythmia, arrhythmia due to myocardial infarction, myocardial stunning, myocardial dysfunction, arrhythmia after PTCA or after thrombolysis, etc.), angina pectoris, cardiac hypertrophy, myocardial infarction, heart failure (e.g. congestive heart failure, acute heart failure, cardiac hypertrophy, etc.), restenosis after PTCA, PTCI, shock (e.g. hemorrhagic shock, endotoxin shock, etc.)], renal diseases (e.g. diabetes mellitus, diabetic nephropathy, ischemic acute renal failure, etc.) organ disorders associated with ischemia or ischemic reperfusion [e.g. heart muscle ischemic reperfusion associated disorders, acute renal failure, or disorders induced by surgical treatment such as coronary artery bypass grafting (CABG) surgeries, vascular surgeries, organ transplantation, non-cardiac surgeries or percutaneous transluminal coronary angioplasty (PTCA)], cerebrovascular diseases (e.g. ischemic stroke, hemorrhagic stroke, etc.), cerebro ischemic disorders (e.g. disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema.

Preferably, the compounds of formula I of this invention can be used in combination with NHE-1 inhibitors as agents for myocardial protection before, during, or after coronary artery bypass grafting (CABG) surgeries, vascular surgeries, percutaneous transluminal coronary angioplasty (PTCA), organ transplantation, or non-cardiac surgeries.

Preferably, the compounds of formula I of this invention can be used in combination with NHE-1 inhibitors as agents for myocardial protection in patients presenting with ongoing cardiac (acute coronary syndromes, e.g. myocardial infarction or unstable angina) or cerebral ischemic events (e.g. stroke).

Preferably, the compounds of formula I of this invention can be used in combination with NHE-1 inhibitors as agents for chronic myocardial protection in patients with diagnosed coronary heart disease (e.g. previous myocardial infarction or unstable angina) or patients who are at high risk for myocardial infarction (age greater than 65 and two or more risk factors for coronary heart disease).

In addition, a combination of the compounds of formula I of this invention with NHE-1 inhibitors has a strong inhibitory effect on the proliferation of cells, for example

the proliferation of fibroblast cells and the proliferation of the smooth muscle cells of the blood vessels. For this reason, the combination of the compounds of formula I of this invention with NHE-1 inhibitors of this invention is a valuable therapeutic agent for use in diseases in which cell proliferation represents a primary or secondary cause and may, therefore, be used as antiatherosclerotic agents, and as agents against diabetic late complications, cancerous diseases, fibrotic diseases such as pulmonary fibrosis, hepatic fibrosis or renal fibrosis, glomerular nephrosclerosis, organ hypertrophies or hyperplasias, in particular hyperplasia or hypertrophy of the prostate, pulmonary fibrosis, diabetic complications or recurrent stricture after PTCA, or diseases caused by endothelial cell injury.

The utility of the combination of compounds of the present invention with NHE-1 inhibitors as medical agents in the treatment of diseases, such as are detailed herein in mammals (e.g. humans) for example, myocardial protection during surgery or mycardial protection in patients presenting with ongoing cardiac or cerebral ischemic events or chronic cardioprotection in patients with diagnosed coronary heart disease, or at risk for coronary heart disease, cardiac dysfunction or myocardial stunning is demonstrated by the activity of said combination in conventional preclinical cardioprotection assays [see the *in vivo* assay in Klein, H. et al., Circulation 92:912-917 (1995); the isolated heart assay in Scholz, W. et al., Cardiovascular Research 29:260-268 (1995); the antiarrhythmic assay in Yasutake M. et al., Am. J. Physiol., 36:H2430-H2440 (1994); the NMR assay in Kolke et al., J. Thorac. Cardiovasc. Surg. 112: 765-775 (1996)] and the additional *in vitro* and *in vivo* assays described below. Such assays also provide a means whereby the activities of the compounds of formula I of this invention can be compared with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

**Measurement of Human NHE-1 Inhibitory Activity**

Methodologies for measurement of human NHE-1 activity and inhibitor potency are based on those published by Watson et al., Am. J. Physiol., 24:G229-G238, 1991), where NHE-mediated recovery of intracellular pH is measured following intracellular acidification. Thus, fibroblasts stably expressing human NHE-1 (Counillon; L. et al., Mol. Pharmacol., 44:1041-1045 (1993) are plated onto collagen coated 96 well plates (50,000/well) and grown to confluence in growth media (DMEM

high glucose, 10% fetal bovine serum, 50 u/ml penicillin and streptomycin). Confluent plates are incubated for 30 minutes at 37°C with the pH sensitive fluorescent probe BCECF (5 μM; Molecular Probes, Eugene, OR). BCECF loaded cells are incubated for 30 minutes at 37°C in acid loading media (70 mM choline chloride, 50 mM $NHCl_4$, 5 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, 5 mM glucose, 10 mM HEPES, pH 7.5), and then placed in a Fluorescent Imaging Plate Reader (Molecular Devices, CA). BCECF fluorescence is monitored using excitation and emission wavelengths of 485 nM and 525 nM, respectively. Intracellular acidification is initiated via rapid replacement of acid loading media with recovery media (120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, 5 mM glucose, 10 mM HEPES, pH 7.5) ± test combination, and NHE-mediated recovery of intracellular pH is monitored as the subsequent time-dependent increase BCECF fluorescence. The potency of the combinations of the compounds of formula I of this invention with NHE-1 inhibitors is calculated as the concentration that reduces recovery of intracellular pH by 50% ($IC_{50}$). Under these conditions reference NHE inhibitors amiloride and HOE-642 had $IC_{50}$ values for human NHE-1 of 50 μM and 0.5 μM, respectively.

As background information, it is noted that brief periods of myocardial ischemia followed by coronary artery reperfusion protects the heart from subsequent severe myocardial ischemia (Murry et al., Circulation 74:1124-1136, 1986).

The therapeutic effects of the combination of the compounds of formula I of this invention with NHE-1 inhibitors in preventing heart tissue damage resulting from an ischemic insult can be demonstrated *in vitro* along lines presented in Liu *et al.* (*Cardiovasc. Res., 28:1057-1061, 1994), as described specifically herein.* Cardioprotection, as indicated by a reduction in infarcted myocardium, can be induced pharmacologically using adenosine receptor agonists in isolated, retrogradely perfused rabbit hearts as an *in vitro* model of myocardial ischemic preconditioning (Liu *et al.*, Cardiovasc. Res., 28:1057-1061, 1994). The *in vitro* test described below demonstrates that a test compound or, in this case a test combination (*i.e.*, a combination of a compound of formula I with an NHE-1 antagonist) can also pharmacologically induce cardioprotection, *i.e.*, reduced myocardial infarct size, when administered to a rabbit isolated heart. The effects of the test combination are compared to ischemic preconditioning and the A1/A3 adenosine agonist, APNEA ($N^6$-[2-(4-aminophenyl)ethyl]adenosine), that has been shown to pharmacologically

induce cardioprotection in the rabbit isolated heart (Liu *et al.*, Cardiovasc. Res., 28:1057-1061, 1994). The exact methodology is described below.

The protocol used for these experiments closely follows that described by Liu *et al.*, Cardiovasc. Res., 28:1057-1061, 1994. Male New Zealand White rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 mg/kg, i.v.). After deep anesthesia is achieved (determined by the absence of an ocular blink reflex) the animal is intubated and ventilated with 100% $O_2$ using a positive pressure ventilator. A left thoracotomy is performed, the heart exposed, and a snare (2-0 silk) is placed loosely around a prominent branch of the left coronary artery, approximately 2/3 of the distance towards the apex of the heart. The heart is removed from the chest and rapidly (<30 sec) mounted on a Langendorff apparatus. The heart is retrogradely perfused in a non-recirculating manner with a modified Krebs solution (NaCl 118.5 mM, KCl 4.7 mM, Mg $SO_4$ 1.2 mM, $KH_2PO_4$ 1.2 mM, $NaHCO_3$ 24.8 mM, $CaCl_2$ 2.5 mM, and glucose 10 mM), at a constant pressure of 80 mmHg and a temperature of 37°C. Perfusate pH is maintained at 7.4-7.5 by bubbling with 95% $O_2$/5% $CO_2$. Heart temperature is tightly controlled by using heated reservoirs for the physiological solution and water jacketing around both the perfusion tubing and the isolated heart. Heart rate and left ventricular pressures are determined via a latex balloon which is inserted in the left ventricle and connected by stainless steel tubing to a pressure transducer. The intraventricular balloon is inflated to provide a systolic pressure of 80-100 mmHg, and a diastolic pressure ≤ 10 mmHg. Total coronary flow is also continuously monitored using an in-line flow probe and normalized for heart weight.

The heart is allowed to equilibrate for 30 minutes, over which time the heart must show stable left ventricular pressures within the parameters outlined above. If the heart rate falls below 180 bpm at any time prior to the 30 minutes period of regional ischemia, the heart is paced at about 200 bpm for the remainder of the experiment. Ischemic preconditioning is induced by total cessation of cardiac perfusion (global ischemia) for 5 minutes, followed by reperfusion for 10 minutes. The regional ischemia is provided by tightening the snare around the coronary artery branch. Following the 30 minutes regional ischemia, the snare is released and the heart reperfused for an additional 120 minutes.

Pharmacological cardioprotection is induced by infusing the test combination, i.e., a combination of a compound of formula I with an NHE-1 inhibitor, at

predetermined concentrations, starting 30 minutes prior to the 30 minutes regional ischemia, and continuing until the end of the 120 minutes reperfusion period. Hearts which receive the test combination do not undergo the period of ischemic preconditioning. The reference compound, APNEA (500 nM) is perfused through hearts (which do not receive the test compound) for a 5 minutes period which ends 10 minutes before the 30 minutes regional ischemia.

At the end of the 120 minutes reperfusion period, the coronary artery snare is tightened, and a 0.5% suspension of fluorescent zinc cadmium sulfate particles (1-10 μM) Duke Scientific Corp.(Palo Alto, CA) is perfused through the heart; this stains all of the myocardium, except that area-at-risk for infarct development (area-at-risk). The heart is removed from the Langendorff apparatus, blotted dry, wrapped in aluminum foil and stored overnight at -20°C. The next day, the heart is sliced into 2 mm transverse sections from the apex to the top of the ventricles. The slices are stained with 1% triphenyl tetrazolium chloride (TTC) in phosphate-buffered saline for 20 minutes at 37°C. Since TTC reacts with living tissue (containing NAD-dependent dehydrogenases), this stain differentiates between living (red stained) tissue, and dead tissue (unstained infarcted tissue). The infarcted area (no stain) and the area-at-risk (no fluorescent particles) are calculated for each slice of left ventricle using a precalibrated image analyzer. To normalize the ischemic injury for differences in the area-at-risk between hearts, the data is expressed as the ratio of infarct area *vs.* area-at-risk (%IA/AAR). All data are expressed as mean ± SE and compared statistically using a Mann-Whitney non-parametric test with a Bonferroni correction for multiple comparisons. Significance is considered as $p < 0.05$.

The results from the above *in vitro* test demonstrate that a combination of a compound of this invention with an NHE-1 inhibitor induce significant cardioprotection relative to the control group.

The therapeutic effects of a combination of a compound of formula I of this invention with an NHE-1 inhibitor in preventing heart tissue damage otherwise resulting from an ischemic insult can also be demonstrated *in vivo* along lines presented in Liu et al. (Circulation, Vol. 84:350-356, 1991) as described specifically herein. The *in vivo* assay tests the cardioprotection of the test combination, i.e., a compound of formula I together with an NHE-1 inhibitor, relative to the control group which receives saline vehicle. Cardioprotection, as indicated by a reduction in

infarcted myocardium, can be induced pharmacologically using intravenously administered adenosine receptor agonists in intact, anesthetized rabbits studied as an *in situ* model of myocardial ischemic preconditioning (Liu et al., Circulation 84:350-356, 1991). The *in vivo* assay tests whether the instant combination of a compound of formula I with an NHE-1 inhibitor can pharmacologically induce cardioprotection, i.e., reduced myocardial infarct size, when parenterally administered to intact, anesthetized rabbits. The effects of the combination of a compound of formula I of this invention with an NHE-11 inhibitor can be compared to ischemic preconditioning using the A1 adenosine agonist, $N^6$-1-(phenyl-2R-isopropyl) adenosine (PIA) that has been shown to pharmacologically induce cardioprotection in intact anesthetized rabbits studied *in situ* (Liu et al., Circulation 84:350-356, 1991). The methodology is described below.

Surgery: New Zealand White male rabbits (3-4 kg) are anesthetized with sodium pentobarbital (30 mg/kg, i.v.). A tracheotomy is performed via a ventral midline cervical incision and the rabbits are ventilated with 100% oxygen using a positive pressure ventilator. Catheters are placed in the left jugular vein for drug administration and in the left carotid artery for blood pressure measurements. The hearts are then exposed through a left thoracotomy and a snare (00 silk) placed around a prominent branch of the left coronary artery. Ischemia is induced by pulling the snare tight and clamping it in place. Releasing the snare allows the affected area to reperfuse. Myocardial ischemia is evidenced by regional cyanosis; reperfusion is evidenced by reactive hyperemia.

Protocol: Once arterial pressure and heart rate have been stable for at least 30 minutes the test is started. Ischemic preconditioning is induced by occluding the coronary artery for 5 minutes followed by a 10 minutes reperfusion. Pharmacological preconditioning is induced by infusing the test combination, i.e., a combination of a compound of formula I of this invention with an NHE-1 inhibitor, over, for example, 5 minutes and allowing 10 minutes before further intervention or by infusing the adenosine agonist, PIA (0.25 mg/kg). Following ischemic preconditioning, pharmacological preconditioning or no conditioning (unconditioned, vehicle control) the artery is occluded for 30 minutes and then reperfused for two hours to induce myocardial infarction. The test combination and PIA are dissolved in saline or other suitable vehicle and delivered at 1 to 5 mg/kg, respectively.

Staining (Liu et al., *Circulation* 84:350-356, 1991): At the end of the 2 hour reperfusion period, the hearts are quickly removed, hung on a Langendorff apparatus, and flushed for 1 minute with normal saline heated to body temperature (38°C). The silk suture used as the snare is then tied tightly to reocclude the artery and a 0.5% suspension of fluorescent zinc cadmium sulphate particles (1-10 μm) Duke Scientific Corp. (Palo Alto, CA) is infused with the perfusate to stain all of the myocardium except the area at risk (nonfluorescent ventricle). The hearts are then quickly frozen and stored overnight at -20°c. On the following day, the hearts are cut into 2 mm slices and stained with 1% triphenyl tetrazolium chloride (TTC). Since TTC reacts with living tissue, this stain differentiates between living (red stained) tissue, and dead tissue (unstained infarcted tissue). The infarcted area (no stain) and the area at risk (no fluorescent particles) are calculated for each slice of left ventricle using a pre-calibrated image analyzer. To normalize the ischemic injury for differences in the area at risk between hearts, the data is expressed as the ratio of infarct area vs. area at risk (%IA/AAR). All data are expressed as Mean±SEM and compared statistically using single factor ANOVA or Mann Whitney non parametric test. Significance is considered as $p<0.05$.

The combination of a compound of formula I of this invention with an NHE-1 inhibitor can be tested for their utility in reducing or preventing ischemic injury in non-cardiac tissues, for example, the brain, or the liver, utilizing procedures reported in the scientific literature. The combination of a compound of formula I of this invention with an NHE-1 inhibitor in such tests can be administered by the preferred route and vehicle of administration and at the preferred time of administration either prior to the ischemic episode, during the ischemic episode, following the ischemic episode (reperfusion period) or during any of the below-mentioned experimental stages.

The benefit of the combination of NHE-1 inhibitors and compounds of formula I of this invention to reduce ischemic brain damage can be demonstrated, for example, in mammals using the method of Park, et al (Ann. Neurol. 1988;24:543-551). According to the procedure of Park, et al., adult male Sprague Dawley rats are anesthetized initially with 2% halothane, and thereafter by mechanical ventilation with a nitrous oxide-oxygen mixture (70%:30%) containing 0.5-1% halothane. A tracheostomy is then performed. The stroke volume of the ventilator is adjusted to maintain arterial carbon dioxide tension at approximately 35 mm Hg and adequate

arterial oxygenation ($PaO_2$>90 mm Hg). Body temperature can be monitored by a rectal thermometer, and the animals can be maintained normothermic, if necessary, by external heating. The animals next undergo subtemporal craniectomy to expose the main trunk of the left middle cerebral artery (MCA) under an operating microscope, and the exposed artery is occluded with microbipolar coagulation to generate large ischemic lesions in the cerebral cortex and basal ganglia. After three hours of MCA occlusion, the rats are deeply anesthetized with 2% halothane and a thoracotomy is performed to infuse heparinized saline into the left ventricle. The effluent is collected via an incision of the right atrium. The saline washout is followed by approximately 200 ml of a 40% formaldehyde, glacial acetic acid and absolute methanol solution (FAM; 1:1:8, v/v/v), then the animals are decapitated and the head is stored in fixative for 24 hours. The brain is then removed, dissected, embedded in paraffin wax, and sectioned (approximately 100 sections 0.2mm per brain). The sections are then stained with hematoxylin-eosin or with a combination of cresyl violet and Luxol fast blue, and examined by light microscopy to identify and quantitate the ischemic damage using a precalibrated image analyzer. The ischemic volumes and areas are expressed in absolute units ($mm^3$ and $mm^2$) and as a percentage of the total region examined. The effect of the compositions and methods of this invention to reduce ischemic brain damage induced by MCA occlusion is noted based on a reduction in the area or volume of relative or absolute ischemic damage in the brain sections from the rats in the treatment group compared to brain sections from rats in a placebo-treated control group.

Other methods which could alternatively be utilized to demonstrate the benefit of the invention to reduce ischemic brain damage include those described by Nakayama, et al. in Neurology 1988, 38:1667-1673; Memezawa, et al. in Stroke 1992, 23:552-559; Folbergrova, et al. in Proc. Natl. Acad. Sci 1995, 92:5057-5059; and Gotti, et al. in Brain Res. 1990, 522:290-307.

The benefit of the compositions and methods of this invention to reduce ischemic liver damage can be demonstrated, for example, in mammals using the method of Yokoyama, et al. (Am. J. Physiol. 1990;258:G564-G570). According to the procedure of Yokoyama, et al., fasted adult male Sprague Dawley rats are anesthetized with sodium pentobarbital (40 mg/kg i.p.), then the animals are tracheotomized and mechanically ventilated with room air. The liver is extirpated and

placed in an environmental chamber maintained at constant temperature (37 °C), then perfused through the portal vein at a constant pressure of 15 cm $H_20$ with a modified, hemoglobin-free Krebs-Henseleit buffer (in mM: 118 NaCl, 4.7 KCl, 27 $NaHCO_3$, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 $KH_2PO_4$, 0.05 EDTA, and 11 mM glucose, plus 300 U heparin). The pH of the perfusate is maintained at 7.4 by gassing the buffer with 95% $O_2$ - 5% $CO_2$. Each liver is perfused at a flow rate of 20 ml/minutes in a single-pass manner for a 30 minutes washout and equilibration period (preischemic period), followed by a 2 hour period of global ischemia, and then a 2 hour period of reperfusion under conditions identical to the preischemic period. Aliquots (20 ml) of the perfusate are collected during the preischemic period, immediately after the occlusive ischemic period, and every 30 minutes of the 2 hour reperfusion period. The perfusate samples are assayed for the appearance of hepatocellular enzymes, for example, aspartate amino-transferase (AST), alanine amino-transferase (ALT), and lactate dehydrogenase (LDH), which are taken to quantitatively reflect the degree of ischemic liver tissue damage during the procedure. AST, ALT, and LDH activities in the perfusate can be determined by several methods, for example, by the reflectometry method using an automatic Kodak Ektachem 500 analyzer reported by Nakano, et al. (Hepatology 1995;22:539-545). The effect of the compositions and methods of this invention in reducing ischemic liver damage induced by occlusion is noted based on a reduction in the release of hepatocellular enzymes immediately following the occlusive period and/or during the postischemic-reperfusion period in the perfused livers from the rats in the treatment group compared to perfused livers from rats in a placebo-treated control group.

Other methods and parameters which could alternatively be utilized to demonstrate the benefit of the compositions and methods of this invention in reducing ischemic liver damage include those described by Nakano, et al. (Hepatology 1995;22:539-545).

Any glycogen phosphorylase inhibitor may be used as the second compound of this invention. The term glycogen phosphorylase inhibitor refers to any substance or agent or any combination of substances and/or agents which reduces, retards, or eliminates the enzymatic action of glycogen phosphorylase. The currently known enzymatic action of glycogen phosphorylase is the degradation of glycogen by catalysis of the reversible reaction of a glycogen macromolecule and inorganic

phosphate to glucose-1-phosphate and a glycogen macromolecule which is one glucosyl residue shorter than the original glycogen macromolecule (forward direction of glycogenolysis). Such actions are readily determined by those skilled in the art according to standard assays (e.g., as described hereinafter). A variety of these compounds are included in the following published PCT patent applications: PCT application publication WO 96/39384 and WO96/39385. However, other glycogen phosphorylase inhibitors will be known to those skilled in the art.

Compounds of formula I, prodrugs thereof, mutual prodrugs of the compounds of formula I with aldose reductase inhibitors, pharmaceutically acceptable salts of any of the above and pharmaceutical compositions comprising a compound of formula I, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and either (a) an aldose reductase inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said aldose reductase inhibitor or said prodrug, (b) a NHE-1 inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug, or a glycogen phosphorylase inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said glycogen phosphorylase inhibitor or said prodrug are hereinafter referred to, collectively, as "the active compounds and comopositions of this invention."

The active compounds and compositions of this invention may be administered to a subject in need of treatment by a variety of conventional routes of administration, including orally, parenterally and topically. In general, compounds of the formula I and their pharmaceutically acceptable salts will be administered orally or parenterally at dosages between about 0.001 and about 100 mg/kg body weight of the subject to be treated per day, preferably from about 0.01 to 10 mg/kg, in single or divided doses. Mutual prodrugs of compounds of the formula I and aldose reductase inhibitors will generally be administered orally or parenterally at dosages between about 0.001 and about 100 mg/kg body weight of the subject to be treated per day, preferably from about 0.01 to about 10 mg/kg, in single or divided doses. Compositions containing both a compound of the formula I and an aldose reductase inhibitor will generally be administered orally or parenterally at dosages between about 0.001 and about 100 mg of each active component (i.e., the compound of formula I and the aldose reductase inhibitor) per kg body weight of the subject to be treated per day, preferably from about 0.01 to about 10 mg/kg. Compositions

containing both a compound of formula I and a NHE-1 inhibitor will generally be administered orally or parenterally at dosages between about 0.001 and 100 mg of said compound of formula I per kg body weight of the subject to be treated per day and about 0.001 to 100 mg/kg/day of the NHE-1 inhibitor. An especially preferred dosage contains between about 0.01 and 10 mg/kg/day of said compound of formula I and between about 0.01 and 50 mg/kg/day of said NHE-1 inhibitor. Compositions containing both a compound of formula I and a glcogen phosphorylase inhibitor will generally be administered orally or parenterally at dosages between about 0.001 and 100 mg of said compound of formula I per kg body weight of the subject to be treated per day and 0.005 to 50 mg/kg/day of said glycogen phosphorylase inhibitor, preferably 0.01 and 10 mg/kg/day of said compound of formula and 0.01 to 25 mg/kg/day of said glycogen phosphorylase inhibitor and most preferably 0.01 and 10 mg/kg/day of said compound of formula and 0.1 to 15 mg/kg/day of said glycogen phosphorylase inhibitor. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active compounds and compositions of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the active compounds of formula I of this invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules.

Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of the active compounds and compositions of this invention in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solutions may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Administration of the compounds of formula I of this invention can be via any method which delivers a compound of this invention preferentially to the desired tissue (e.g., nerve, kidney, retina and/or cardiac tissues). These methods include oral routes, parenteral, intraduodenal routes, etc. Generally, the compounds of the present invention are administered in single (e.g., once daily) or multiple doses or via constant infusion.

The compositions of this invention comprising a compound of formula I in combination with an NHE-1 inhibitor are useful, for example, in reducing or minimizing damage effected directly to any tissue that may be susceptible to ischemia/reperfusion injury (e.g., heart, brain, lung, kidney, liver, gut, skeletal muscle, retina) as the result of an ischemic event (e.g., myocardial infarction). The composition is therefore usefully employed prophylactically to prevent, i.e. (prospectively or prophylactically) to blunt or stem, tissue damage (e.g., myocardial tissue) in patients who are at risk for ischemia (e.g., myocardial ischemia).

Generally, a compound of formula I of this invention is administered orally, or parenterally (e.g., intravenous, intramuscular, subcutaneous or intramedullary). Topical administration may also be indicated, for example, where the patient is suffering from gastrointestinal disorders or whenever the medication is best applied to the surface of a tissue or organ as determined by the attending physician.

The amount and timing of compounds administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgement of the prescribing physician. Thus, because of patient to patient variability, the dosages given below are a guideline and the physician may titrate doses of the drug to achieve the treatment that the physician considers appropriate for the patient. In considering the degree of treatment desired, the physician must balance a variety of factors such as age of the patient, presence of preexisting disease, as well as presence of other diseases.

Thus, for example, in one mode of administration the compounds of formula I of this invention may be administered just prior to surgery (e.g., within twenty-four hours before surgery for example cardiac surgery) during or subsequent to surgery (e.g., within twenty-four hours after surgery) where there is risk of myocardial ischemia. The compounds of formula I of this invention may also be administered in a chronic daily mode.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of formula I of this invention together with a pharmaceutically acceptable vehicle or diluent. Thus, the compounds of formula I of this invention can be administered individually or together in any conventional oral, parenteral, rectal or transdermal dosage form.

For purposes of transdermal (e.g.,topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1995).

Pharmaceutical compositions according to the invention may contain for example 0.0001%-95% of the compound(s) of this invention. In any event, the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the disease/condition of the subject being treated.

The two different compounds of this combination of this invention can be co-administered simultaneously or sequentially in any order, or as a single pharmaceutical composition comprising a compound of Formula I and an aldose reductase inhibitor as described above or a glycogen phosphorylase inhibitor as described above or a cardiovascular agent.

Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of Formula I a prodrug thereof or a salt of such compound or prodrug and a second compound as described above. The kit comprises means for containing the separate compositions such as a container, a divided bottle or a divided foil packet. Typically the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of Formula I compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of formula I of this invention generally will be administered in a convenient formulation. The following formulation examples are illustrative only and are not intended to limit the scope of the present invention.

In the formulations which follow, "active ingredient" means a compound(s) of this invention.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Active ingredient | 0.25-100 |
| Starch, NF | 0-650 |
| Starch flowable powder | 0-50 |
| Silicone fluid 350 centistokes | 0-15 |

A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

| Ingredient | Quantity (mg/tablet) |
|---|---|
| Active ingredient | 0.25-100 |
| Cellulose, microcrystalline | 200-650 |
| Silicon dioxide, fumed | 10-650 |
| Stearate acid | 5-15 |

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.25-100 mg of active ingredients are made up as follows:

Formulation 3: Tablets

| Ingredient | Quantity (mg/tablet) |
|---|---|
| Active ingredient | 0.25-100 |
| Starch | 45 |
| Cellulose, microcrystalline | 35 |
| Polyvinylpyrrolidone (as 10% solution in water) | 4 |
| Sodium carboxymethyl cellulose | 4.5 |
| Magnesium stearate | 0.5 |
| Talc | 1 |

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° - 60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.25-100 mg of active ingredient per 5 ml dose are made as follows:

Formulation 4: Suspensions

| Ingredient | Quantity (mg/5 ml) |
|---|---|
| Active ingredient | 0.25-100 mg |
| Sodium carboxymethyl cellulose | 50 mg |
| Syrup | 1.25 mg |
| Benzoic acid solution | 0.10 mL |
| Flavor | q.v. |
| Color | q.v. |
| Purified Water to | 5 mL |

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume. An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

| Ingredient | Quantity (% by weight) |
|---|---|
| Active ingredient | 0.25 |
| Ethanol | 25.75 |
| Propellant 22 (Chlorodifluoromethane) | 74.00 |

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Suppositories are prepared as follows:

Formulation 6: Suppositories

| Ingredient | Quantity (mg/suppository) |
|---|---|
| Active ingredient | 250 |
| Saturated fatty acid glycerides | 2,000 |

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal

necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

An intravenous formulation is prepared as follows:

Formulation 7: Intravenous Solution

| Ingredient | Quantity |
|---|---|
| Active ingredient | 25 mg-10,000 mg |
| Isotonic saline | 1,000 mL |

The solution of the above ingredients is intravenously administered to a patient.

The active ingredient above may also be a combination of agents.

GENERAL EXPERIMENTAL PROCEDURES

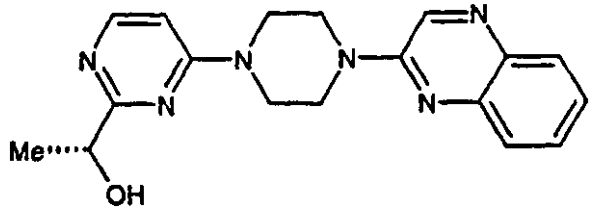
Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are uncorrected. $^1$H NMR spectra were obtained on a Bruker AM-250 (Bruker Co., Billerica, Massachusetts), a Bruker AM-300, a Varian XL-300 (Varian Co., Palo Alto, California), or a Varian Unity 400 at about 23 °C at 250, 300, or 400 MHz for proton. Chemical shifts are reported in parts per million (δ) relative to residual chloroform (7.26 ppm), dimethylsulfoxide (2.49 ppm), or methanol (3.30 ppm) as an internal reference. The peak shapes and descriptors for the peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; c, complex; br, broad; app, apparent. Low-resolution mass spectra were obtained under thermospray (TS) conditions on a Fisons (now Micromass) Trio 1000 Mass Spectrometer (Micromass Inc., Beverly, Massachusetts), under chemical-ionization (CI) conditions on a Hewlett Packard 5989A Particle Beam Mass Spectrometer (Hewlett Packard Co., Palo Alto, California), or under atmospheric pressure chemical ionization (APCI) on a Fisons (now Micromass) Platform II Spectrometer. Optical rotations were obtained on a Perkin-Elmer 241 MC Polarimeter (Perkin-Elmer, Norwalk, Connecticut) using a standard path length of 1 dcm at about 23 °C at the indicated concentration in the indicated solvent.

Liquid column chromatography was performed using forced flow (flash chromatography) of the indicated solvent on either Baker Silica Gel (40 μm, J. T. Baker, Phillipsburg, New Jersey) or Silica Gel 60 (EM Sciences, Gibbstown, New Jersey) in glass columns or using low nitrogen or air pressure in Flash 40™ or Flash

12™ (Biotage, Charlottesville, Virginia) cartridges. Radial chromatography was performed using a Chromatron (Harrison Research, Palo Alto, California). The terms "concentrated" and "evaporated" refer to removal of solvent using a rotary evaporator at water aspirator pressure or at similar pressures generated by a Büchi B-171 Vacobox (Brinkmann Instruments, Inc., Westbury, New York) or a Büchi B-177 Vacobox with a bath temperature equal to or less than 50 °C. Reactions requiring the use of hydrogen gas at pressures greater than 1 atmosphere were run using a Parr hydrogen apparatus (Parr Instrument Co., Moline, Illinois). Unless otherwise specified, reagents were obtained from commercial sources. The abbreviations "d", "h", and "min" stand for "day(s)", "hour(s)", and "minute(s)", respectively.

Example 1

(R)-1-[4-(4-Quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



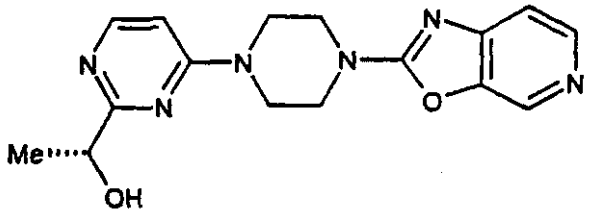

**Step A:** (R)-1-[4-(4-Quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate. To a solution of (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl acetate (prepared according to the method of Preparation Five, 7.3 g, 36.2 mmol) in isopropanol (240 mL) was added triethylamine (10.1 mL, 72.4 mmol) followed by 2-(1-piperazinyl)quinoxaline (10.1 g, 47.1 mmol; *J. Med. Chem.* **1981**, *24*, 93). This mixture was stirred at room temperature overnight then concentrated. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with chloroform (5x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (2% methanol/chloroform) to give 12.4 g (91%) of the title compound of Example 1, Step A as a yellow foam. $^1$H NMR ($CDCl_3$, 250 MHz) δ 8.61 (s, 1H), 8.27 (d, 1H), 7.91 (dd, 1H), 7.72 (dd, 1H), 7.61 (td, 1H), 7.44 (td, 1H), 6.43 (d, 1H), 5.70 (q, 1H), 3.96-3.84 (c, 8H), 2.18 (s, 3H), 1.61 (d, 3H); MS (CI/$NH_3$) 379 ($MH^+$).

**Step B:** (R)-1-[4-(4-Quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol. To a solution of (R)-1-[4-(4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate (prepared according to the method of Example 1, Step A, 14.1 g, 37.2 mmol) in a

3:1:1 mixture of tetrahydrofuran/water/methanol (375 mL) was added lithium hydroxide hydrate (4.7 g, 112 mmol). This mixture was stirred at room temperature for 1 h 45 min, concentrated, and extracted with chloroform (6x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (2x; 2% methanol/chloroform) to give 11.3 g (90%) of the title compound as a pale yellow solid after tritration with hexanes. mp: 106.5-108 °C; $^1$H NMR ($CDCl_3$, 250 MHz) δ 8.62 (s, 1H), 8.26 (d, 1H), 7.92 (dd, 1H), 7.72 (dd, 1H), 7.61 (td, 1H), 7.44 (td, 1H), 6.45 (d, 1H), 4.75 (m, 1H), 3.95-3.85 (c, 8H), 1.54 (d, 3H); MS (CI/$NH_3$) 337 ($MH^+$); $[\alpha]_D$ +15.3 (c 2.3, MeOH).

Example 2

(R)-1-[4-(4-Oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



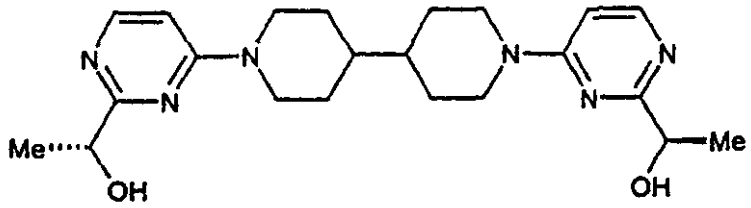

**Step A:** (R)-1-[4-(4-Oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of 2-(1-piperazinyl)oxazolo[5,4-c]pyridine (775 mg, 3.8 mmol; *J. Org. Chem.* **1995**, *60*, 5721) in isopropanol (38 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 868 mg, 3.8 mmol) followed by triethylamine (1.6 mL, 11.4 mmol). This mixture was stirred at reflux overnight, cooled to room temperature, and evaporated. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (2x; 3% methanol/chloroform then 6→8% methanol/ethyl acetate, where used herein, the arrow symbol, →, indicates a gradient) to give 1.2 g (79%) of the title compound of Example 2, Step A as a pale yellow oil which solidified upon standing. $^1$H NMR ($CDCl_3$, 250 MHz) δ 8.57 (s, 1H), 8.39 (d, 1H), 8.28 (d, 1H), 7.30 (d, 1H), 6.44 (d, 1H), 5.70 (q, 1H), 3.85 (s, 8H), 2.42 (t, 2H), 1.78 -1.61 (c, 2H), 1.60 (d, 3H), 0.98 (t, 3H); MS (APCI) 397 ($MH^+$).

**Step B:** (R)-1-[4-(4-Oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol. To a solution of (R)-1-[4-(4-oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-

ethyl butyrate (prepared according to the method of Example 2, Step A, 1.2 g, 3.0 mmol) in methanol (30 mL) was added potassium carbonate (823 mg, 6.0 mmol). This mixture was stirred at room temperature for 5 h, diluted with saturated aqueous ammonium chloride, concentrated, and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (6% methanol/chloroform) to give 915 mg (94%) of the title compound as a white solid after tritration with hexanes. mp: 181-183 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, 1H), 8.35 (d, 1H), 8.25 (d, 1H), 7.27 (dd, 1H), 6.44 (d, 1H), 4.71 (q, 1H), 4.25 (br s, 1H), 3.86-3.83 (c, 8H), 1.50 (d, 3H); MS (APCI) 327 ($MH^+$); $[\alpha]_D$ +15.3 (c 0.5, MeOH).

Example 3

1R-(4-{1'-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-[4,4']bipiperidinyl-1-yl}-pyrimidin-2-yl)-ethanol.



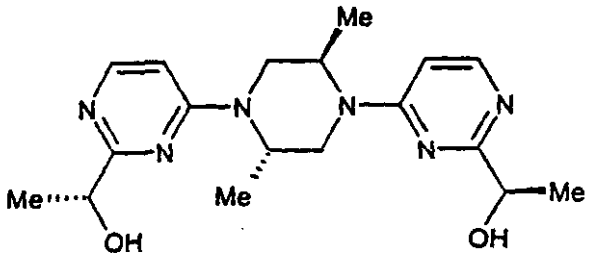

A mixture of (R)-1-(4-chloro-pyrimidin-2-yl)-ethanol (prepared according to the method of Preparation Ten, 100 mg, 0.63 mmol), 4,4'-bipiperidine dihydrochloride (76 mg, 0.32 mmol), and triethylamine (0.44 mL, 3.2 mmol) in isopropanol (3 mL) was refluxed overnight and cooled to room temperature. The reaction mixture was diluted with saturated aqueous sodium bicarbonate and extracted with chloroform (4x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (Biotage Flash 40S™, 5% methanol/chloroform) to give 110 mg (85%) of the title compound as a white solid. mp: 144-153 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, 2H), 6.36 (d, 2H), 4.67 (q, 2H), 4.53-4.28 (c, 4H), 2.84 (t, 4H), 1.82 (d, 4H), 1.49 (d, 6H), 1.43-1.40 (c, 2H), 1.30-1.18 (c, 4H); MS (APCI) 413 ($MH^+$); $[\alpha]_D$ +22.6 (c 1.0, MeOH).

Examples 4 to 8

Examples 4 to 8 were prepared from the appropriate starting materials in a manner analogous to the method of Example 3.

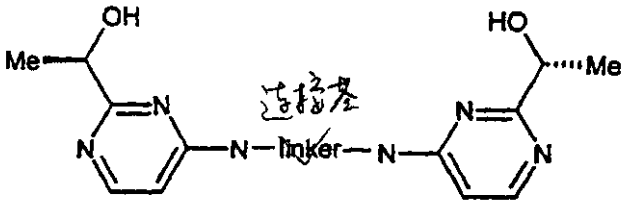
Example 4

1R-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 153-155 °C, $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 2H), 6.40 (d, 2H), 4.71 (m, 2H), 4.28 (dd, 2H), 3.51-3.45 (c, 4H), 1.51 (d, 6H), 1.23 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +18.6 (c 1.2, $CHCl_3$).

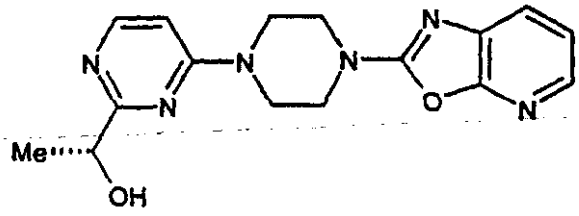
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| Example | N-linker-N | mp (°C) | MS ($MH^+$) |
|---|---|---|---|
| 5 | N,N'-ethylenediamine | 141-143 | 333 |
| 6 | [1,4]diazepane | 136-138 | 345 |
| 7 | 4,4'-ethylenebipiperidine | | 441 |
| 8 | methyl-piperidin-4-ylmethyl-amine | | 373 |

Example 9

(R)-1-[4-(4-Oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



**Step A:** 2-(1-Piperazinyl)oxazolo[5,4-b]pyridine. A mixture of 2-(thiomethyl)oxazolo[5,4-b]pyridine (9.2 g, 55.5 mmol; *J. Org. Chem.* **1995**, *60*, 5721)

and piperazine (23.9 g, 277 mmol), with a small amount of ethyl acetate which was used for washing the compound down the sides of the flask, was heated at 90 °C for 1.5 h. The reaction mixture was cooled to room temperature, diluted with ~20% saturated aqueous sodium bicarbonate solution, and extracted with chloroform (4x). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (1x), dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (3→5% methanol/chloroform + 1% ammonium hydroxide) to give 9.1 g (81%) of the title compound of Example 9, Step A as an off-white solid. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.92 (dd, 1H), 7.55 (dd, 1H), 7.10 (dd, 1H), 3.74-3.70 (c, 4H), 3.02-2.97 (c, 4H); MS (APCI) 205 ($MH^+$).

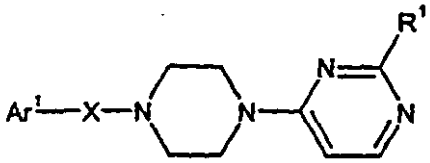
**Step B:** (R)-1-[4-(4-Oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 6.8 g, 29.9 mmol) and triethylamine (12.5 mL, 89.6 mmol) in isopropanol (100 mL) was added 2-(1-piperazinyl)oxazolo[5,4-b]pyridine (prepared according to the method of Example 9, Step A, 6.1 g, 29.9 mmol). This mixture was stirred at reflux overnight, cooled to room temperature, and evaporated. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1.5→2% methanol/chloroform) to give 11.1 g (94%) of the title compound of Example 9, Step B as a yellow oil which solidified upon standing. $^1$H NMR ($CDCl_3$, 250 MHz) δ 8.28 (d, 1H), 7.97 (dd, 1H), 7.60 (dd, 1H), 7.25 (dd, 1H), 6.44 (d, 1H), 5.70 (q, 1H), 3.85 (app s, 8H), 2.42 (t, 2H), 1.78 -1.61 (c, 2H), 1.60 (d, 3H), 0.98 (t, 3H); MS (APCI) 397 ($MH^+$).

**Step C:** (R)-1-[4-(4-Oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol. To a solution of (R)-1-[4-(4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 9, Step B, 11.0 g, 27.6 mmol) in dioxane (11.5 mL) was added concentrated hydrochloric acid (23 mL, 276 mmol). This mixture was stirred at room temperature overnight, neutralized with 6 N aqueous sodium hydroxide, and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (3.5% methanol/chloroform) to give 8.4 g (93%) of the title compound as a white solid. mp: 153-156 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.25

(d, 1H), 7.95 (dd, 1H), 7.58 (dd, 1H), 7.15 (dd, 1H), 6.45 (d, 1H), 4.72 (q, 1H), 4.25 (br s, 1H), 3.85-3.82 (c, 8H), 1.51 (d, 3H); MS (CI/$NH_3$) 327 ($MH^+$); $[\alpha]_D$ +16.1 (c 1.0, MeOH).

Examples 10 to15

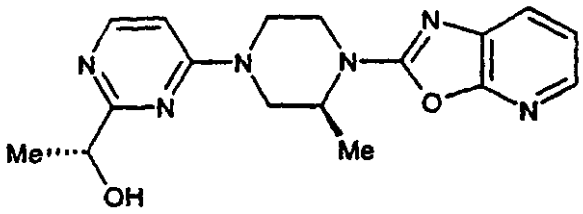
Examples 10 to 15 were prepared from the appropriate starting materials in a manner analogous to the method of Example 9.



| Example | X-Ar¹ | R¹ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|
| 10 | oxazolo[4,5-c]pyridin-2-yl | (R)-$CH(CH_3)OH$ | 178-180 | 327 |
| 11 | oxazolo[5,4-c]pyridin-2-yl | -$C(CH_3)_2OH$ | 181-184 | 341 |
| 12 | oxazolo[5,4-c]pyridin-2-yl | (±)-$CH(CH_3)OH$ | 153-158 | 327 |
| 13 | oxazolo[5,4-c]pyridin-2-yl | (S)-$CH(CH_3)OH$ | 175-179 | 327 |
| 14 | quinoxalin-2-yl | (±)-$CH(CH_3)OH$ | 102-105 | 337 |
| 15 | (5-iodo)-benzoxazol-2-yl | (R)-$CH(CH_3)OH$ | | 452 |

Example 16

1R-[4-(3S-Methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



**Step A:** (S)-2-(4-Benzyl-2-methyl-piperazin-1-yl)-oxazolo[5,4-b]pyridine. A mixture of 2-(thiomethyl)oxazolo[5,4-b]pyridine (44 g, 264 mmol; *J. Org. Chem.* **1995**, *60*, 5721) and (S)-1-benzyl-3-methyl-piperazine (25 g, 132 mmol; *J. Org. Chem.* **1995**, *60*, 4177) was stirred at 130 °C for 3 d, cooled to room temperature, and purified by flash column chromatography (17→83% ethyl acetate/hexanes) to give 30 g (74%) of the title compound of Example 16, Step A as a dark yellow oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, 1H), 7.53 (d, 1H), 7.34-7.25 (c, 5H), 7.10 (dd, 1H), 4.45 (m, 1H), 4.11 (d,

1H), 3.59 (d, 1H), 3.52-3.45 (c, 2H), 2.90 (d, 1H), 2.73 (d, 1H), 2.32 (dd, 1H), 2.21 (td, 1H), 1.41 (d, 3H); MS (APCI) 309 ($MH^+$).

**Step B:** (S)-2-(2-Methyl-piperazin-1-yl)-oxazolo[5,4-b]pyridine. To a solution of (S)-2-(4-benzyl-2-methyl-piperazin-1-yl)-oxazolo[5,4-b]pyridine (prepared according to the method of Example 16, Step A, 30 g, 97 mmol) in methanol (970 mL) was added hydrogen chloride (5.85 M in methanol, 20 mL, 116 mmol), ammonium formate (122 g, 1.95 mol), and 10 % palladium on carbon (60 g, 200 wt%). This mixture was stirred at reflux for 50 min, cooled, and filtered through Celite. The filtrate was concentrated, diluted with saturated aqueous sodium bicarbonate, and extracted with chloroform (1x) followed by 10% isopropanol/chloroform (4x). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated to give 16 g (76%) of the title compound of Example 16, Step B as a green oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.89 (m, 1H), 7.53 (m, 1H), 7.09 (m, 1H), 4.42 (m, 1H), 4.11 (d, 1H), 3.35 (td, 1H), 3.09-3.03 (c, 2H), 2.85 (d, 1H), 2.82 (td, 1H), 1.38 (d, 3H); MS (APCI) 219 ($MH^+$).

**Step C:** 1R-[4-(3S-Methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. A mixture of (S)-2-(2-methyl-piperazin-1-yl)-oxazolo[5,4-b]pyridine (prepared according to the method of Example 16, Step B, 10 g, 45.9 mmol), (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 9.5 g, 41.7 mmol), and triethylamine (17.3 mL, 125 mmol) in isopropanol (230 mL) was heated at reflux for 30 h, cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, and extracted with chloroform (4x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1.5% methanol/chloroform) to give 16 g (93%) of the title compound of Example 16, Step C as a yellow oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 1H), 7.93 (dd, 1H), 7.57 (d, 1H), 7.13 (dd, 1H), 6.39 (d, 1H), 5.67 (q, 1H), 4.61 (m, 1H), 4.42 (m, 1H), 4.28 (m, 1H), 4.18 (dt, 1H), 3.51 (td, 1H), 3.41 (dd, 1H), 3.17 (td, 1H), 2.39 (t, 2H), 1.72-1.59 (c, 2H), 1.57 (d, 3H), 1.30 (d, 3H), 0.95 (t, 3H); MS (APCI) 411 ($MH^+$).

**Step D:** 1R-[4-(3S-Methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol. A mixture of 1R-[4-(3S-methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 16, Step C, 16 g, 39.0 mmol) and potassium carbonate (10.8 g, 78.1 mmol) in methanol (195 mL) was stirred at room temperature for 4 h, diluted with saturated aqueous sodium

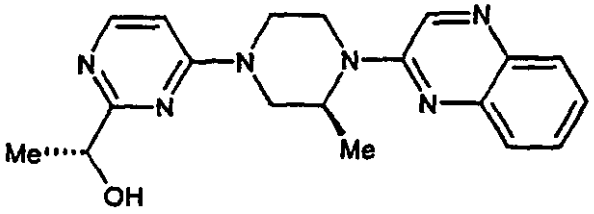
bicarbonate, and extracted with chloroform (1x) followed by 10% isopropanol/chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1→2.5% methanol/chloroform) to give a white foam that was recrystallized from ether/chloroform to give 8.9 g (67%) of the title compound as a white solid. mp: 147-149 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H), 7.94 (dd, 1H), 7.58 (d, 1H), 7.14 (dd, 1H), 6.42 (d, 1H), 4.72 (m, 1H), 4.64 (m, 1H), 4.42 (m, 1H), 4.32 (m, 1H), 4.25 (d, 1H), 4.21 (dt, 1H), 3.54 (td, 1H), 3.46 (dd, 1H), 3.24 (td, 1H), 1.51 (d, 3H), 1.33 (d, 3H); MS (APCI) 411 ($MH^+$); $[\alpha]_D$ +70.4 (c 1.1, MeOH).

Examples 17 to 25

Examples 17 to 25 were prepared from the appropriate starting materials in a manner analogous to the method of Example 16.

Example 17

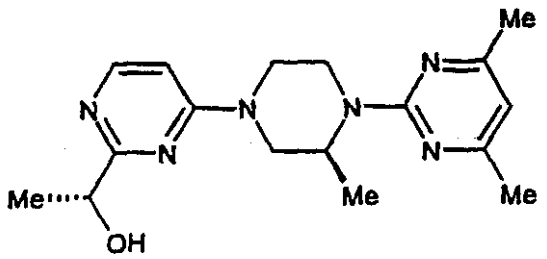
1R-[4-(3S-Methyl-4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.56 (d, 1H), 8.23 (d, 1H), 7.89 (d, 1H), 7.69 (d, 1H), 7.59 (t, 1H), 7.41 (t, 1H), 6.42 (d, 1H), 4.78 (m, 1H), 4.73 (m, 1H), 4.43 (m, 1H), 4.38-4.23 (c, 2H), 3.64-3.52 (c, 2H), 3.38 (m, 1H), 1.52 (d, 3H), 1.30 (d, 3H); MS (APCI) 351 ($MH^+$); $[\alpha]_D$ +57.0 (c 1.2, $CHCl_3$).

Example 18

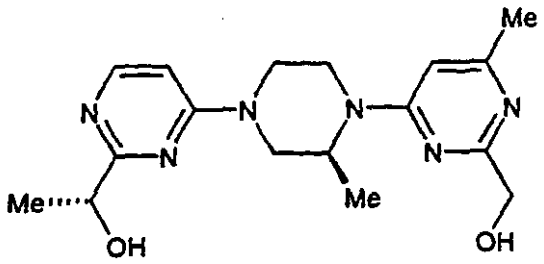
1R-[4-[4-(4,6-Dimethyl-pyrimidin-2-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.



$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, 1H), 6.37 (d, 1H), 6.30 (s, 1H), 5.04 (m, 1H), 4.70 (q, 1H), 4.60 (dt, 1H), 4.37 (br s, 1H), 4.36-4.12 (c, 2H), 3.40 (dd, 1H), 3.34 (td, 1H), 3.16 (td, 1H), 2.28 (s, 6H), 1.51 (d, 3H), 1.16 (d, 3H); MS (APCI) 329 ($MH^+$); $[\alpha]_D$ +78.8 (*c* 1.6, MeOH).

Example 19

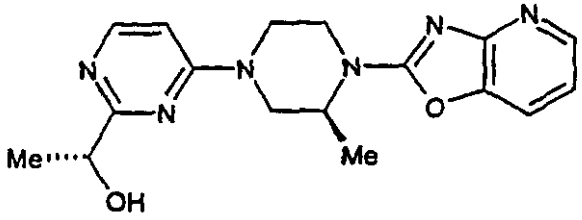
1R-[4-[4-(2-Hydroxymethyl-6-methyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.




$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 1H), 6.38 (d, 1H), 6.23 (s, 1H), 4.71 (q, 1H), 4.58 (s, 3H), 4.36-4.18 (c, 4H), 3.86 (br s, 1H), 3.57 (dd, 1H), 3.46 (td, 1H), 3.32 (td, 1H), 2.38 (s, 3H), 1.51 (d, 3H), 1.22 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ +72.6 (c 1.1, MeOH).

Example 20

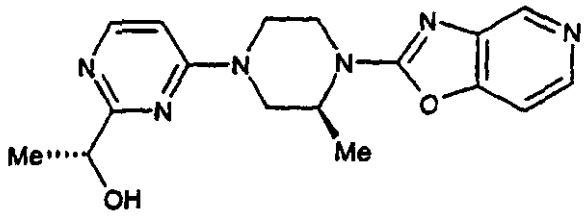
1R-[4-(3S-Methyl-4-oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.




mp: 158-161 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.22-8.15 (c, 2H), 7.40 (dd, 1H), 6.86 (dd, 1H), 6.40 (d, 1H), 4.65 (m, 1H), 4.61 (m, 1H), 4.44-4.20 (c, 3H), 4.18 (dt, 1H), 3.50 (td, 1H), 3.41 (dd, 1H), 3.19 (td, 1H), 1.45 (d, 3H), 1.26 (d, 3H); MS (APCI) 341 ($MH^+$); $[\alpha]_D$ +58.2 (c 1.1, MeOH).

Example 21

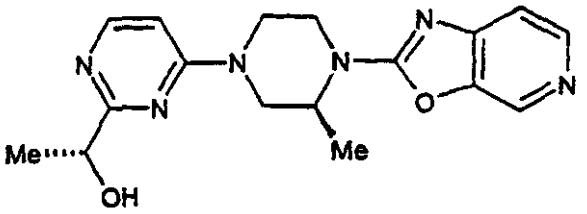
1R-[4-(3S-Methyl-4-oxazolo[4,5-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



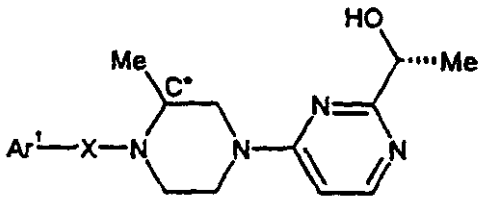
$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.68 (d, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 7.25 (dd, 1H), 6.42 (d, 1H), 4.71 (m, 1H), 4.60 (m, 1H), 4.42 (m, 1H), 4.32-4.23 (c, 2H), 4.17 (dt, 1H), 3.56 (td, 1H), 3.47 (dd, 1H), 3.24 (td, 1H), 1.51 (d, 3H), 1.32 (d, 3H); MS (APCI) 341 ($MH^+$); $[\alpha]_D$ +57.9 (c 1.6, MeOH).

Example 22

1R-[4-(3S-Methyl-4-oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



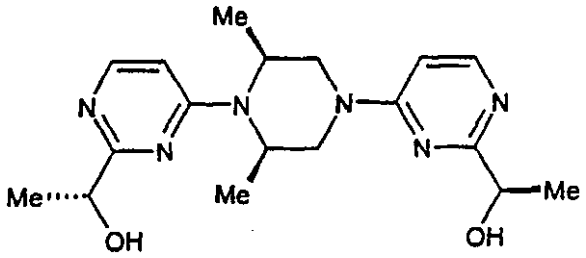
$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1H), 8.37 (d, 1H), 8.25 (d, 1H), 7.29 (d, 1H), 6.43 (d, 1H), 4.72 (m, 1H), 4.65 (m, 1H), 4.45 (m, 1H), 4.29 (m, 1H), 4.26-4.20 (c, 2H), 3.58 (td, 1H), 3.48 (dd, 1H), 3.26 (td, 1H), 1.51 (d, 3H), 1.34 (d, 3H); MS (APCI) 341 ($MH^+$); $[\alpha]_D$ +61.1 (c 1.0, MeOH).



| Example | X-Ar$^1$ | C* | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|
| 23 | quinoxalin-2-yl | R | | 351 |
| 24 | (2-[C($CH_3$)$_2$OH])- pyrimidin-4-yl | S | | 359 |
| 25 | benzoxazol-2-yl | S | | 340 |

Example 26

1R-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



**Method 1:** To a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Four, 72.8 g, 238 mmol) and triethylamine (50 mL, 357 mmol) in isopropanol (793 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 54.3 g, 238 mmol). This mixture was stirred at reflux for 12 h and concentrated. The residue was dissolved in a 3:1:1 mixture of tetrahydrofuran/methanol/water (1200 mL) and lithium hydroxide hydrate (60 g, 1.43 mol) was added. This mixture was stirred at room temperature for 2.5 h, concentrated somewhat, diluted with saturated aqueous sodium bicarbonate, and extracted with 10% isopropanol/chloroform (6x). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. The residue was diluted with 1:1 ethyl acetate/methanol (1100 mL) and stirred at room temperature for 1 h. The precipitate was collected by filtration and the filtrate was concentrated to about 850 mL. After 1 h, more precipitate had formed and this material was collected by filtration. The filtrate was concentrated somewhat and ethyl acetate was added. After 1 h more precipitate had again formed and this material was collected by filtration. This was repeated one more time to give in total 65.9 g (77%) of the title compound as a white solid. mp: 163-164.5 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.74-4.70 (c, 2H), 4.70-4.50 (c, 2H), 4.50-4.30 (c, 2H), 4.30 (d, 1H), 4.27 (d, 1H), 3.31 (dt, 2H), 1.51 (d, 6H), 1.26 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +42.3 (c 1.0, MeOH).

**Method 2, Step A:** 1R-(4-{4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate. To a solution of (R)-2-(1-butyryloxy-ethyl)-3H-pyrimidin-4-one (828 g, 3.9 mol) in dichloromethane (50 L) was added

triethylamine (576 mL, 4.1 mol) and the resulting solution was cooled to 5 °C. A solution of trifluoromethanesulfonic anhydride (729 mL, 4.3 mol) in dichloromethane (6 L) was added slowly such that the internal temperature was maintained at <10 °C. After the addition was complete, the reaction was judged complete by TLC and quenched by the addition of water (5.3 L). The organic layer was separated, washed with water (20 L) and saturated aqueous sodium bicarbonate (20 L), and dried over sodium sulfate. This solution was then slowly added to a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate dibenzoyl-L-tartrate salt (prepared according to the method of Preparation Fifteen, 2.49 kg, 3.75 mol) and triethylamine (1.6 L, 11.6 mol) in dimethylacetamide (18 L) such that the internal temperature was maintained at <10 °C. The resulting solution was allowed to stir for 12 h at 10 °C and then diluted with ethyl acetate (40 L) and water (27 L). The aqueous layer was removed and the organic layer was washed twice with water (40 L) and once with brine (20 L), and dried over sodium sulfate. The resulting solution was partially concentrated (8 L) and then hexanes (23 L) was added. The resulting suspension was allowed to granulate for 12 h and then filtered over cotton. The solids were dried under vacuum (40 °C) to provide 1178 gm (63%) of the title compound of Example 26, Method 2, Step A as a white solid. The $^1$H NMR and MS data for this compound are in agreement with that of Example 266.

**Method 2, Step B:** 1R-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol. To a solution of 1R-(4-{4-[2-(1R-butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Example 26, Method 2, Step A, 1140 g, 2.28 mol) in isopropanol (11.4 L) was added 40% aqueous potassium hydroxide (800 mL) at room temperature. The resulting solution was allowed to stir for 16 h and then diluted with water (5 L) and dichloromethane (4 L). The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 L). The combined organic layers were washed twice with 1 M aqueous sodium hydroxide (10 L) and twice with water (5 L), partially concentrated (5 L), diluted with ethyl acetate (4 L), and again partially concentrated (6 L). Hexanes (10 L) was added and the resulting slurry was allowed to stir at reflux for 12 h, cooled to room temperature, and filtered. The resulting solid was dried under vacuum to provide 758 g (93%) of the title compound

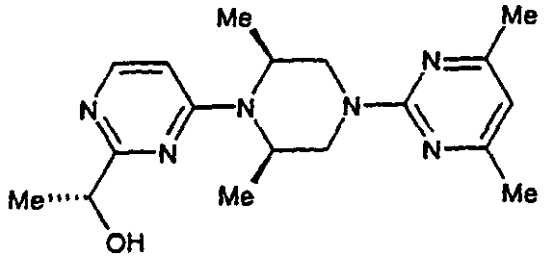
as a white solid. The mp, $^1$H NMR, MS, and optical rotation data for this compound are in agreement with that of Example 26, Method 1.

Examples 27 to 62

Examples 27 to 62 were prepared from the appropriate starting materials in a manner analogous to the method of Example 26.

Example 27

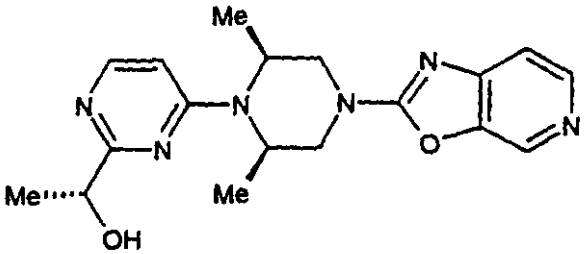
1R-{4-[4-(4,6-Dimethyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



mp: 150.5-152 °C; $^1$H NMR ($CD_3OD$, 300 MHz) δ 8.14 (d, 1H), 6.62 (d, 1H), 6.46 (d, 1H), 6.40 (s, 1H), 4.83 (d, 2 H), 4.72-4.52 (c, 3H), 3.30 (dd, 2H), 2.28 (s, 6H), 1.46 (d, 3H), 1.23 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +12.0 (c 1.3, MeOH).

Example 28

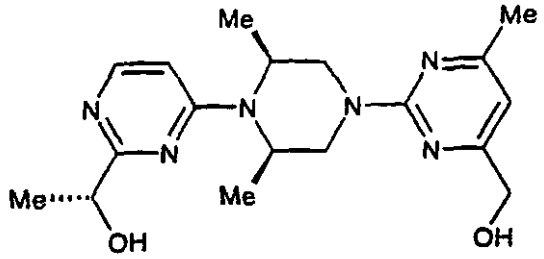
1R-[4-(2R,6S-Dimethyl-4-oxazolo[5,4-c]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



$^1$H NMR ($CD_3OD$, 300 MHz) δ 8.53 (d, 1H), 8.28 (d, 1H), 8.20 (d, 1H), 7.34 (dd, 1H), 6.68 (d, 1H), 4.90-4.72 (c, 2H), 4.69 (q, 1H), 4.32 (d, 2H), 3.56 (dd, 2H), 1.47 (d, 3H), 1.33 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +8.1 (c 1.3, MeOH).

Example 29

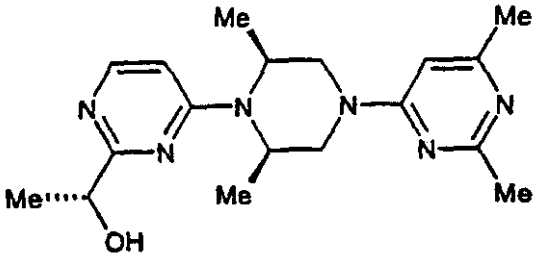
1R-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



mp: 139-141 °C; $^1$H NMR ($CD_3OD$, 300 MHz) δ 8.24 (d, 1H), 6.51 (d, 1H), 6.38 (s, 1H), 4.90 (m, 1H), 4.84 (d, 2H), 4.77-4.53 (c, 2H), 4.55 (s, 2H), 3.24 (dd, 2H), 2.37 (s, 3H), 1.61 (d, 3H), 1.32 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +14.8 (c 1.0, MeOH).

Example 30

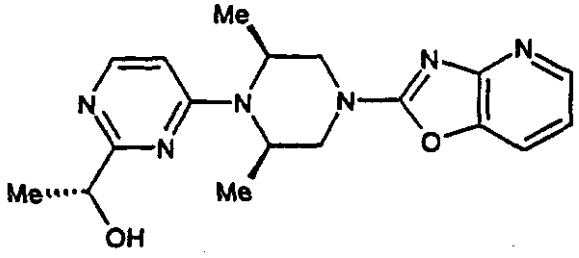
1R-{4-[4-(2,6-Dimethyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



$^1$H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, 1H), 6.36 (d, 1H), 6.26 (s, 1H), 4.71 (m, 1H), 4.65-4.50 (c, 2H), 4.42-4.28 (c, 3H), 3.24 (dd, 2H), 2.49 (s, 3H), 2.35 (s, 3H), 1.52 (d, 3H), 1.26 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +11.4 (c 0.8, MeOH).

Example 31

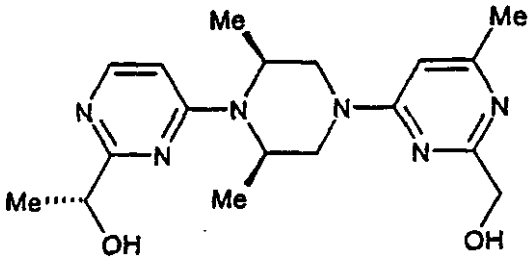
1R-[4-(2R,6S-Dimethyl-4-oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



mp: 231-233 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.26-8.23 (c, 2H), 7.47 (d, 1H), 6.94 (dd, 1H), 6.39 (d, 1H), 4.75-4.53 (c, 2H), 4.72 (q, 1H), 4.35 (d, 1H), 4.28 (m, 1H), 3.44 (dd, 2H), 1.51 (d, 3H), 1.34 (d, 6H); MS (APCI) 355 ($MH^+$); $[\alpha]_D$ +8.0 (c 0.8, MeOH).

Example 32

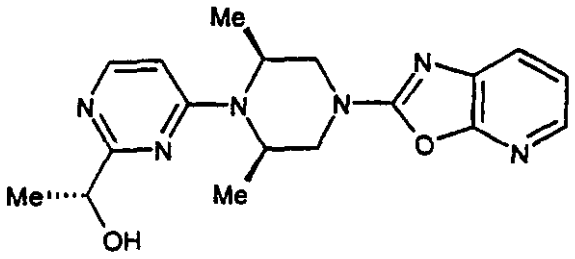
1R-[4-[4-(2-Hydroxymethyl-6-methyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl)-ethanol.



$^1$H NMR ($CD_3OD$, 300 MHz) δ 8.16 (d, 1H), 6.66 (s, 1H), 6.63 (d, 1H), 4.85-4.63 (c, 2H), 4.67 (q, 1H), 4.58 (d, 2H), 4.50 (s, 2H), 3.26 (dd, 2H), 2.35 (s, 3H), 1.46 (d, 3H), 1.24 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +11.8 (c 0.9, MeOH).

Example 33

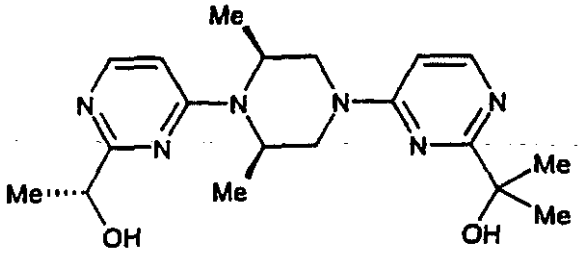
1R-[4-(2R,6S-Dimethyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.



mp: 204-207 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, 1H), 7.95 (dd, 1H), 7.59 (dd, 1H), 7.15 (dd, 1H), 6.39 (d, 1H), 4.80-4.57 (c, 2H), 4.73 (q, 1H), 4.30 (d, 2H), 3.42 (dd, 2H), 1.51 (d, 3H), 1.35 (d, 6H); MS (APCI) 355 ($MH^+$); $[\alpha]_D$ +7.5 (c 0.7, MeOH).

Example 34

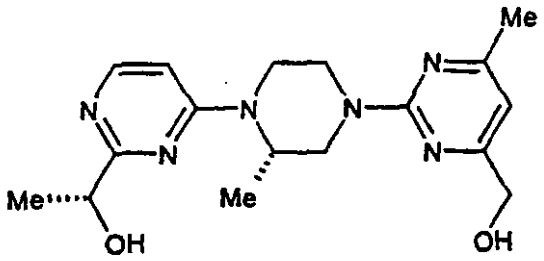
2-(4-[4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl)-propan-2-ol.



mp: 138-140 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 2H), 6.45 (d, 1H), 6.36 (d, 1H), 4.86 (s, 1H), 4.70 (m, 1H), 4.67-4.33 (c, 4H), 4.30 (d, 1H), 3.31 (dd, 2H), 1.53 (s, 6H), 1.51 (d, 3H), 1.25 (d, 6H); MS (APCI) 373 ($MH^+$); $[\alpha]_D$ +15.5 (c 1.2, MeOH).

Example 35

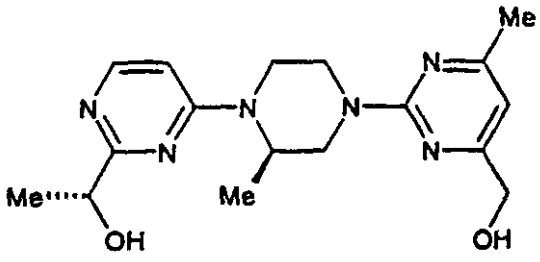
1R-[4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-2S-methyl-piperazin-1-yl]-pyrimidin-2-yl)-ethanol.




$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, 1H), 6.36 (d, 1H), 6.32 (s, 1H), 4.69 (q, 1H), 4.60-4.53 (c, 3H), 4.52 (s, 2H), 4.38-4.18 (c, 2H), 3.63 (m, 1H), 3.40-3.29 (c, 2H), 3.24 (m, 1H), 2.32 (s, 3H), 1.49 (d, 3H), 1.20 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ +66.5 (c 1.0, MeOH).

Example 36

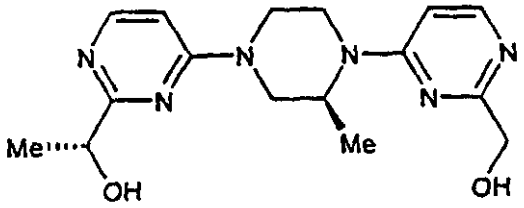
1R-[4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-2R-methyl-piperazin-1-yl]-pyrimidin-2-yl)-ethanol.




$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, 1H), 6.37 (d, 1H), 6.33 (s, 1H), 4.72 (m, 1H), 4.67-4.54 (c, 3H), 4.54 (s, 2H), 4.34 (d, 1H), 4.20 (d, 1H), 3.58 (br s, 1H), 3.42-3.32 (c, 2H), 3.26 (td, 1H), 2.34 (s, 3H), 1.51 (d, 3H), 1.21 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ -35.0 (c 1.1, MeOH).

Example 37

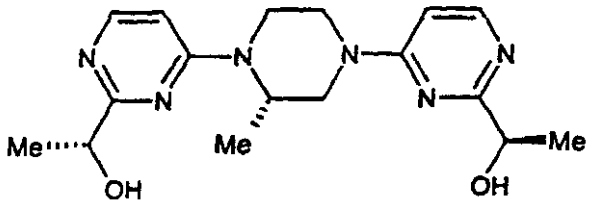
1R-{4-[4-(2-Hydroxymethyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



mp: 178-181 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 2H), 6.38 (d, 2H), 4.60 (q, 1H), 4.60 (s, 2H), 4.56 (m, 1H), 4.28-4.15 (c, 4H), 3.72 (br s, 1H), 3.58 (dd, 1H), 3.48 (m, 1H), 3.33 (td, 1H), 1.51 (d, 3H), 1.23 (d, 3H); MS (APCI) 331 ($MH^+$); $[\alpha]_D$ +88.9 (c 1.1, MeOH).

Example 38

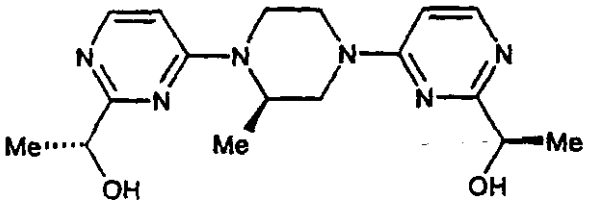
1R-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2S-methyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 158-160 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 2H), 6.39 (d, 1H), 6.38 (d, 1H), 4.71 (m, 2H), 4.55 (br s, 1H), 4.32-4.16 (c, 5H), 3.60 (dd, 1H), 3.48 (td, 1H), 3.38 (td, 1H), 1.52 (d, 6H), 1.24 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ +82.5 (c 1.0, MeOH).

Example 39

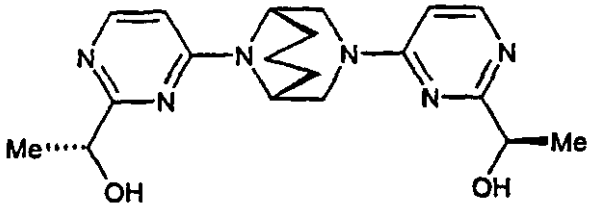
1R-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R-methyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 155-157 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 2H), 6.39 (d, 1H), 6.38 (d, 1H), 4.73 (m, 2H), 4.58 (br s, 1H), 4.32-4.16 (c, 5H), 3.59 (dd, 1H), 3.50 (m, 1H), 3.38 (m, 1H), 1.52 (d, 6H), 1.25 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ -30.4 (c 0.9, MeOH).

Example 40

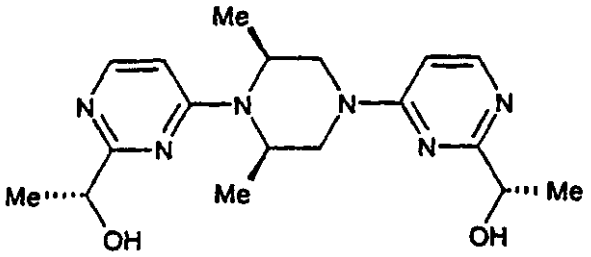
1R-(4-{3-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-3,9-diaza-bicyclo[3.3.1]non-9-yl}-pyrimidin-2-yl)-ethanol.



mp: 151-158 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 2H), 6.42 (d, 1H), 6.41 (d, 1H), 4.72 (m, 2H), 4.48-4.18 (c, 2H), 4.29 (dd, 2H), 3.28 (d, 2H), 2.03 (m, 1H), 1.98-1.82 (c, 4 H), 1.58 (m, 1 H), 1.51 (d, 3H), 1.50 (d, 3H); MS (APCI) 371 ($MH^+$); $[\alpha]_D$ +27.6 (c 0.9, MeOH).

Example 41

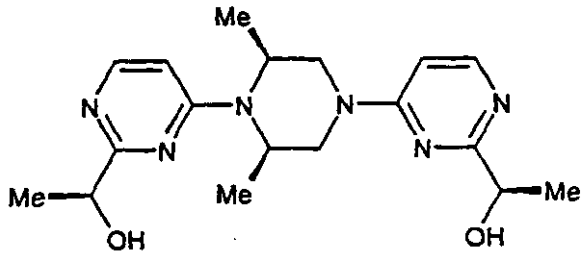
1R-(4-{4-[2-(1S-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 222-223.5 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.75-4.51 (c, 4H), 4.50-4.30 (c, 4H), 3.31 (dt, 2H), 1.51 (d, 6H), 1.26 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ -3.4 (c 0.5, $CHCl_3$).

Example 42

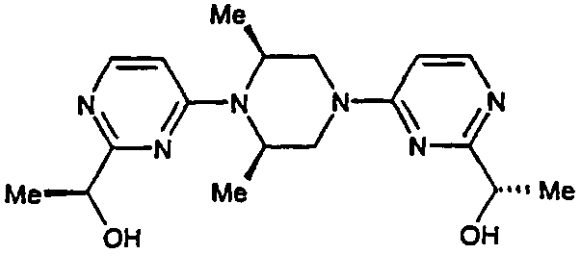
1S-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 224-226 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.76-4.51 (c, 4H), 4.50-4.23 (c, 4H), 3.33 (dt, 2H), 1.51 (d, 6H), 1.25 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +64.2 (c 0.5, $CHCl_3$).

Example 43

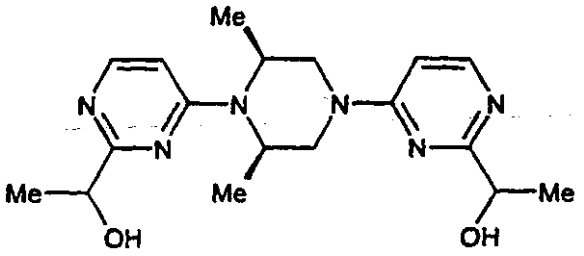
1S-(4-{4-[2-(1S-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 164-165.5 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.75-4.51 (c, 4H), 4.50-4.23 (c, 4H), 3.47-3.28 (c, 2H), 1.51 (d, 6H), 1.25 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ -43.8 (c 1.0, MeOH).

Example 44

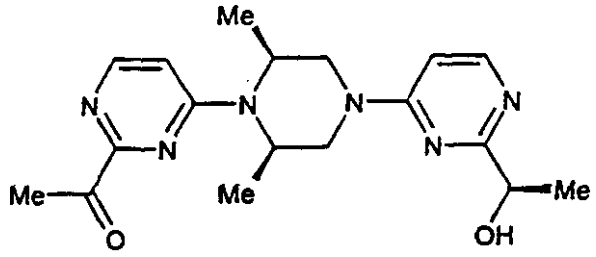
1RS-(4-{4-[2-(1RS-Hydroxy-ethyl)-pyrimidin-4-yl]-2R*,6S*-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 180-186 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.75-4.51 (c, 4H), 4.50-4.23 (c, 4H), 3.47-3.28 (c, 2H), 1.51 (d, 6H), 1.25 (d, 6H); MS (APCI) 359 ($MH^+$).

Example 45

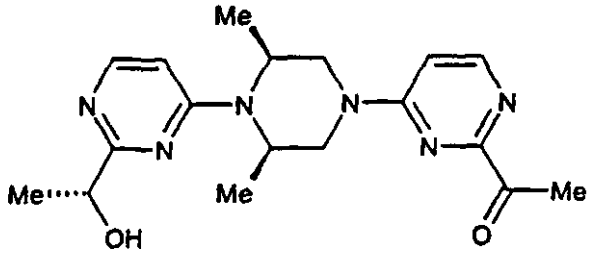
1-{4-[4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone.



mp: 123-127 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.41 (d, 1H), 8.24 (d, 1H), 6.56 (d, 1H), 6.47 (d, 1H), 4.75-4.53 (c, 3H), 4.52-4.28 (c, 2H), 4.26 (m, 1H), 3.36-3.29 (c, 2H), 2.68 (s, 3H), 1.51 (d, 3H), 1.28 (d, 6H); MS (APCI) 357 ($MH^+$); $[\alpha]_D$+19.4 (c 1.0, MeOH).

Example 46

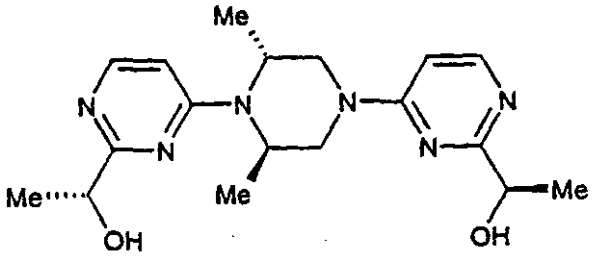
1-{4-[4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone.



mp: 150-164 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, 1H), 8.24 (d, 1H), 6.66 (d, 1H), 6.37 (d, 1H), 4.74-4.52 (c, 3H), 4.51-4.31 (c, 2H), 4.29 (m, 1H), 3.36 (dd, 2H), 2.69 (s, 3H), 1.51 (d, 3H), 1.27 (d, 6H); MS (APCI) 357 ($MH^+$); $[\alpha]_D$+21.8 (c 1.1, MeOH).

Example 47

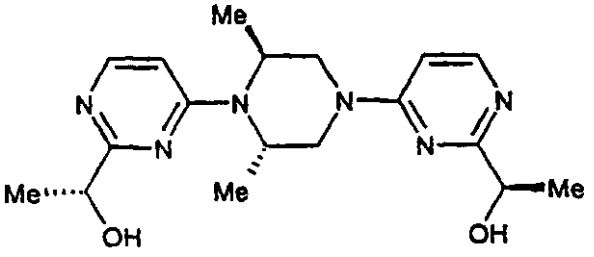
1R-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6R-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



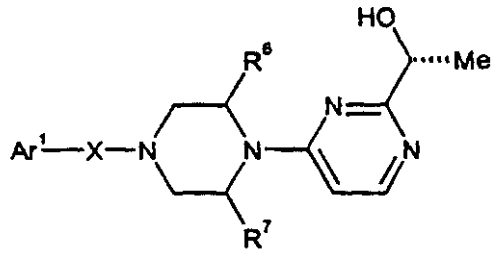
mp: 168-171 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, 1H), 8.23 (d, 1H), 6.33 (d, 1H), 6.30 (d, 1H), 4.78-4.69 (c, 2H), 4.68-4.28 (c, 5H), 3.83-3.69 (c, 2H), 3.54 (m, 1H), 1.53 (d, 3H), 1.52 (d, 3H), 1.43-1.22 (c, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +92.2 (c 0.5, MeOH).

Example 48

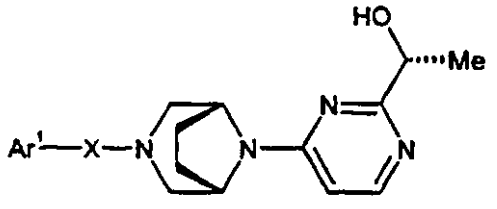
1R-(4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2S,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.



mp: 168-178 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, 1H), 8.23 (d, 1H), 6.32 (d, 1H), 6.29 (d, 1H), 4.78-4.68 (c, 2H), 4.65-4.27 (c, 5H), 3.82-3.71 (c, 2H), 3.55 (m, 1H), 1.52 (d, 3H), 1.51 (d, 3H), 1.43-1.20 (c, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$- 32.4 (c 0.7, MeOH).



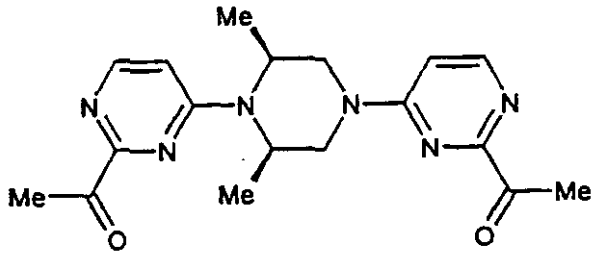
| Example | X-Ar¹ | R⁶ | R⁷ | mp (°C) | MS (MH⁺) |
|---|---|---|---|---|---|
| 49 | benzoxazol-2-yl | (R)-Me | (S)-Me | | 354 |
| 50 | benzothiazol-2-yl | (R)-Me | (S)-Me | | 370 |
| 51 | oxazolo[4,5-c]pyridin-2-yl | (R)-Me | (S)-Me | | 355 |
| 52 | quinoxalin-2-yl | (R)-Me | H | | 351 |
| 53 | quinoxalin-2-yl | (S)-Me | H | | 351 |
| 54 | quinoxalin-2-yl | (R)-Me | (S)-Me | | 365 |
| 55 | (4,6-dimethyl)-pyrimidin-2-yl | H | H | 132-133 | 315 |
| 56 | (4,6-dimethyl)-pyrimidin-2-yl | (S)-Me | H | | 329 |
| 57 | (2,6-dimethyl)-pyrimidin-4-yl | H | H | 125.5-127 | 314 |
| 58 | (2-hydroxymethyl)-pyrimidin-4-yl | (S)-Me | H | 146-148 | 331 |
| 59 | (2-hydroxymethyl)-pyrimidin-4-yl | (R)-Me | (S)-Me | 168-171 | 345 |
| 60 | (2-hydroxymethyl-6-methyl)-pyrimidin-4-yl | (S)-Me | H | | 345 |



| Example | X-Ar¹ | mp (°C) | MS (MH⁺) |
|---|---|---|---|
| 61 | (4-hydroxymethyl-6-methy)-lpyrimidin-2-yl | | 357 |
| 62 | (R )-[2-(1-hydroxy-ethyl)]-pyrimidin-4-yl | | 357 |

Example 63

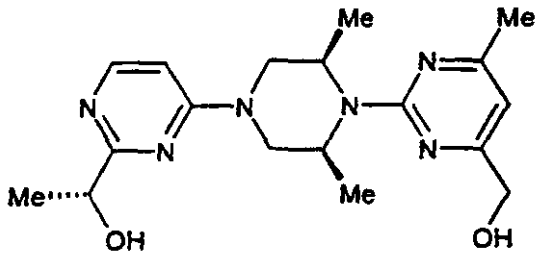
1-{4-[4-(2-Acetyl-pyrimidin-4-yl)-2R*,6S*-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanone.



A mixture of 1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol (prepared according to the method of Example 42, 1.05 g, 2.93 mmol) and manganese(IV) oxide (5.15 g, 59.3 mmol) in dichloroethane (28 mL) was heated at reflux for 7 h, and filtered through Celite (hot). The filtrate was concentrated and purified by flash column chromatography (Flash 40M™, 5% methanol/chloroform) to give 0.67 g (64%) of the title compound as a white solid. mp: >235 °C (dec); $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.42 (d, 1H), 8.41 (d, 1H), 6.68 (d, 1H), 6.57 (d, 1H), 4.81-4.36 (c, 4H), 3.39 (dd, 2H), 2.69 (s, 3H), 2.68 (s, 3H), 1.29 (d, 6H); MS (APCI) 355 ($MH^+$).

Example 64

1R-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



**Step A:** 1R-{4-[4-(tert-Butoxycarbonylamino-tert-butoxycarbonylimino-methyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a mixture of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 10 g, 32.7 mmol), N,N'-bis(tert-butoxycarbonyl)thiourea (8.6 g, 32.7 mmol; *Synth. Commun.* **1993**, 23, 1443), and triethylamine (9.0 mL, 65.4

mmol) in dimethylformamide (110 mL) at 0 °C was added mercury(II) chloride (9.8 g, 36.0 mmol). This mixture was stirred overnight with warming to room temperature, diluted with ethyl acetate, and washed with water (3x) and brine (1x). The organic phase was dried over sodium sulfate, filtered, and evaporated to give 17.9 g (100%) of the title compound of Example 64, Step A as a yellow foam. $^1$H NMR ($CDCl_3$, 300 MHz) δ 9.61 (s, 1H), 8.19 (d, 1H), 6.37 (d, 1H), 5.66 (q, 1H), 4.51-4.14 (c, 4H), 3.36-3.23 (c, 2H), 2.37 (t, 2H), 1.75-1.60 (c, 2H), 1.55 (d, 3H), 1.49 (s, 9H), 1.46 (s, 9H), 1.28 (d, 3H), 1.26 (d, 3H), 0.94 (t, 3H); MS (APCI) 549 ($MH^+$).

**Step B**: 1R-[4-(4-Carbamimidoyl-3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate trifluoroacetic acid salt. A mixture of 1R-{4-[4-(tert-butoxycarbonylamino-tert-butoxycarbonylimino-methyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 64, Step A, 17.9 g, 32.7 mmol) in a 3:1 mixture of dichloromethane/trifluoroacetic acid (300 mL) was stirred at room temperature overnight and concentrated to provide ~36 g of the title compound of Example 64, Step B as an oil that was used as is. $^1$H NMR ($CD_3OD$, 400 MHz) δ 8.24 (d, 1H), 7.25 (d, 1H), 5.69 (q, 1H), 4.19-4.10 (c, 4H), 3.79-3.42 (c, 2H), 2.45 (t, 2H), 1.67-1.45 (c, 2H), 1.63 (d, 3H), 1.32-1.25 (c, 6H), 0.95 (t, 3H); MS (APCI) 349 ($MH^+$).

**Step C:** 1R-[4-[4-(4-Methoxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl]-ethanol. A solution of 1 M sodium isopropoxide in isopropanol was prepared by adding sodium metal (3.8 g, 160 mmol) to isopropanol (160 mL) and heating at reflux until all the metal was consumed. 1R-[4-(4-Carbamimidoyl-3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate trifluoroacetic acid salt (prepared according to the method of Example 64, Step B, 32.7 mmol theory) was added to the refluxing sodium isopropoxide/isopropanol solution followed, after 1 h, by 1-methoxy-pentane-2,4-dione (21.2 g, 163 mmol; *J. Am. Chem. Soc.* **1944**, *22*, 2092). After 12 h, another aliquot of sodium isopropoxide (1 M in isopropanol, 65 mL, 65 mmol) was added. After refluxing overnight, the reaction mixture was cooled to room temperature and diluted with water (100 mL). Lithium hydroxide hydrate (6.9 g, 163 mmol) was added and this mixture was stirred for 3 h, concentrated, and extracted with 10% isopropanol/chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1→2.5% methanol/chloroform) to give 10.5

g (87%, 2 steps) of the title compound of Example 64, Step C as a yellow solid. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, 1H), 6.54 (s, 1H), 6.43 (d, 1H), 5.00-4.94 (c, 2H), 4.69 (m, 1H), 4.37-4.34 (c, 2H), 4.33 (s, 2H), 3.45 (s, 3H), 3.29-3.23 (c, 2H), 2.33 (s, 3H), 1.51 (d, 3H), 1.20 (s, 6H); MS (APCI) 373 ($MH^+$).

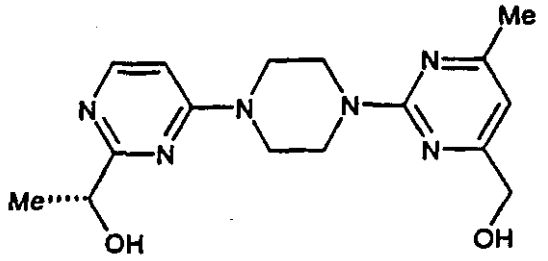
**Step D:** 1R-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol. To a solution of 1R-{4-[4-(4-methoxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol (prepared according to the method of Example 64, Step C, 8.0 g, 21.5 mmol) in dichloromethane (150 mL) at 0 °C was added boron tribromide (1 M in dichloromethane, 64.3 mL, 64.3 mmol). This mixture was stirred overnight with warming to room temperature and quenched by careful addition of saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted with 10% isopropanol/chloroform (3x). The combined organic extracts were washed with brine (1x), dried over sodium sulfate, filtered, and evaporated. The resulting solid was refluxed in ethyl acetate and filtered (hot). This procedure was repeated and the combined filtrates were concentrated to a minimal volume. After standing at room temperature overnight, a tan solid was collected by filtration. The resulting filtrate was again allowed to stand at room temperature overnight to yield an additional crop of the desired product to give all together 6.0 g (78%) of the title compound as a tan solid. mp: 149-151 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, 1H), 6.45 (d, 1H), 6.32 (s, 1H), 5.02-4.96 (c, 2H), 4.71 (q, 1H), 4.53 (s, 2H), 4.50-4.23 (c, 2H), 3.31-3.25 (c, 2H), 2.33 (s, 3H), 1.51 (d, 3H), 1.23 (s, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +18.9 (c 1.1, MeOH).

Examples 65 to 74

Examples 65 to 74 were prepared from the appropriate starting materials in a manner analogous to the method of Example 64.

Example 65

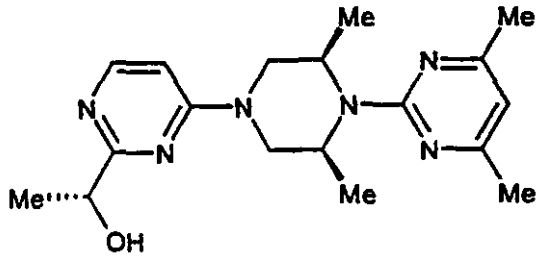
(R)-1-{4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



mp: 139-140 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, 1H), 6.41 (d, 1H), 6.37 (s, 1H), 4.71 (m, 1H), 4.54 (s, 2H), 4.32 (d, 1H), 4.02-3.93 (c, 4H), 3.78-3.68 (c, 4H), 3.65 (br s, 1H), 2.34 (s, 3H), 1.19 (d, 3H); MS (TS) 331 ($MH^+$); $[\alpha]_D$ +21.6 (c 2.0, MeOH).

Example 66

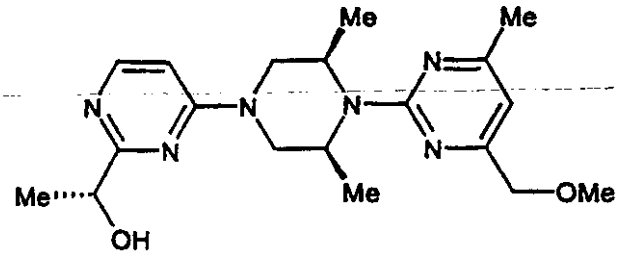
1R-{4-[4-(4,6-Dimethyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



mp: 141.5-142.5 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, 1H), 6.43 (d, 1H), 6.28 (s, 1H), 5.03-4.97 (c, 2H), 4.70 (q, 1H), 4.44-4.18 (c, 2H), 3.32-3.20 (c, 2H), 2.27 (s, 6H), 1.50 (d, 3H), 1.20 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +19.2 (c 1.1, MeOH).

Example 67

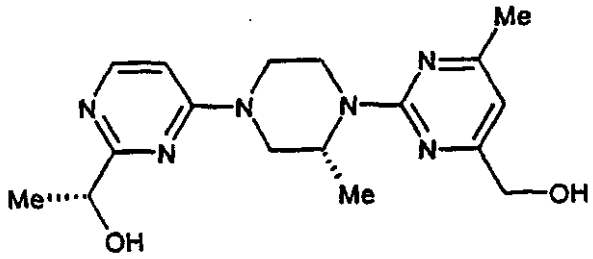
1R-{4-[4-(4-Methoxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, 1H), 6.55 (s, 1H), 6.43 (d, 1H), 5.02-4.93 (c, 2H), 4.69 (m, 1H), 4.43-4.20 (c, 2H), 4.36 (d, 1H), 4.33 (s, 2H), 3.46 (s, 3H), 3.30-3.21 (c, 2H), 2.34 (s, 3H), 1.51 (d, 3H), 1.20 (d, 6H); MS (APCI) 373 ($MH^+$); $[\alpha]_D$ +16.0 (c 0.9, MeOH).

Example 68

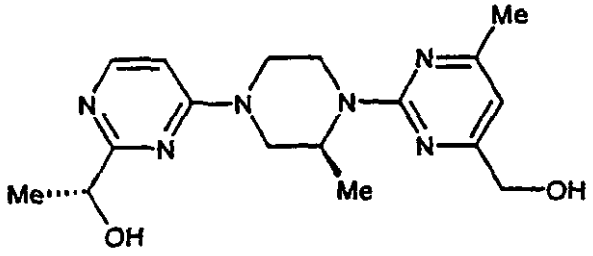
1R-[4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-3R-methyl-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.



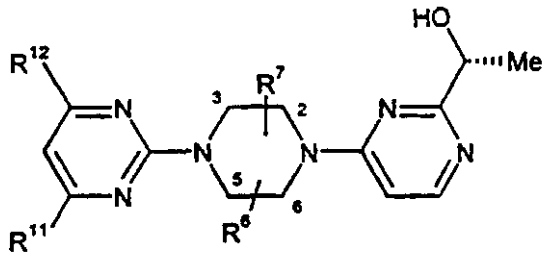
$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, 1H), 6.36 (d, 1H), 6.32 (s, 1H), 4.98 (m, 1H), 4.69 (q, 1H), 4.58 (dt, 1H), 4.51 (s, 2H), 4.37-4.11 (c, 3H), 3.62 (br s, 1H), 3.48-3.36 (c, 2H), 3.18 (td, 1H), 2.31 (s, 3H), 1.49 (d, 3H), 1.17 (s, 3H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ -40.6 (c 1.0, MeOH).

Example 69

1R-[4-[4-(4-Hydroxymethyl-6-methyl-pyrimidin-2-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.



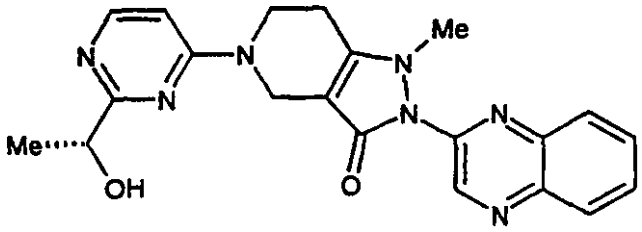
$^1$H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, 1H), 6.36 (d, 1H), 6.33 (s, 1H), 4.99 (m, 1H), 4.69 (q, 1H), 4.58 (m, 1H), 4.52 (s, 2H), 4.40-4.11 (c, 3H), 3.60 (br s, 1H), 3.45-3.34 (c, 2H), 3.19 (td, 1H), 2.32 (s, 3H), 1.49 (d, 3H), 1.16 (s, 3H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +68.1 (c 0.7, MeOH).



| Example | $R^{11}$ | $R^{12}$ | $R^7$ | $R^6$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|---|
| 70 | H | OH | 3R-Me | 5S-Me | | 331 |
| 71 | Me | OH | 3R-Me | 5S-Me | 231-232 | 345 |
| 72 | Ph | OH | 3R-Me | 5S-Me | | 407 |
| 73 | Me | ethoxymethyl | 3R-Me | 5S-Me | | 387 |
| 74 | Me | ethoxymethyl | 2R-Me | 6S-Me | 106-108 | 387 |

Example 75

(R)-5-[2-(1-Hydroxy-ethyl)-pyrimidin-4-yl]-1-methyl-2-quinoxalin-2-yl-1,2,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one.



**Step A:** 3-Oxo-2-quinoxalin-2-yl-1,2,3,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester. To a solution of 4-oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (500 mg, 1.84 mmol; *Tetrahedron* **1994**, *50*, 515) in toluene (10 mL) was added quinoxalin-2-yl-hydrazine (295 mg, 1.85 mmol; *Heterocycles* **1985**, 23, 2603). This mixture was stirred at reflux overnight, cooled to room temperature, concentrated, and purified by flash column chromatography (25→75% ethyl acetate/hexanes) to give 600 mg (89%) of the title compound of Example 75, Step A as a light orange solid. $^1H$ NMR ($CDCl_3$, 250 MHz, 5:1 mixture of tautomers) δ 11.94 (br s, 0.83H), 10.16 (s, 0.17H), 9.57 (s, 0.83H), 8.13 (dd, 1H), 7.91-7.69 (c, 3H), 4.45 (s, 1.66H), 4.33 (s, 0.34H), 3.79-3.72 (c, 2H), 2.82-2.72 (c, 2H), 1.52 (s, 9H); MS (APCI) 368 ($MH^+$).

**Step B:** 1-Methyl-3-oxo-2-quinoxalin-2-yl-1,2,3,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester. To a solution of 3-oxo-2-quinoxalin-2-yl-1,2,3,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (prepared according to the method of Example 75, Step A, 250 mg, 0.68 mmol) in dimethylformamide (2 mL) at 0 °C with stirring under nitrogen was added sodium hydride (60% dispersion in mineral oil, 41 mg, 1.02 mmol). After 10 min, iodomethane (51 µL, 0.82 mmol) was added. This mixture was allowed to stir at 0 °C for 2 h, quenched by addition of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (4x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (40% ethyl acetate/hexanes) to give 164 mg (63%) of the title compound of Example 75, Step B as a yellow foam. $^1$H NMR ($CDCl_3$, 250 MHz) δ 9.71 (s, 1H), 8.15 (dd, 1H), 8.02 (m, 1H), 7.80-7.70 (c, 2H), 4.29 (s, 2H), 4.14 (t, 2H), 3.79 (s, 3H), 2.72-2.67 (c, 2H), 1.50 (s, 9H); MS (APCI) 382 ($MH^+$).

**Step C:** 1-Methyl-2-quinoxalin-2-yl-1,2,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one hydrochloride. To a solution of 1-methyl-3-oxo-2-quinoxalin-2-yl-1,2,3,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (prepared according to the method of Example 75, Step B, 279 mg, 0.73 mmol) in methanol (6 mL) was added hydrogen chloride (5.85 M in methanol, 1.25 mL, 7.3 mmol). This mixture was heated at 60 °C for 30 min, cooled to room temperature, and concentrated to give 249 mg (>100%) of the title compound of Example 75, Step C as a dark red solid. $^1$H NMR ($CD_3OD$, 250 MHz) δ 9.45 (s, 1H), 8.13 (dd, 1H), 8.05 (m, 1H), 7.91-7.83 (c, 2H), 4.05 (s, 2H), 3.64 (t, 2H), 3.56 (s, 3H), 3.12 (t, 2H); MS (APCI) 282 ($MH^+$).

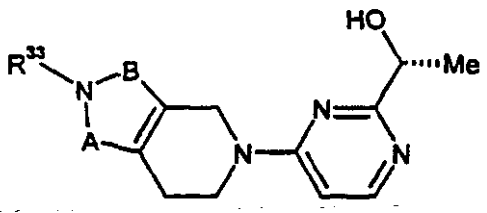
**Step D:** (R)-1-[4-(1-Methyl-3-oxo-2-quinoxalin-2-yl-1,2,3,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-pyrimidin-2-yl]-ethyl butyrate. To a stirred solution of 1-methyl-2-quinoxalin-2-yl-1,2,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one hydrochloride (prepared according to the method of Example 75, Step C, 175 mg, 0.55 mmol) and (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 126 mg, 0.55 mmol) in isopropanol (6 mL) was added triethylamine (230 µL, 1.66 mmol). This mixture was heated to reflux overnight, cooled to room temperature, and evaporated. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with chloroform (3x). The combined

organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1.5% methanol/chloroform) to give 248 mg (95%) of the title compound of Example 75, Step D as a yellow oil. $^1$H NMR ($CDCl_3$, 250 MHz) δ 9.70 (s, 1H), 8.29 (d, 1H), 8.15 (dd, 1H), 8.03 (m, 1H), 7.82-7.70 (c, 2H), 6.48 (d, 1H) 5.72 (q, 1H), 4.36 (s, 2H), 4.35-4.15 (c, 2H), 3.42 (s, 3H), 2.77-2.82 (c, 2H), 2.43 (t, 2H), 1.79-1.60 (c, 2H), 1.61 (d, 3H), 0.99 (t, 3H); MS (APCI) 474 ($MH^+$).

**Step E:** (R)-5-[2-(1-Hydroxy-ethyl)-pyrimidin-4-yl]-1-methyl-2-quinoxalin-2-yl-1,2,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one. To a solution of (R)-1-[4-(1-methyl-3-oxo-2-quinoxalin-2-yl-1,2,3,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 75, Step D, 248 mg, 0.52 mmol) in a 5:2 mixture of methanol/tetrahydrofuran (7 mL) was added potassium carbonate (218 mg, 1.57 mmol). This mixture was stirred at room temperature overnight and evaporated. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1.5→3% methanol/chloroform) to give 150 mg (71%) of the title compound as a white solid. mp: 217-219 °C (dec); $^1$H NMR ($CDCl_3$, 250 MHz) δ 9.66 (s, 1H), 8.25 (d, 1H), 8.12 (dd, 1H), 7.99 (m, 1H), 7.68-7.78 (c, 2H), 6.47 (d, 1H), 4.72 (q, 12H), 4.32 (s, 2H), 4.19-4.14 (c, 3H), 3.41 (s, 3H), 2.80 (t, 2H), 1.51 (d, 3H); MS (APCI) 404 ($MH^+$); $[\alpha]_D$ +13.4 (c 1.5, $CHCl_3$).

Examples 76 and 77

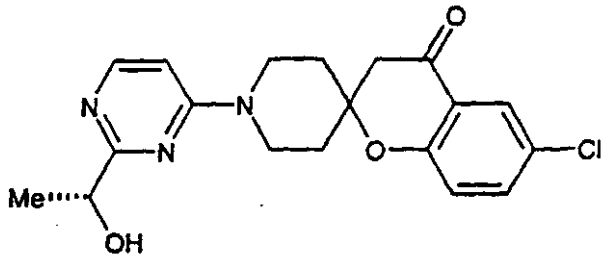
Examples 76 and 77 were prepared from the appropriate starting materials in a manner analogous to the method of Example 75.




| Example | A | $R^{33}$ | B | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 76 | N-Me | benzothiazol-2-yl | CO | 176-178 | 409 |
| 77 | CO | quinoxalin-2-yl | N-Me | 201-204 (dec) | 404 |

Example 78

(R)-6-Chloro-1'-[2-(1-hydroxy-ethyl)-pyrimidin-4-yl]-spiro[chroman-2,4'-piperidin]-4-one.



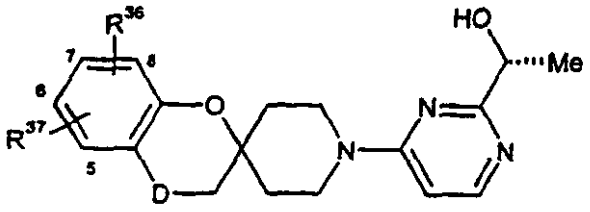
**Step A:** 6-Chloro-spiro[chroman-2,4'-piperidin]-4-one hydrochloride. To a solution of 1'-benzyl-6-chloro-spiro[chroman-2,4'-piperidin]-4-one (300 mg, 0.88 mmol, *Chem. Pharm. Bull.* **1981**, *29*, 3494) in acetone (5 mL) at 0 °C was added 1-chloroethyl chloroformate (0.29 mL, 2.64 mmol). This mixture was warmed to room temperature, stirred overnight, and concentrated. The residue was purified by flash column chromatography (10→20% ethyl acetate/hexanes) to give the intermediate carbamate which was refluxed in methanol (3 mL) for 1 h. Evaporation of the reaction mixture provided 149 mg (59%) of the title compound of Example 78, Step A as a colorless solid. $^1$H NMR ($CD_3OD$, 250 MHz) δ 7.77 (d, 1H), 7.58 (dd, 1H), 7.15 (d, 1H), 3.33 (buried, 4H), 2.90 (s, 2H), 2.46-2.20 (c, 2H), 2.04-1.81 (c, 2H); MS (APCI) 252, 254 ($MH^+$).

**Step B:** (R)-1'-[2-(1-Butyryloxy-ethyl)-pyrimidin-4-yl]-6-chloro-spiro[chroman-2,4'-piperidin]-4-one. To a solution of 6-chloro-spiro[chroman-2,4'-piperidin]-4-one hydrochloride (prepared according to the method of Example 78, Step A, 175 mg, 0.61 mmol) in isopropanol (5 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 160 mg, 0.70 mmol) followed by triethylamine (0.29 mL, 2.1 mmol). This mixture was stirred at reflux for 1.5 h, concentrated, and purified by flash column chromatography (1% methanol/chloroform) to give 270 mg (100%) of the title compound of Example 78, Step B as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, 1H), 7.83 (d, 1H), 7.44 (dd, 1H), 6.97 (d, 1H), 6.37 (d, 1H), 5.64 (q, 1H), 4.18 (app s, 2H), 3.34 (t, 2H), 2.72 (s, 2H), 2.37 (t, 2H), 2.10 (d, 2H), 1.71-1.60 (c, 4H), 1.55 (d, 3H), 0.94 (t, 3H); MS (APCI) 444, 446 ($MH^+$).

**Step C:** (R)-6-Chloro-1'-[2-(1-hydroxy-ethyl)-pyrimidin-4-yl]-spiro[chroman-2,4'-piperidin]-4-one. A mixture of (R)-1'-[2-(1-butyryloxy-ethyl)-pyrimidin-4-yl]-6-chloro-spiro[chroman-2,4'-piperidin]-4-one (prepared according to the method of Example 78, Step B, 270 mg, 0.61 mmol) and lithium hydroxide hydrate (80 mg, 1.83 mmol) in a 3:1:1 mixture of tetrahydrofuran/methanol/water (5 mL) was stirred at room temperature for 1.5 h. The organic solvents were evaporated and the residue was extracted with chloroform (4x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (ethyl acetate) to give 41 mg (18%) of the title compound as a reddish foam. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, 1H), 7.82 (d, 1H), 7.44 (dd, 1H), 6.96 (d, 1H), 6.40 (d, 1H), 4.65 (q, 1H), 4.20 (app s, 2H), 3.42-3.32 (c, 2H), 2.73 (s, 2H), 2.14 (d, 2H), 1.67 (td, 2H), 1.48 (d, 3H); MS (APCI) 374, 376 ($MH^+$); $[\alpha]_D$ +12.6 (c 0.5, MeOH).

Examples 79 to 85

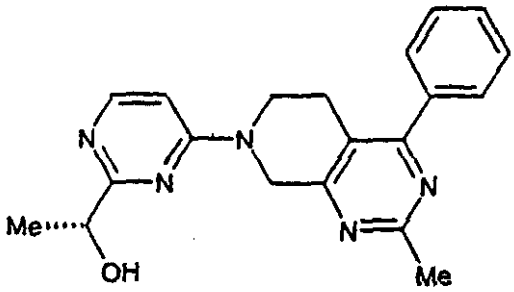
Examples 79 to 85 were prepared from the appropriate starting materials in a manner analogous to the method of Example 78.




| Example | $R^{36}$ | $R^{37}$ | D | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 79 | 6-Ph | H | $CH_2$ | | 402 |
| 80 | 6-Ph | H | CHOH | | 418 |
| 81 | 6-Ph | H | CO | | 416 |
| 82 | 6-OMe | H | CO | 156.5-157.5 | 370 |
| 83 | 7-Br | H | CO | | 418,420 |
| 84 | 5-Cl | 6-Cl | CO | | 408,410 |
| 85 | 6-OMe | 7-OMe | CO | | 400 |

Example 86

(R)-1-[4-(2-Methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-pyrimidin-2-yl]-ethanol.




**Step A:** 7-Benzyl-2-methyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one. A solution of sodium ethoxide in ethanol was prepared by addition of sodium metal (5.7 g, 247 mmol) to absolute ethanol (141 mL). After the sodium metal had all dissolved, ethyl 1-benzyl-3-oxo-4-piperidine carboxylate hydrochloride (21 g, 70.5 mmol) was added followed by acetamidine hydrochloride (13.3 g, 141 mmol). This mixture was stirred at reflux for 1 h, cooled to room temperature, and concentrated. The residue was dissolved in a minimum amount of water and the pH was adjusted to about 7 with glacial acetic acid. The resulting yellow precipitate was filtered, washed with water (3x), air-dried for 2 h, then vacuum-dried overnight to provide 17.1 g (95%) of the title compound of Example 86, Step A as a yellow solid. $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.35-7.25 (c, 5H), 3.70 (s, 2H), 3.42 (s, 2H), 2.73-2.64 (c, 2H), 2.64-2.60 (c, 2H), 2.41 (s, 3H); MS (APCI) 256 ($MH^+$).

**Step B:** 7-Benzyl-4-chloro-2-methyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine. 7-Benzyl-2-methyl-5,6,7,8-tetrahydro-3H-pyrido[3,4-d]pyrimidin-4-one (prepared according to the method of Example 86, Step A, 17.1 g, 67.0 mmol) was suspended in phosphorus oxychloride (66 mL, 335 mmol). This mixture was stirred at reflux for 1 h, cooled to room temperature, evaporated, then chased with toluene. The residue was carefully diluted with ice/water/chloroform and the layers were separated. The aqueous phase was extracted with chloroform (3x) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (1x) and water (1x), dried over sodium sulfate, filtered, and evaporated to give the title compound of Example 86, Step B as a brown oil that was used without purification in the next step. $^1$H NMR

($CDCl_3$, 250 MHz) δ 7.36-7.23 (c, 5H), 3.73 (s, 2H), 3.63 (s, 2H), 2.63 (app s, 4H), 2.36 (s, 3H); MS (APCI) 274, 276 ($MH^+$).

**Step C:** 7-Benzyl-2-methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine. To a suspension of 1,4-diphenylphosphinobutane (1.43 g, 3.35 mmol) in toluene (50 mL) was added bis(benzonitrile)palladium(II) chloride (1.28 g, 3.35 mmol). This mixture was stirred for 25 min at room temperature, then was added to a suspension of 7-benzyl-4-chloro-2-methyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine (prepared according to the method of Example 86, Step B, 67.0 mmol, assumed) and phenylboronic acid (10.6 g, 87.1 mmol) in a mixture of absolute ethanol (40 mL), toluene (175 mL), and 2 N aqueous sodium carbonate (33.5 mL). This mixture was stirred at reflux for 6.5 h, cooled to room temperature and stirred for ~2.5 d, then filtered through a pad of Celite. The filtrate was concentrated and the residue was diluted with water and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (45→50% ethyl acetate/hexanes) to give 16.5 g (78%, two steps) of the title compound of Example 86, Step C as a yellow oil. $^1H$ NMR ($CDCl_3$, 250 MHz) δ 7.57-7.54 (c, 2H), 7.48-7.24 (c, 8H), 3.71 (app s, 4H), 2.85 (t, 2H), 2.71-2.67 (c, 2H), 2.69 (s, 3H); MS (APCI) 316 ($MH^+$).

**Step D:** 2-Methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine. 7-Benzyl-2-methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine hydrochloride was formed in situ by addition of hydrogen chloride (1.9 M in methanol, 31.1 mL, 51.1 mmol) to a solution of 7-benzyl-2-methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine (prepared according to the method of Example 86, Step C, 16.5 g, 52.2 mmol) in methanol (75 mL). After stirring 10 min at room temperature, a precipitate formed, and another aliquot of methanol (100 mL) was added to obtain a homogeneous solution. To this mixture was added a slurry of 10% palladium on carbon (3.3 g, 20 wt%) in methanol followed by ammonium formate (16.5 g, 261 mmol). This mixture was stirred at reflux for 5 h, cooled to room temperature, and filtered through Celite. The filtrate was evaporated, diluted with saturated aqueous sodium bicarbonate, and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (3% methanol/chloroform + 1% ammonium hydroxide) to give 6.7 g (57%) of the title compound of Example 86, Step D as an off-white solid and 2.4 g (19%) of 7-formyl-2-

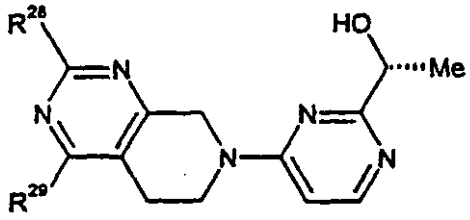
methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine as a yellow gum. Treatment of the 7-formyl byproduct with methanolic hydrogen chloride at room temperature overnight followed by aqueous workup and column chromatography provided an additional 1.4 g (12%) of the title compound of Example 86, Step D. $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.55-7.40 (c, 5H), 4.09 (s, 2H), 3.05 (t, 2H), 2.75 (t, 2H), 2.79 (s, 3H); MS (APCI) 226 ($MH^+$).

**Step E:** (R)-1-[4-(2-Methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of 2-methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidine (prepared according to the method of Example 86, Step D, 6.8 g, 30.0 mmol) in isopropanol (125 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 6.8 g, 30 mmol) followed by triethylamine (12.5 mL, 89.9 mmol). This mixture was stirred at reflux for 8 h, cooled to room temperature overnight, and evaporated. The residue was diluted with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (2% methanol/ethyl acetate) to give 11.0 g (88%) of the title compound of Example 86, Step E, as a yellow oil. $^1$H NMR ($CDCl_3$, 250 MHz) δ 8.28 (d, 1H), 7.62-7.40 (c, 5H), 6.45 (d, 1H), 5.69 (q, 1H), 4.78 (s, 2H), 3.93 (app s, 2H), 2.95 (t, 2H), 2.77 (s, 3H), 2.40 (t, 2H), 1.77-1.63 (c, 2H), 1.60 (d, 3H), 0.98 (t, 3H); MS (APCI) 418 ($MH^+$).

**Step F:** (R)-1-[4-(2-Methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-pyrimidin-2-yl]-ethanol. To a solution of (R)-1-[4-(2-methyl-4-phenyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 86, Step E, 11.0 g, 26.4 mmol) in dioxane (13 mL) was added concentrated hydrochloric acid (22 mL, 264 mmol). This mixture was stirred at room temperature overnight, cooled to 0 °C, neutralized via slow addition of 6 N aqueous sodium hydroxide, and extracted with ethyl acetate (4x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (2→5% methanol/ethyl acetate) to give an oil which after tritration with hexanes provided 8.0 g (88%) of the title compound as a white solid. mp: 114-116 °C; $^1$H NMR ($CD_3OD$, 250 MHz) δ 8.26 (d, 1H), 7.62-7.47 (c, 5H), 6.52 (d, 1H), 4.79 (s, 2H), 4.66 (q, 1H), 4.24 (br s, 1H), 3.90-3.80 (c, 2H), 2.95 (t, 2H), 2.70 (s, 3H), 1.49 (d, 3H); MS (APCI) 348 ($MH^+$), $[\alpha]_D$ +15.6 (c 1.0, MeOH).

Examples 87 to 100

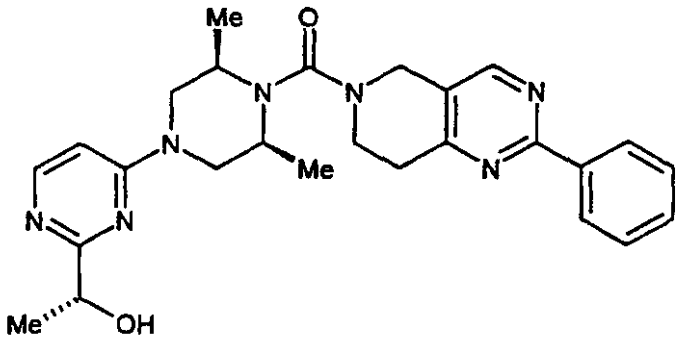
Examples 87 to 100 were prepared from the appropriate starting materials in a manner analogous to the method of Example 86.



| Example | $R^{29}$ | $R^{28}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|
| 87 | H | Ph | 72-74 | 334 |
| 88 | Ph | H | | 334 |
| 89 | Ph | Et | | 362 |
| 90 | Ph | $NH_2$ | 225-228 (dec) | 349 |
| 91 | Ph | Ph | 73-75 | 410 |
| 92 | Ph | 4-pyridyl | | 411 |
| 93 | (4-OMe)Ph | Me | 62-64 | 378 |
| 94 | (4-F)Ph | Me | 55-58 | 366 |
| 95 | (4-Cl)Ph | H | | 368, 370 |
| 96 | OMe | Me | | 302 |
| 97 | OPh | Me | 156-158 | 364 |
| 98 | SPh | Me | 103-105 | 380 |
| 99 | N-indolinyl | Me | 128-131 | 389 |
| 100 | $NMe_2$ | Et | | 329 |

Example 101

{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-(2-phenyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone.



**Step A:** 4-Oxo-piperidine-1-carboxylic acid tert-butyl ester. A mixture of 4-piperidone monohydrate hydrochloride (9.22 g, 60 mmol) and di-tert-butyl dicarbonate (10.9 g, 50 mmol) in a 1:1 mixture of dichloromethane/saturated aqueous sodium bicarbonate (100 mL) was stirred at room temperature for 15.5 h. The layers were separated and the aqueous layer was extracted with chloroform (3x). The combined organic extracts were washed with 1 N aqueous phosphoric acid (3x), dried over sodium sulfate, filtered, and evaporated to give 10.0 g (100%) of the title compound of Example 101, Step A as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.70 (t, 4H), 2.42 (t, 4H), 1.47 (s, 9H).

**Step B:** 3-Dimethylaminomethylene-4-oxo-piperidine-1-carboxylic acid tert-butyl ester. To a solution of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (prepared according to the method of Example 101, Step A, 4.0 g, 20.0 mmol) in dimethylformamide (40 mL) was added tert-butoxybis(dimethylamino)methane (4.35 mL, 22 mmol). This mixture was stirred at reflux for 15 h, cooled to room temperature, diluted with water, and extracted with ethyl acetate (5x). The combined organic extracts were washed with water (3x) and brine (1x), dried over sodium sulfate, filtered, and evaporated to give 3.64 g (72%) of the title compound of Example 101, Step B as a brown oil that was sufficiently pure to carry on to the next step. $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.47 (s, 1H), 4.53 (s, 2H), 3.58 (t, 2H), 3.09 (s, 6H), 2.43 (t, 2H), 1.46 (s, 9H); MS (APCI) 255 ($MH^+$).

**Step C:** 2-Phenyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylic acid tert-butyl ester. A mixture of 3-dimethylaminomethylene-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (prepared according to the method of Example 101, Step B, 509 mg, 2.0 mmol), benzamidine hydrochloride hydrate (470 mg, 3.0 mmol), and sodium ethoxide (1 M in ethanol, 6.0 mL, 6.0 mmol) in absolute ethanol (4 mL) was heated to reflux for about 3 d, cooled to room temperature, and concentrated. The residue was diluted

with saturated aqueous sodium bicarbonate and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (Biotage Flash 40S™, 10→15% ethyl acetate/hexanes) to give 304 mg (49%) of the title compound of Example 101, Step C as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.52 (s, 1H), 8.40-8.38 (c, 2H), 7.50-7.44 (c, 3H), 4.62 (s, 2H), 3.78 (t, 2H) 3.02 (t, 2H), 1.50 (s, 9H); MS (APCI) 312 ($MH^+$).

**Step D:** 2-Phenyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine hydrochloride. To a solution of 2-phenyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylic acid tert-butyl ester (prepared according to the method of Example 101, Step C, 304 mg, 0.98 mmol) in ethyl acetate (2 mL) was added hydrogen chloride (2.5 M in ethyl acetate, 3.9 mL, 9.76 mmol). This mixture was stirred at room temperature for 16 h and concentrated to give 256 mg (>100%) of the title compound of Example 101, Step D as a pale yellow solid. $^1$H NMR ($CD_3OD$, 400 MHz) δ 8.75 (s, 1H), 8.42-8.38 (c, 2H), 7.51-7.45 (c, 3H), 4.48 (s, 2H), 3.68 (t, 2H) 3.35-3.25 (buried, 2H); MS (APCI) 212 ($MH^+$).

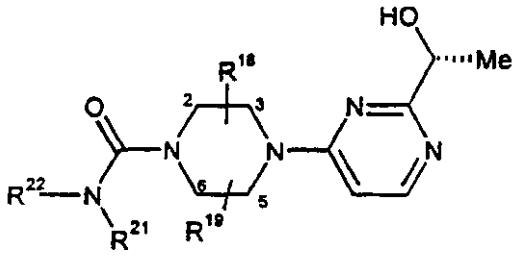
**Step E:** 1R-[4-(4-Chlorocarbonyl-3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 1.36 g, 4.44 mmol) in dichloromethane (22 mL) at 0°C under nitrogen was added pyridine (0.36 mL, 4.44 mmol) followed by triphosgene (883 mg, 2.97 mmol). This mixture was stirred with warming to room temperature for 1.5 h and quenched with saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1→2% methanol/chloroform) to give 1.59 g (97%) of the title compound of Example 101, Step E as a brown oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 1H), 6.39 (d, 1H), 5.66 (q, 1H), 4.54-4.47 (c, 2H), 4.35 (m, 1H), 4.25 (m, 1H), 3.20 (dt, 2H), 2.38 (t, 2H), 1.72-1.62 (c, 2H), 1.56 (d, 3H), 1.31 (d, 3H), 1.30 (d, 3H), 0.95 (t, 3H); MS (APCI) 369, 371 ($MH^+$).

**Step F:** {4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-(2-phenyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone. A mixture of 2-phenyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine hydrochloride (prepared according to the method of Example 101, Step D, 160 mg, 0.65 mmol), 1R-[4-(4-chlorocarbonyl-3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 101, Step E, 200 mg, 0.54 mmol), and triethylamine (0.19 mL,

1.36 mmol) in tetrahydrofuran (5 mL) was stirred at reflux for 3 h, cooled to room temperature overnight, and concentrated. The residue was diluted with a 4:1 mixture of methanol/water (5 mL) and lithium hydroxide hydrate (114 mg, 2.71 mmol) was added. This mixture was stirred for 2.5 h, concentrated, and partitioned between saturated aqueous sodium bicarbonate and chloroform. The layers were separated and the aqueous phase was extracted with 20% isopropanol/chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (2→5% methanol/chloroform) to give 183 mg (71%) the title compound as a white foam. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1H), 8.41-8.39 (c, 2H), 8.20 (d, 1H), 7.50-7.46 (c, 3H), 6.38 (d, 1H), 4.71 (s, 2H), 4.69 (m, 1H), 4.28 (d, 1H), 3.89 (t, 2H) 3.83 (d, 2H), 3.60-3.56 (c, 2H), 3.46-3.39 (c, 2H), 3.09 (t, 2H), 1.50 (d, 3H), 1.18 (d, 6H); MS (APCI) 212 ($MH^+$); $[\alpha]_D$ +6.1 (c 1.8, $CHCl_3$).

Examples 102 to 110

Examples 102 to 110 were prepared from the appropriate starting materials in a manner analogous to the method of Example 101.

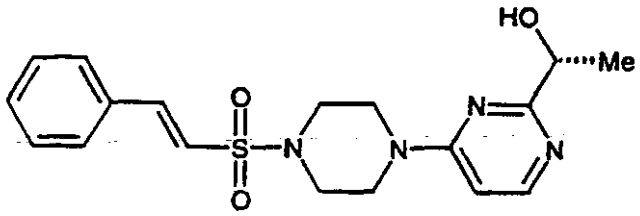


| Example | $R^{22}$ | $R^{21}$ | $R^{18}$ | $R^{19}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|---|
| 102 | quinolin-2-yl | H | 3R-Me | 5S-Me | 172-174.5 | 407 |
| 103 | quinolin-3-yl | H | 2R-Me | 6S-Me | | 407 |
| 104 | quinolin-4-yl | H | 3R-Me | 5S-Me | | 407 |
| 105 | quinolin-6-yl | H | 3R-Me | 5S-Me | | 407 |
| 106 | pyridin-3-yl-methyl | pyridin-3-yl-methyl | 2R-Me | 6S-Me | | 462 |

| Example | $NR^{21}R^{22}$ | $R^{18}$ | $R^{19}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 107 | 2-amino-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl | 2R-Me | 6S-Me | 225-228 | 413 |
| 108 | 2-(1-hydroxy-1-methyl-ethyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl | 2R-Me | 6S-Me | | 456 |
| 109 | 5,7-dihydro-dibenzo[c,e]azepin-6-yl | 2R-Me | 6S-Me | | 458 |
| 110 | 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl | 3R-Me | 5S-Me | | 499 |

Example 111

(E)-1R-[4-[4-(2-Phenyl-ethenesulfonyl)-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.

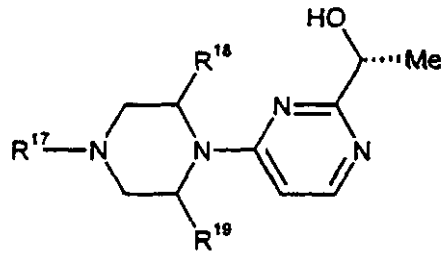


**Step A:** (E)-1R-[4-[4-(2-Phenyl-ethenesulfonyl)-piperazin-1-yl]-pyrimidin-2-yl]-ethyl acetate. To a solution of (R)-1-[4-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate (prepared according to the method of Preparation Two, 0.25 g, 1.0 mmol) and triethylamine (0.10 g, 1.0 mmol) in tetrahydrofuran (5 mL) was added β-styrenesulfonyl chloride (0.21 g, 1.0 mmol) at ambient temperature and stirred for 1 h. The mixture was diluted with water and extracted twice with ethyl acetate. The extract was dried over magnesium sulfate, filtered, and the filtrate was concentrated to an oil, which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 111, Step A as an oil, 0.15 g (34%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, 3H), 2.15 (s, 3H), 3.23 (m, 4H), 3.84 (m, 4H), 5.61 (q, 1H), 6.40 (d, 1H), 6.65 (d, 1H), 7.39-7.52 (m, 6H), 8.21 (d, 1H); MS (TS) 417 ($MH^+$).

**Step B:** (E)-1R-[4-[4-(2-Phenyl-ethenesulfonyl)-piperazin-1-yl]-pyrimidin-2-yl]-ethanol. To a solution (E)-1R-[4-[4-(2-phenyl-ethenesulfonyl)-piperazin-1-yl]-pyrimidin-2-yl]-ethyl acetate (prepared according the method of Example 111, Step A, 0.14 g, 0.33 mmol) in methanol (1 mL) was added at ambient temperature 6 N aqueous potassium hydroxide (0.25 mL). After stirring for 3 h, the solution was diluted with ethyl acetate and washed twice with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the filtrate was concentrated to give the title compound as a white solid, 0.09 g (69%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, 3H), 3.23 (m, 4H), 3.84 (m, 4H), 4.20 (br s,1H), 4.71 (q, 1H), 6.40 (d, 1H), 6.65 (d, 1H), 7.39-7.52 (m, 6H), 8.21 (d, 1H); mp: 68-70 °C; MS (TS) 375 ($MH^+$); $[\alpha]_D$ +20.9 (c 1.0, MeOH).

Examples 112 and 113

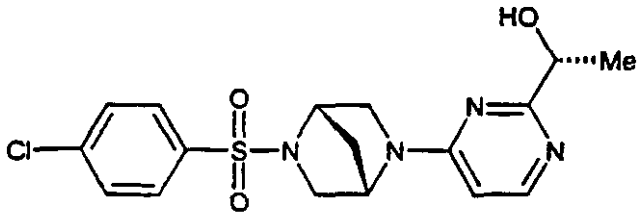
Examples 112 and 113 were prepared from the appropriate starting materials in a manner analogous to the method of Example 111.



| Example | $R^{18}$ | $R^{19}$ | $R^{17}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 112 | (R)-Me | (S)-Me | isopropylsulfonyl | 152-154 | 343 |
| 113 | (R)-Me | (S)-Me | 1-methyl-1H-imidazol-4-yl-sulfonyl | 157-158 | 381 |

Example 114

1R-[4-[5-(4-Bromobenzenesulfonyl)-2R,5S-diaza-bicyclo[2.2.1]hept-2-yl]-pyrimidin-2-yl]-ethanol.



**Step A:** 1R-[4-(2R,5S-Diaza-bicyclo[2.2.1]hept-2-yl)-pyrimidin-2-yl]-ethyl butyrate. To a suspension of 2,5-diaza-bicyclo[2.2.1]heptane dihydrobromide (7.57 g, 88.0 mmol; *Synthesis* **1990**, *10*, 925) in dichloromethane (90 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (13.7 g, 90 mmol) and stirred until homogeneous. A solution of (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 10.2 g, 45 mmol) in dichloromethane (10 mL) was added and stirred at reflux for 14 h. The mixture was filtered and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product which was purified by flash chromatography (9:1→5:1 dichloromethane:methanol) to give the title compound of Example 114, Step A as an oil, 6.75 g (51%). $^1H$ NMR ($CDCl_3$, 300

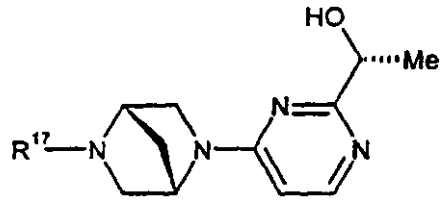
MHz) δ 0.92 (t, 3H), 1.54 (d, 3H), 1.68-1.78 (m, 5H), 2.68 (t, 2H), 3.38 (m, 1H), 3.76 (m, 3H), 4.42 (m, 1H), 5.35 (q, 1H), 6.16 (d, 1H), 8.12 (d, 1H); MS (CI) 291 ($MH^+$).

**Step B:** 1R-{4-[5-(4-Bromobenzenesulfonyl)-2R,5S-diaza-bicyclo[2.2.1]hept-2-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 1R-[4-(2R,5S-diaza-bicyclo[2.2.1]hept-2-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 114, Step A, 0.58 g, 2.0 mmol) and triethylamine (0.22 g, 2.2 mmol) in chloroform (10 mL) was added 4-bromobenzenesulfonyl chloride (0.56 g, 2.2 mmol) and stirred at ambient temperature for 16 h. The mixture was washed once with water, once with brine, dried over magnesium sulfate, filtered, and the filtrate was concentrated to give the title compound of Example 114, Step B as a clear oil, 0.92 g (90%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H), 1.54 (d, 3H), 1.68-1.78 (m, 5H), 2.68 (t, 2H), 3.25 (m, 1H), 3.46 (m, 3H), 4.28 (m, 1H), 5.25 (q, 1H), 6.16 (d, 1H), 7.58 -7.64 (m, 4H), 8.12 (d, 1H); MS (CI) 510 ($MH^+$).

**Step C:** 1R-{4-[5-(4-Bromobenzenesulfonyl)-2R,5S-diaza-bicyclo[2.2.1]hept-2-yl]-pyrimidin-2-yl}-ethanol. To a solution of 1R-{4-[5-(4-bromobenzenesulfonyl)-2R,5S-diaza-bicyclo[2.2.1]hept-2-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 114, Step B, 0.85 g, 1.6 mmol) in a 2:1 mixture of tetrahydrofuran:methanol (10 mL) was added at ambient temperature 6 N aqueous potassium hydroxide (1 mL). After stirring for 6 h the solution was diluted with dichloromethane and washed twice with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the filtrate was concentrated to a viscous oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound as a white foam, 0.49 g (66%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.54 (d, 3H), 1.68 (m, 2H), 1.78 (m, 1H), 3.25 (m, 1H), 3.46 (m, 3H), 4.28 (m, 1H), 4.78 (q, 1H), 6.16 (d, 1H), 7.64 (m, 4H), 8.12 (d, 1H); mp: 83-88 °C; MS (CI) 440 ($MH^+$); $[\alpha]_D$ -49.2 (c 1.0, MeOH).

Examples 115 to 120

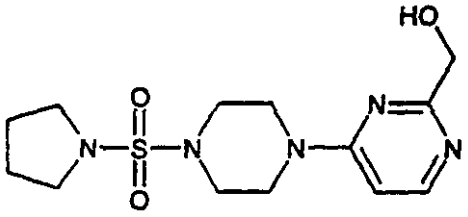
Examples 115 to 120 were prepared from the appropriate starting materials in a manner analogous to the method of Example 114.



| Example | $R^{17}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|
| 115 | 4-chlorophenylsulfonyl | 83-88 | 395, 397 |
| 116 | 2-thienylsulfonyl | 84-86 | 367 |
| 117 | 2-(5-chlorothienyl)-sulfonyl | 62-64 | 401, 403 |
| 118 | 4-carboxamidoylphenyl-sulfonyl | 148-151 | 404 |
| 119 | 4-(tert-butylphenyl)-sulfonyl | 72-75 | 417 |
| 120 | N,N-dimethylsulfamoyl | 110-111 | 328 |

Example 121

{4-[4-(Pyrrolidine-1-sulfonyl)-piperazin-1-yl]-pyrimidin-2-yl}-methanol.

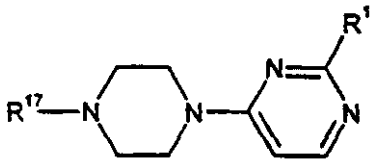


**Step A:** 2-Methoxymethyl-4-[4-(pyrrolidine-1-sulfonyl)-piperazin-1-yl]-pyrimidine. To a solution of 2-methoxymethyl-4-piperazin-1-yl-pyrimidine (prepared according to the method of Preparation One, 2.08 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in tetrahydrofuran (20 mL) was added N-pyrrolidinesulfonyl chloride (1.69 g, 10 mmol) at 0 °C and stirred for 3 h at ambient temperature. The mixture was diluted with ethyl acetate and washed twice with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the filtrate was concentrated to an oil which was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound of Example 121, Step A as a clear oil, 3.24 g (93%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.81-1.85 (m, 4H), 3.12-3.18 (m, 8H), 3.59 (s, 3H), 3.81(m, 4H), 4.43 (s, 2H), 6.71 (d, 1H), 8.18 (d, 1H); MS (TS) 342 ($MH^+$).

**Step B:** {4-[4-(Pyrrolidine-1-sulfonyl)-piperazin-1-yl]-pyrimidin-2-yl}-methanol. To a solution of 2-methoxymethyl-4-[4-(pyrrolidine-1-sulfonyl)-piperazin-1-yl]-pyrimidine (prepared according to the method of Example 121, Step A, 3.1 g, 9.4 mmol) in dichloromethane (47 mL) was added boron tribromide (1 M in dichloromethane, 19 mL, 18.7 mmol) at 0 °C then stirred at ambient temperature for 2 h. The mixture was washed twice with saturated aqueous sodium bicarbonate, and the organic layer was separated, dried over magnesium sulfate, filtered, and the filtrate was concentrated to give an oil which was crystallized from isopropyl ether to give the title compound as a white solid, 2.43 g (77%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.82 (m, 4H), 3.15 (m, 8H), 3.81 (m, 4H), 4.35 (d, 2H), 4.83 (t, 1H), 6.71 (d, 1H), 8.18 (d, 1H); mp: 128-131 °C; MS (CI) 328 ($MH^+$).

Examples 122 to 125

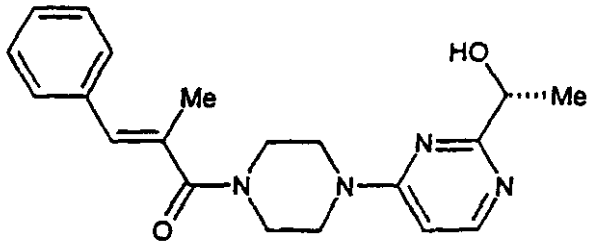
Examples 122 to 125 were prepared from the appropriate starting materials in a manner analogous to the method of Example 121.



| Example | $R^1$ | $R^{17}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|
| 122 | $CH_2OH$ | 2,5-dimethylpyrrolidin-1-ylsulfonyl | 128-131 | 356 |
| 123 | $CH_2OH$ | piperidin-1-ylsulfonyl | 141-142 | 342 |
| 124 | (R)-CH(Me)OH | aza-bicyclo[3.2.1]octan-8-ylsulfonyl | 111-112 | 382 |
| 125 | (R)-CH(Me)OH | aza-bicyclo[3.2.1]octan-3-one-8-yl-sulfonyl | 113-114 | 396 |

Example 126

(E)-1-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-piperazin-1-yl}-2-methyl-3-phenyl-propenone.

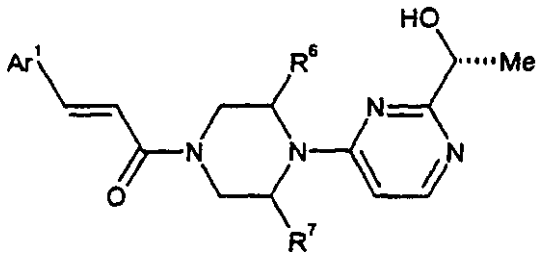



**Step A:** (E)-1R-{4-[4-(2-Methyl-3-phenyl-acryloyl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl acetate. To a solution of (R)-1-(4-piperazin-1-yl-pyrimidin-2-yl)-ethyl acetate (prepared according to the method of Preparation Two, 0.54 g, 2.1 mmol) and α-methylcinnamic acid (0.34 g, 2.1 mmol) in dichloromethane (10 mL) was added 1-hydroxybenzotriazole (0.50 g, 3.6 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.45 g, 2.4 mmol) at ambient temperature and stirred for 48 h. The mixture was washed once with water, once with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and the filtrate was concentrated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 126, Step A as a clear viscous oil, 0.53 g (63%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.51 (d, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 3.75 (m, 8H), 5.68 (q, 1H), 6.41 (d, 1H), 6.59 (s, 1H), 7.25-7.43 (m, 5H), 8.23 (d, 1H); MS (CI) 395 ($MH^+$); $[\alpha]_D$ +38.6 (c 1.0, MeOH).

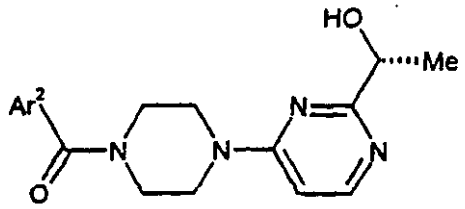
**Step B:** (E)-1-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-piperazin-1-yl}-2-methyl-3-phenyl-propenone. To a solution of (E)-1R-{4-[4-(2-methyl-3-phenyl-acryloyl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl acetate (prepared according to the method of Example 126, Step A, 0.51 g, 1.3mmol) in methanol (5 mL) was added at ambient temperature 6 N aqueous potassium hydroxide (1 mL). After stirring for 1 h the solution was diluted with ethyl acetate and washed twice with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the filtrate was concentrated to give the title compound as a white solid, 0.25 g (55%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.51 (d, 3H), 2.14 (s, 3H), 3.75 (m, 8H), 4.22 (br s, 1H), 4.71 (q, 1H), 6.41 (d, 1H), 6.59 (s, 1H), 7.25-7.43 (m, 5H), 8.23 (d, 1H); mp: 119-121 °C; MS (CI) 353 ($MH^+$); $[\alpha]_D$ +16.0 (c 1.0, MeOH).

Examples 127 to 129

Examples 127 to 129 were prepared from the appropriate starting materials in a manner analogous to the method of Example 126.



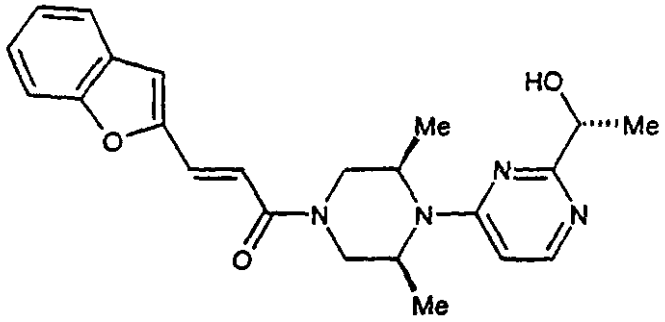
| Example | $Ar^1$ | $R^6$ | $R^7$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 127 | thien-2-yl | H | H | 104-106 | 345 |
| 128 | thien-2-yl | (R)-Me | (S)-Me | 69-73 | 373 |



| Example | $Ar^2$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|
| 129 | 4-(o-tolylcarbamoyl)-phenyl | 98-103 | 446 |

Example 130

(E)-3-Benzofuran-2-yl-1-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-propenone.



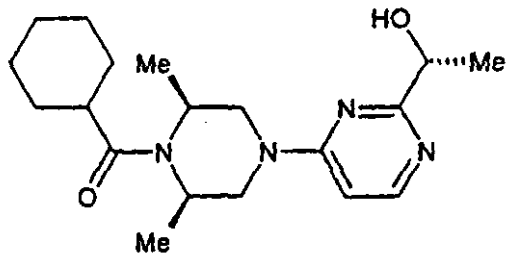
**Step A:** (E)-1R-{4-[4-(3-Benzofuran-2-yl-acryloyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 0.79 g, 2.6 mmol) and triethylamine (0.26 g, 2.6 mmol) in dichloromethane (90 mL) was added (E)-3-benzofuran-2-yl-acryloyl chloride (0.54 g, 2.6 mmol) and stirred at ambient temperature for 16 h, then at reflux for 2.5 h. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product, which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 130, Step A as a viscous oil, 0.79 g (54%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.40 (d, 6H), 1.56 (d, 3H), 1.67 (q, 2H), 2.38 (t, 2H), 3.25 (d, 2H), 4.33 (m, 2H), 4.75 (m, 2H), 5.66 (q, 1H), 5.95 (d, 1H), 6.40 (d, 1H), 7.14-7.37, (m, 5H), 8.06 (d, 1H), 8.22 (d, 1H); MS (CI) 477 ($MH^+$); $[\alpha]_D$ +49.1 (c 1.0, MeOH).

**Step B:** (E)-3-Benzofuran-2-yl-1-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-propenone. To a solution of (E)-1R-{4-[4-(3-benzofuran-2-yl-acryloyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 130, Step A, 0.51 g, 1.1 mmol) in methanol (5 mL) was added at ambient temperature 6 N aqueous potassium hydroxide (1 mL). After stirring for 1 h the solution was diluted with ethyl acetate and washed twice with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the filtrate was concentrated to give the title compound as a white solid, 0.49 g (75%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.40 (d, 6H), 1.56 (d, 3H), 3.25 (d, 2H), 4.33 (m, 2H),

4.75 (m, 2H), 4.68 (q, 1H), 5.95 (d, 1H), 6.40 (d, 1H), 7.14-7.37, (m, 5H), 8.06 (d, 1H), 8.22 (d, 1H); *mp*: 80-82 °C; MS (CI) 407 ($MH^+$); $[\alpha]_D$ +17.7 (c 1.0, MeOH).

Example 131

Cyclohexyl-[4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl)-methanone.



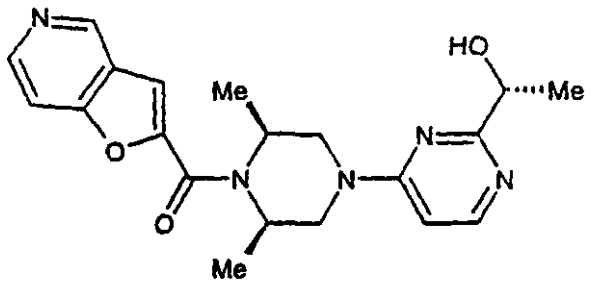

**Step A:** 1R-[4-(4-Cyclohexanecarbonyl-3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 306 mg, 1.0 mmol) and triethylamine (230 mg, 1.2 mmol) in dichloromethane (10 mL) was added at ambient temperature cyclohexanecarbonyl chloride (161 mg, 1.1 mmol). After 1 h the mixture was washed with water, and the dichloromethane layer was dried over magnesium sulfate and filtered. The filtrate was concentrated to give the title compound of Example 131, Step A as an oil, 388 mg (94%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H), 1.2-1.4 (m, 6H), 1.54 (d, 3H), 1.5-1.83 (m, 12H), 2.44 (m, 3H), 3.2-3.3 (m, 2H), 4.4-4.6 (m, 4H), 5.52 (q, 1H), 6.44 (d, 1H), 8.22 (d, 1H); MS (CI) 417 ($MH^+$).

**Step B:** Cyclohexyl-[4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl]-methanone. To a solution of 1R-[4-(4-cyclohexanecarbonyl-3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 131, Step A, 375 mg, 9.0 mmol) in methanol (5 mL) was added 6 N aqueous potassium hydroxide (0.5 mL) and stirred at ambient temperature for 4 h. The reaction mixture was concentrated, diluted with water, and extracted into dichloromethane. The extract was washed twice with water, dried over magnesium sulfate, and evaporated to an oil. The crude product was crystallized from ethyl ether to give the title compound as a white solid, 106 mg (34%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.2-1.4 (m, 6H), 1.55 (d, 3H), 1.6-1.8 (m, 10H), 2.46 (m, 1H), 3.2-3.3 (m, 2H), 4.2-

4.6 (m, 4H), 4.78 (q, 1H), 6.43 (d, 1H), 8.22 (d, 1H); mp: 174-175 °C; MS (CI) 347($MH^+$); $[\alpha]_D$ +18.4 (c 1.0, MeOH).

Example 132

Furo[3,2-c]pyridin-2-yl-[4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl]-methanone.



**Step A:** 7-Chloro-furo[3,2-c]pyridine-2-carboxylic acid. To a solution of n-butyllithium (2.5 M in hexanes, 17 mL, g, 42.6 mmol) in anhydrous ethyl ether (90 mL) was added dropwise a solution of 4-chloro-furo[3,2-c]pyridine (5.81 g, 37.8 mmol; *J. Heterocycl. Chem.* **1975**, *12*, 705) in ethyl ether (85 mL) at –78 °C under nitrogen atmosphere. This mixture was stirred for 1.5 h at –65 °C, poured onto dry ice (100 cc) and warmed to ambient temperature and quenched into water. The separated organic layer was extracted once with water and the combined aqueous layers were acidified to pH 2 with concentrated hydrochloric acid to give the title compound of Example 132, Step A as a white solid, 3.33 g (45%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.69 (s, 1H), 7.85 (d, 1H), 8.42 (d, 1H); mp: 233-235 °C (dec); MS (CI) 153 ($MH^+ - CO_2$).

**Step B:** 7-Chloro-furo[3,2-c]pyridine-2-carboxylic acid chloride. 7-Chloro-furo[3,2-c]pyridine-2-carboxylic acid (prepared according to the method of Example 132, Step A, 8.94 g, 45.2 mmol) was combined with thionyl chloride (30 mL) and sodium carbonate (9.59 g, 90.5 mmol) and heated to reflux for 16 h under nitrogen atmosphere. The cooled mixture was diluted with dichloromethane and filtered. The filtrate was evaporated to give the title compound of Example 132, Step B as an orange oil, 9.19 g (94%). The acid chloride was used directly without further purification.

**Step C:** 1R-[4-[4-(4-Chloro-furo[3,2-c]pyridine-2-carbonyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation

Three, 13.04 g, 42.5 mmol) and triethylamine (8.61 g, 85.1 mmol) in dichloromethane (90 mL) was added 7-chloro-furo[3,2-c]pyridine-2-carboxylic acid chloride (prepared according to the method of Example 132, Step B, 9.1 g, 84.0 mmol) and stirred at ambient temperature for 2 h. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 132, Step C as a viscous oil, 18.9 g (91%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.40 (d, 6H), 1.56 (d, 3H), 1.67 (m, 2H), 2.38 (t, 2H), 3.25 (d, 2H), 4.33 (m, 2H), 4.75 (m, 2H), 5.66 (q, 1H), 6.40 (d, 1H), 7.33 (s, 1H), 7.41 (d, 1H), 8.23 (d, 1H), 8.35 (d, 1H); MS (CI) 487 ($MH^+$); $[\alpha]_D$ +33.3 (c 1.0, MeOH).

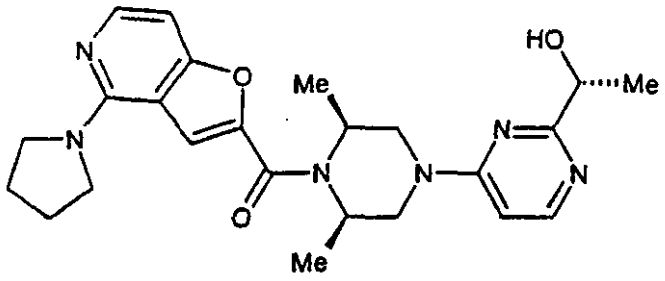
**Step D:** 1R-{4-[4-(Furo[3,2-c]pyridine-2-carbonyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 1R-{4-[4-(4-chloro-furo[3,2-c]pyridine-2-carbonyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 132, Step C, 18.6 g, 38.4 mmol) in ethanol (160 mL) was added sodium carbonate (4.07 g, 38.4 mmol) and 10% palladium on carbon (6.10 g, 33 wt%). This mixture was hydrogenated at 50 psi hydrogen for 6 h using a Parr apparatus. The catalyst was filtered and the filtrate was evaporated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 132, Step D as a yellow oil, 14.2 g (82%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.40 (d, 6H), 1.56 (d, 3H), 1.67 (q, 2H), 2.38 (t, 2H), 3.25 (d, 2H), 4.33 (m, 2H), 4.75 (m, 2H), 5.68 (q, 1H), 6.40 (d, 1H), 7.37 (s, 1H), 7.48 (d, 1H), 8.22 (d, 1H), 9.04 (s, 1H); MS (CI) 452 ($MH^+$); $[\alpha]_D$ +36.7 (c 1.0, MeOH).

**Step E:** Furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-methanone. 1R-{4-[4-(Furo[3,2-c]pyridine-2-carbonyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 132, Step D, 5.48 g, 12.1 mmol) was combined with concentrated hydrochloric acid (15 mL) and stirred at ambient temperature for 6 h. The mixture was poured into cold 6 M aqueous sodium hydroxide and extracted twice with ethyl acetate. The organic extract was washed once with water, dried over sodium sulfate and evaporated to a foam which crystallized from isopropyl ether to give the title compound as a white solid, 3.33 g (72%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.43 (d, 6H), 1.52 (d, 3H), 3.37 (m, 2H), 4.38 (m, 2H), 4.71 (q, 1H), 4.83 (m, 2H), 6.43 (d, 1H), 7.38

(s, 1H), 7.47 (m, 1H), 8.22 (m, 1H), 8.54 (d, 1H), 8.58 (d, 1H), 9.04 (s, 1H); mp: 142-143 °C; MS (CI) 382 ($MH^+$); $[\alpha]_D$ +15.9 (c 1.0, MeOH).

Example 133

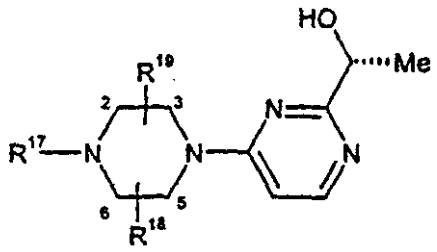
{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-(4-pyrrolidin-1-yl-furo[3,2-c]pyridin-2-yl)-methanone.



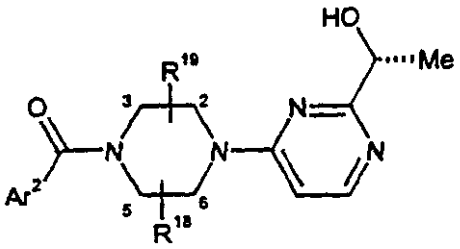

A solution of 1R-{4-[4-(4-chloro-furo[3,2-c]pyridine-2-carbonyl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 132, Step C, 0.046 g, 0.11 mmol) in pyrrolidine (0.037 mL, 0.44 mmol) was heated to reflux for 14 h and evaporated to give the title compound as a tan solid, 0.04 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.43 (d, 6H), 1.53 (d, 3H), 2.08 (m, 4H), 3.43 (m, 2H), 3.77 (m, 4H), 4.43 (m, 2H), 4.71 (q, 1H), 4.92 (m, 2H), 6.43 (d, 1H), 6.70 (d, 1H), 7.60 (s, 1H), 8.08 (d, 1H), 8.23 (d, 1H); MS (CI) 451 ($MH^+$).

Examples 134 to 158

Examples 140 and 142 to 158 were prepared from the appropriate starting materials in a manner analogous to the method of Example 131. Example 141 was prepared from the appropriate starting materials in a manner analogous to the method of Example 133.



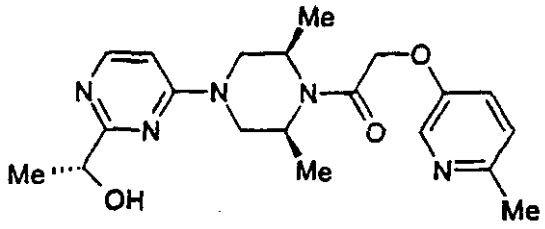

| Example | $R^{17}$ | $R^{18}$ | $R^{19}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 134 | cyclopropylcarbonyl | 2R-Me | 6S-Me | 110-111 | 305 |
| 135 | cyclobutylcarbonyl | 2R-Me | 6S-Me | 134-135 | 319 |
| 136 | cyclopentylcarbonyl | 2R-Me | 6S-Me | 199-200 | 333 |
| 137 | tert-butylcarbonyl | 2R-Me | 6S-Me | 168-169 | 321 |



| Example | $Ar^2$ | $R^{18}$ | $R^{19}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 138 | benzofuran-2-yl | 2R-Me | 6S-Me | 124-126 | 381 |
| 139 | furo[3,2-c]pyridin-2-yl | H | H | 55-65 | 354 |
| 140 | furo[3,2-c]pyridin-2-yl | 3R-Me | 5S-Me | | 382 |
| 141 | morpholin-4-yl-furo[3,2-c]pyridin-2-yl | 2R-Me | 6S-Me | | 467 |
| 142 | furo[2,3-c]pyridine-2-yl | 2R-Me | 6S-Me | 129-131 | 382 |
| 143 | 5-chlorobenzofuran-2-yl | H | H | | 387, 389 |
| 144 | 5-chlorobenzofuran-2-yl | 3R-Me | 5S-Me | 114-116 | 415, 417 |
| 145 | 5,7-dichlorobenzofuran-2-yl | 2R-Me | 6S-Me | 136-137 | 450, 452 |
| 146 | 5,7-dichlorobenzofuran-2-yl | 3R-Me | 5S-Me | 152-153 | 450, 452 |
| 147 | 5-nitrobenzofuran-2-yl | 2R-Me | 6S-Me | 153-154 | 426 |
| 148 | 5,7-dimethylbenzofuran-2-yl | 3R-Me | 5S-Me | 134-136 | 409 |
| 149 | 5-methoxybenzofuran-2-yl | 3R-Me | 5S-Me | 137-138 | 411 |
| 150 | 5-methoxybenzofuran-2-yl | 2R-Me | 6S-Me | 118-119 | 411 |
| 151 | imidazo[1,2-a]pyridin-2-yl | H | H | 149-150 | 353 |
| 152 | imidazo[1,2-a]pyridin-2-yl | 3R-Me | 5S-Me | 171-173 | 381 |
| 153 | imidazo[1,2-a]pyridin-2-yl | 2R-Me | 6S-Me | 147-149 | 381 |
| 154 | 6-chloroimidazo[1,2-b]pyridazin-2-yl | 2R-Me | 6S-Me | 76-84 | 416, 418 |
| 155 | 6-methylimidazo[1,2-a]pyridin-2-yl | 3R-Me | 5S-Me | 164-165 | 395 |
| 156 | benzoxazol-2-yl | 2R-Me | 6S-Me | 126-127 | 382 |
| 157 | 4-cyanophenyl | 2R-Me | 6S-Me | 90-100 | 366 |
| 158 | 6-hydroxy-pyridazin-3-yl | 2R-Me | 6S-Me | | 359 |

Example 159

1-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-2-(6-methyl-pyridin-3-yloxy)-ethanone.



**Step A:** 1R-[4-(4-Chloroacetyl-3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 9.69 g, 31.3 mmol) and triethylamine (4.74 g, 46.9 mmol) in chloroform (150 mL) was added dropwise chloroacetyl chloride (3.00 mL, 37.6 mmol) at 0 °C then stirred at ambient temperature for 12 h under nitrogen atmosphere. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, and the organic layer was dried over sodium sulfate, treated with activated carbon, and filtered. The filtrate was concentrated to obtain an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 159, Step A as an oil, 8.98 g (75%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, 3H), 1.32 (d, 6H), 1.59 (d, 3H), 1.71 (m, 2H), 2.40 (t, 2H), 3.28 (m, 2H), 4.28 (s, 2H), 4.35 (m, 4H), 5.68 (q, 1H), 6.41 (d, 1H), 8.23 (d, 1H); MS (CI) 383, 385 ($MH^+$).

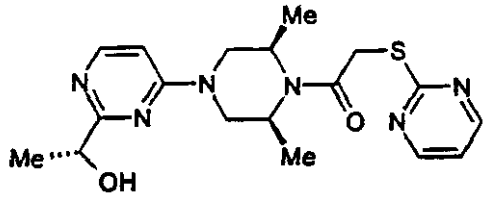
**Step B:** 1R-(4-{3R,5S-Dimethyl-4-[(6-methyl-pyridin-3-yloxy)-acetyl]-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate. To a suspension of sodium hydride (60% dispersion in oil, 0.05 g, 1.3 mmol) in tetrahydrofuran (2 mL) was added a solution of 6-methyl-3-pyridinol (0.14 g, 1.3 mmol) in tetrahydrofuran (3 mL) at 0 °C under nitrogen atmosphere and stirred for 0.5 h warming to ambient temperature. Next, a solution of 1R-[4-(4-chloroacetyl-3R,5R-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 159, Step A, 0.40 g, 1.1 mmol) in tetrahydrofuran (2 mL) was added and refluxed for 1 h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of

Example 159, Step B as an oil, 0.31 g (66%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, 3H), 1.32 (d, 6H), 1.59 (d, 3H), 1.71 (m, 2H), 2.40 (t, 2H), 2.46 (s, 3H), 3.28 (m, 2H), 3,78 (s, 2H), 4.35 (m, 4H), 5.68 (q, 1H), 6.41 (d, 1H), 6.83 (m, 1H), 7.14 (m, 1H), 8.08, (d, 1H), 8.23 (d, 1H); MS (CI) 456 ($MH^+$).

**Step C:** 1-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-2-(6-methyl-pyridin-3-yloxy)-ethanone. 1R-(4-{3R,5S-Dimethyl-4-[(6-methyl-pyridin-3-yloxy)-acetyl]-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Example 159, Step B, 0.30 g, 0.65 mmol) was combined with concentrated hydrochloric acid (3 mL) and stirred at ambient temperature for 6 h. The mixture was neutralized with 6 N aqueous sodium hydroxide to pH 9 and extracted twice with ethyl acetate. The organic extract was washed once with water, dried over sodium sulfate and filtered. The filtrate was concentrated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound as a white foam, 0.14 g (55%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.38 (d, 6H), 1.55 (d, 3H), 2.46 (s, 3H), 3.28 (m, 2H), 3.76 (s, 2H), 4.35-4.65 (m, 4H), 4.67 (q, 1H), 6.38 (d, 1H), 6.83 (m, 1H), 7.11 (m, 1H), 8.08, (d, 1H), 8.21 (d, 1H); mp: 55-65 °C; MS (CI) 330 ($MH^+$); $[\alpha]_D$ +16.0 (c 1.0, MeOH).

Example 160

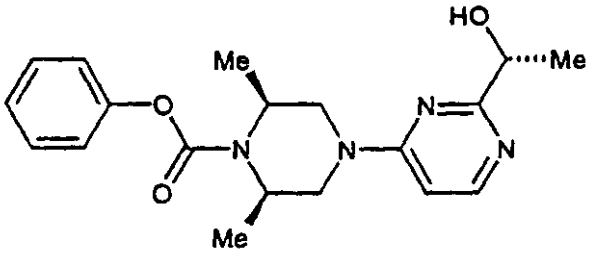
1-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-2-(pyrimidin-2-ylsulfanyl)-ethanone.




Example 160 was prepared from the appropriate starting materials in a manner analogous to example 159. $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.38 (m, 6H), 1.48 (d, 3H), 3.28 (m, 2H), 3.96 (s, 2H), 4.35 (m, 4H), 4.65-4.97 (m, 3H), 6.28 (d, 1H), 6.93 (m, 1H), 7.11 (m, 1H), 8.21 (d, 1H), 8.45, (m, 2H); mp: 60-70 °C; MS (CI) 389 ($MH^+$); $[\alpha]_D$ +16.8 (c 1.0, MeOH).

Example 161

4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid phenyl ester.



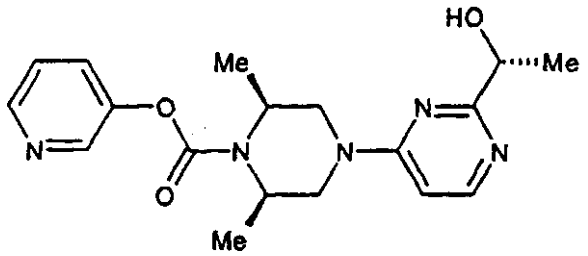
**Step A:** 4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid phenyl ester. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 0.30 g, 0.98 mmol) and triethylamine (0.20 g, 1.9 mmol) in dichloromethane (5 mL) was added phenyl chloroformate (0.76 g, 4.8 mmol) and stirred at ambient temperature for 2 h under nitrogen atmosphere. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 161, Step A as an oil, 0.35 g (84%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, 3H), 1.32 (d, 6H), 1.59 (d, 3H), 1.71 (q, 2H), 2.40 (t, 2H), 3.28 (m, 2H), 4.35 (m, 4H), 5.68 (q, 1H), 6.41 (d, 1H), 7.12 (d, 2H), 7.22 (m, 1H), 7.35 (m, 2H), 8.23 (d, 1H); MS (CI) 427 ($MH^+$); $[\alpha]_D$ +39.6 (c 1.0, MeOH).

**Step B:** 4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid phenyl ester. 4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid phenyl ester (prepared according to the method of Example 161, Step A, 0.31 g, 0.70 mmol) was combined with concentrated hydrochloric acid (5 mL) and stirred at ambient temperature for 6 h. The mixture was neutralized with 6 N aqueous sodium hydroxide to pH 9 and extracted twice with ethyl acetate. The organic extract was washed once with water, dried over sodium sulfate and filtered. The filtrate was concentrated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound as a white solid, 0.12 g (81%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.41 (d, 6H), 1.51 (d, 3H), 3.34 (m,

2H), 4.43 (m, 2H), 4.52 (m, 2H), 4.71 (q, 1H), 6.46 (d, 1H), 7.12 (m, 2H), 7.23 (m, 1H), 7.35 (m, 2H), 8.23 (d, 1H); MS (CI) 357 ($MH^+$); $[\alpha]_D$ +16.9 (c 1.0, MeOH).

Example 162

4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid pyridin-3-yl ester.




**Step A:** 4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carbonyl chloride. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 3.61, 11.8 mmol) and pyridine (0.93 g, 11.8 mmol) in dichloromethane (50 mL) was added triphosgene (1.17 g, 3.9 mmol) and stirred at ambient temperature for 16 h under nitrogen atmosphere. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain an oil which was purified by flash chromatography (ethyl acetate) to give the title compound of Example 162, Step A as a yellow oil, 2.12 g, (51%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H), 1.31 (d, 6H), 1.56 (d, 3H), 1.68 (m, 2H), 2.38 (t, 2H), 3.21(m, 2H), 3.88-4.40 (m, 4H), 5.66 (q, 1H), 6.43 (d, 1H), 8.22 (d, 1H); MS (CI) 369, 371 ($MH^+$).

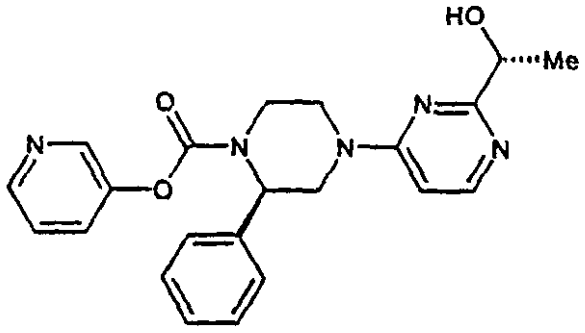
**Step B:** {4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine}-1-carboxylic acid pyridin-3-yl ester. To a suspension of sodium hydride (60% dispersion in oil, 0.046 g, 1.15 mmol) in anhydrous tetrahydrofuran (8 mL) was added 3-hydroxypyridine (0.11 g, 1.15 mmol) at 0 °C. After a homogeneous solution was obtained, a solution of 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carbonyl chloride (prepared according to the method of Example 162, Step A, 0.36 g, 0.96 mmol) in tetrahydrofuran (3 mL) was added at 0 °C and this mixture was warmed to ambient temperature, then heated to reflux for 6 h. The mixture was quenched in water and extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered. The filtrate was

concentrated to obtain an oil, which was purified by flash chromatography (ethyl acetate) to give the title compound of Example 162, Step B as a semi-solid, 0.31 g (78%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H), 1.35 (m, 6H), 1.61 (d, 3H), 1.69 (m, 2H), 2.41 (t, 2H), 3.30 (m, 2H), 4.11-4.38 (m, 4H), 5.69 (q, 1H), 6.41 (d, 1H), 7.32 (m, 1H), 7.52 (m, 1H), 8.22 (d, 1H), 8.46 (s, 1H), 8.48, (d, 1H); MS (CI) 428 ($MH^+$).

**Step C:** 4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid pyridin-3-yl ester. {4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine}-1-carboxylic acid pyridin-3-yl ester (prepared according to the method of Example 162, Step B, 0.31 g, 0.70 mmol) was combined with concentrated hydrochloric acid (5 mL) and stirred at ambient temperature for 6 h. The mixture was neutralized with 6 N aqueous sodium hydroxide to pH 9 and extracted twice with ethyl acetate. The extract was washed once with water, dried over sodium sulfate and filtered. The filtrate was concentrated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound as a white solid, 0.12 g (81%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.41 (d, 6H), 1.51 (d, 3H), 3.33 (m, 2H), 4.25-4.45 (m, 4H), 4.71 (q, 1H), 6.43 (d, 1H), 7.33 (m, 1H), 7.56 (m, 1H), 8.23 (d, 1H), 8.25 (d, 1H), 8.48 (d, 1H); MS (CI) 358 ($MH^+$); $[\alpha]_D$ +18.5 (c 1.0, MeOH).

Example 163

4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R-phenyl-piperazine-1-carboxylic acid pyridin-3-yl ester.




**Step A:** 1R-[4-(3R-Phenyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of (R)-2-phenylpiperazine (0.48 g, 3.0 mmol, *Indian J. Chem. Sect. B* **1994**, 33, 285) and triethylamine (1.21 g, 12.0 mmol) in tetrahydrofuran (10 mL) was added (R)-1-(4-chloropyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 0.68 g, 3.0 mmol) and stirred at ambient temperature for 18 h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with ethyl

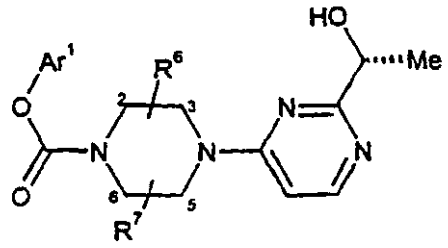
acetate. The combined organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product which was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound of Example 163, Step A as a viscous oil, 0.70 g (67%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.56 (d, 3H), 1.67 (m, 2H), 2.40 (t, 2H), 3.55 (m, 2H), 4.0 (m, 2H), 4.32 (m, 2H), 4.70 (m, 1H), 5.69 (q, 1H), 6.49 (d, 1H), 7.40 (m, 5H), 8.21 (d, 1H); MS (CI) 355 ($MH^+$).

**Step B:** 4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R-phenyl-piperazine-1-carboxylic acid pyridin-3-yl ester. To a solution 1R-[4-(3R-phenyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 163, Step A, 0.22 g, 0.6 mmol) and triethylamine (0.31 g, 3.1 mmol) in toluene (5 mL) was added dipyridin-3-yl carbonate (0.67 g, 3.1 mmol) and heated to reflux for 3 h. The mixture was poured into saturated aqueous sodium bicarbonate, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 163, Step B as a yellow oil, 0.22 g (73%). MS (CI) 476 ($MH^+$).

**Step C:** 4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R-phenyl-piperazine-1-carboxylic acid pyridin-3-yl ester. 4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R-phenyl-piperazine-1-carboxylic acid pyridin-3-yl ester (prepared according to the method of Example 163, Step B, 0.21 g, 0.44 mmol) was combined with concentrated hydrochloric acid (2 mL) and stirred at ambient temperature for 6 h. The mixture was neutralized with 6 N aqueous sodium hydroxide to pH 9 and extracted twice with ethyl acetate. The combined extracts were washed once with water, dried over sodium sulfate and filtered. The filtrate was concentrated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound as a white solid, 0.13 g (73%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.55 (d, 3H), 3.55 (m, 2H), 4.0 (m, 2H), 4.32 (m, 2H), 4.71 (m, 1H), 4.75 (q, 1H), 6.40 (d, 1H), 7.18-7.41 (m, 7H), 8.24 (d, 1H), 8.35 (br s, 1H), 8.45 (d, 1H); MS (CI) 406 ($MH^+$).

Examples 164 to 173

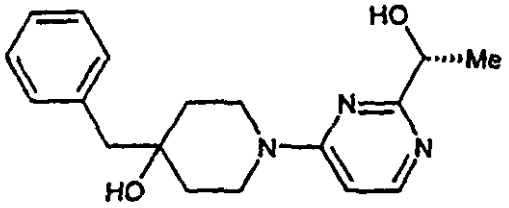
Examples 164 to 173 were prepared from the appropriate starting materials in a manner analogous to the method of Example 163.



| Example | $R^7$ | $R^6$ | $Ar^1$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 164 | 3R-Me | 5S-Me | phenyl | | 357 |
| 165 | 3R-Me | 5S-Me | 2-methyl-pyridin-3-yl | 65-75 | 372 |
| 166 | H | H | pyridin-3-yl | 107-110 | 330 |
| 167 | 3R-Me | 5S-Me | 2-chloro-pyridin-3-yl | 60-70 | 392, 394 |
| 168 | 3R-Me | 5S-Me | 5-chloro-pyridin-3-yl | 65-69 | 392, 394 |
| 169 | 3R-Me | 5S-Me | isoquinolin-5-yl | 60-70 | 407 |
| 170 | 3R-Me | 5S-Me | 4-chloro-pyridin-3-yl | 60-70 | 392, 394 |
| 171 | 3R-Me | 5S-Me | 6-methyl-pyridin-3-yl | 60-70 | 372 |
| 172 | 2RS-$CH_2OMe$ | H | pyridin-3-yl | | 388 |
| 173 | 2RS-$CO_2Et$ | H | pyridin-3-yl | | 402 |

Example 174

(R)-4-Benzyl-1-[2-(1-hydroxy-ethyl)-pyrimidin-4-yl]-piperidin-4-ol.



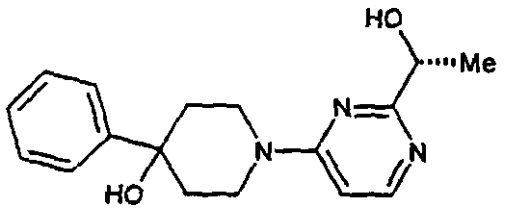
**Step A:** (R)-1-[4-(4-Benzyl-4-hydroxy-piperidin-1-yl)-pyrimidin-2-yl]-ethyl acetate. To a solution of 4-benzyl-4-hydroxypiperidine (0.95 g, 5.0 mmol) and triethylamine (0.51 g, 5.0 mmol) in dichloromethane (10 mL) was added (R)-1-(4-methanesulfonyloxy-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Eight, 1.23 g, 4.0 mmol) and stirred at ambient temperature for 18 h. The mixture was

washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound of Example 174, Step A as a viscous oil, 0.99 g (52%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.53 (d, 3H), 1.65-1.78 (m, 4H), 1.88 (m, 2H), 2.08 (m, 2H), 2.48 (t, 2H), 3.45 (m, 2H), 4.42 (br s, 1H), 5.68 (q, 1H), 6.41 (d, 1H), 7.30-7.48 (m, 5H), 8.18 (d, 1H); MS (CI) 384 ($MH^+$).

**Step B:** (R)-4-Benzyl-1-[2-(1-hydroxy-ethyl)-pyrimidin-4-yl]-piperidin-4-ol. To a solution of (R)-1-[4-(4-benzyl-4-hydroxy-piperidin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 174, Step A, 0.20 g, 0.52 mmol) in methanol (5 mL) was added 1 N aqueous sodium hydroxide (1 mL) and stirred for 4 h at ambient temperature. The mixture was diluted with dichloromethane and washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to give the title compound as a foam, 0.12 g (68%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.49 (d, 3H), 1.74 (br s, 2H), 1.82 (m, 2H), 2.08 (m, 2H), 3.42 (m, 2H), 4.42 (br s, 1H), 4.71 (q, 1H), 6.43 (d, 1H), 7.33-7.48 (m, 5H), 8.21 (d, 1H); MS (CI) 314 ($MH^+$).

Example 175

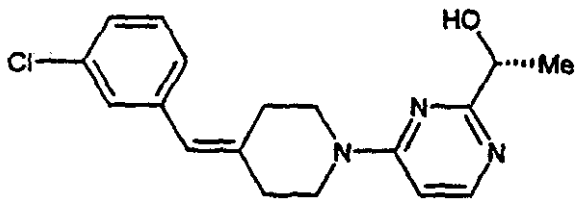
(R)-4-Phenyl-1-[2-(1-hydroxy-ethyl)-pyrimidin-4-yl]-piperidin-4-ol.




Example 175 was prepared from the appropriate starting materials in a manner analogous to the method of Example 174. mp: 114 °C; MS (CI) 300 ($MH^+$).

Example 176

(R)-1-{4-[4-(3-Chlorobenzylidene)-piperidin-1-yl]-pyrimidin-2-yl}-ethanol.



**Step A:** 1-[4-(3-Chlorobenzylidene)-piperidine-1-yl]-1-carboxylic acid tert-butyl ester. To a suspension of 4-chlorobenzyltriphenylphosphonium chloride (4.23 g, 10.0 mmol) in tetrahydrofuran (40 mL) was added n-butyllithium in hexanes (2.5 M in hexanes, 4.4 mL, 11.0 mmol) at 0 °C under nitrogen atmosphere and stirred 0.5 h. A solution of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (prepared according to the method of Example 101, Step A, 1.99 g, 10.0 mmol) in tetrahydrofuran (10 mL) was added at 10-15 °C and warmed to ambient temperature. The mixture was evaporated to an oil which was purified by flash chromatography (9:1 hexanes:ethyl acetate) to give the title compound of Example 176, Step A as an oil, 2.63 g (85%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H), 2.48 (m, 2H), 2.57 (m, 2H), 3.68-3.82 (m, 4H), 6.36 (s, 1H), 7.08 (m, 1H), 7.12-7.28 (m, 3 H); MS (CI) 308 ($MH^+$).

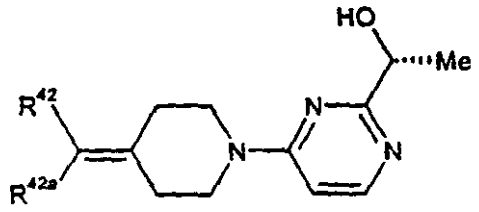
**Step B:** 4-(3-Chloro-benzylidene)-piperidine hydrochloride. To a solution of 1-[4-(3-chlorobenzylidene)-piperidine-1-yl]-1-carboxylic acid tert-butyl ester (prepared according to the method of Example 176, Step A, 2.5 g, 8.1 mmol) in dichloromethane (20 mL) was added hydrogen chloride (4 M in dioxane, 4.0 mL, 16.0 mmol) at ambient temperature and stirred for 4 h. The mixture was evaporated to dryness, suspended in ethyl ether and filtered to give the title compound of Example 176, Step B as a white solid, 1.63 g (82%). $^1$H NMR ($CDCl_3/D_2O$, 300 MHz) δ 2.48 (m, 2H), 2.57 (m, 2H), 3.63 (m, 2H), 3.77 (m, 2H), 6.36 (s, 1H), 7.10 (m, 1H), 7.12-7.28 (m, 3H); $m_p$: 147-151 °C.

**Step C:** (R)-1-[4-[4-(3-Chloro-benzylidene)-piperidin-1-yl]-pyrimidin-2-yl]-ethyl butyrate. To a solution of 4-(3-chlorobenzylidene)-piperidine hydrochloride (prepared according to the method of Example 176, Step B, 0.46 g, 2.0 mmol) and triethylamine (0.61 g, 6.0 mmol) in dichloromethane (10 mL) was added (R)-1-(4-chloropyrimidin-2-yl)-ethyl acetate (prepared according to the method of Preparation Five, 0.54 g, 2.2 mmol) and stirred at ambient temperature for 12 h. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product which was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound of Example 176, Step C as a viscous oil, 0.64 g (80%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, 6H), 1.51 (d, 3H), 1.68 (m, 2H) 2.35 (m, 2H), 2.47-2.64 (m, 4H), 3.67-3.75 (m, 4H), 5.68 (q, 1H), 6.36 (s, 1H), 6.40 (d, 1H), 6.98 (m, 1H), 7.12-7.28 (m, 3H), 8.18 (m, 1H); MS (CI) 400 ($MH^+$).

**Step D:** (R)-1-[4-[4-(3-Chlorobenzylidene)-piperidin-1-yl]-pyrimidin-2-yl}-ethanol. To a solution of (R)-1-{4-[4-(3-chloro-benzylidene)-piperidin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 176, Step C, 0.62 g, 1.55 mmol) in methanol (8 mL) was added 1 N aqueous sodium hydroxide (1 mL) then stirred for 4 h at ambient temperature. The mixture was diluted with chloroform and washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product which was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound as a white solid, 0.31 g (61%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.51 (d, 3H), 2.46 (m, 2H), 2.56 (m, 2H), 3.07 (m, 2H), 3.77 (m, 2H), 4.35 (d, 1H), 4.69 (q, 1H), 6.36 (s, 1H), 6.40 (d, 1H), 7.07 (m, 1H), 7.12-7.28 (m, 3H), 8.18 (m, 1H); mp: 45-55 °C; MS (CI) 330 ($MH^+$); $[\alpha]_D$ +16.8 (c 1.0, MeOH).

Examples 177 to 181

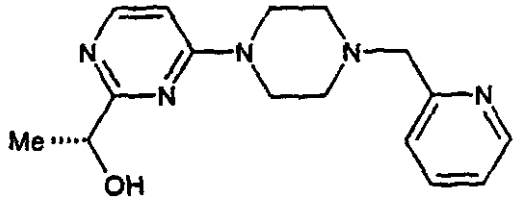
Examples 177 to 181 were prepared from the appropriate starting materials in a manner analogous to the method of Example 176.




| Example | $R^{42}$ | $R^{42a}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|
| 177 | 4-chlorophenyl | H | | 330, 332 |
| 178 | (E)-2-phenyl-ethen-1-yl | H | | 322 |
| 179 | benzoyl | H | 44-59 | 324 |
| 180 | phenyl | phenyl | 108-109 | 372 |
| 181 | phenyl | pyrid-2-yl | 98-101 | 373 |

Example 182

(R)-1-[4-(4-Pyridin-2-ylmethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol.

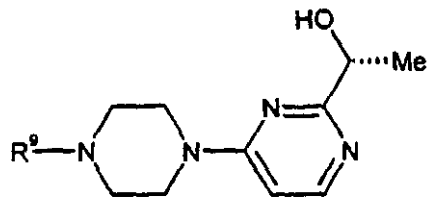


**Step A:** (R)-1-[4-(4-Pyridin-2-ylmethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate. To a solution of (R)-1-[4-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate (prepared according to the method of Preparation Two, 1.55 g, 6.2 mmol) and triethylamine (0.86 mL, 6.2 mmol) in tetrahydrofuran (20 mL) was added 2-picolylchloride hydrochloride (1.01 g, 6.2 mmol) at ambient temperature and stirred for 1 h. The mixture was diluted with water and extracted twice with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered, and the filtrate was concentrated to an oil which was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound of Example 182, Step A, 0.98 g (46%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.58 (d, 3H), 2.15 (s, 3H) 2.62 (t, 4H), 3.72 (t, 4H), 3.75 (s, 2H), 5.67 (q, 1H), 6.35 (d, 1H), 7.22 (m, 1H), 7.46 (d, 1H), 7.73 (m, 1H), 8.21 (d, 1H), 8.62 (d, 1H); MS (CI) 342 ($MH^+$).

**Step B:** (R)-1-[4-(4-Pyridin-2-ylmethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol. To a solution of (R)-1-[4-(4-pyridin-2-ylmethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate (prepared according to the method of Example 182, Step A, 0.14 g, 0.33 mmol) in dioxane (6 mL) was added at ambient temperature 6 N aqueous potassium hydroxide (0.5 mL). After stirring for 3 h the solution was diluted with ethyl acetate and washed twice with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the filtrate was concentrated to give the title compound as a white solid, 0.09 g (69%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.52 (d, 3H), 2.38-2.59 (m, 4H), 3.72-3.77 (m, 6H), 4.69 (q, 1H), 6.37 (d, 1H), 7.22 (d, 1H), 7.41 (d, 1H), 7.69 (m, 1H), 8.21 (d, 1H) 8.58, (d, 1H); mp: 68-70 °C; MS (CI) 300 ($MH^+$); $[\alpha]_D$ +16.2 (c 1.0, MeOH).

Examples 183 to 187

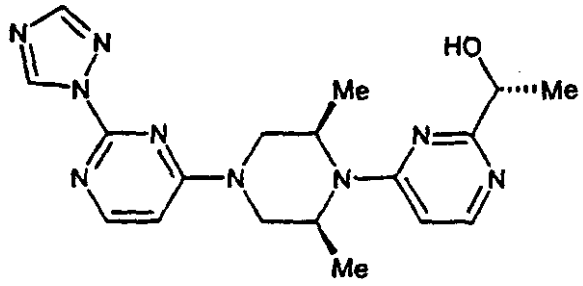
Examples 183 to 187 were prepared from the appropriate starting materials in a manner analogous to the method of Example 182.



| Example | $R^9$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|
| 183 | phenylmethyl | | 299 |
| 184 | isoquinolin-2-yl-methyl | | 350 |
| 185 | benzothien-2-yl-methyl | | 355 |
| 186 | benzothiazol-2-yl-methyl | | 356 |
| 187 | benzofuran-2-yl-methyl | | 339 |

Example 188

1R-[4-[2R,6S-Dimethyl-4-(2-[1,2,4]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.



**Step A:** 4-(3R,5S-Dimethyl-piperazin-1-yl)-2-methanesulfonyl-pyrimidine. To a solution of cis-2,6-dimethylpiperazine (10.7 g, 94.1 mmol) and triethylamine (9.52 g, 94.1 mmol) in chloroform (300 mL) was added 4-chloro-2-methanesulfonylpyrimidine (15.1 g, 78.4 mmol; *Heterocycles* **1985**, 23, 611) at ambient temperature and stirred for 1 h. The mixture was partitioned with saturated aqueous sodium bicarbonate and the separated organic layer was washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an orange solid which was slurried in ethyl ether and filtered to give the title compound of Example 188, Step A as a white solid,

15.4 g (73%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.01 (m, 6H), 2.35-2.78 (m, 4H), 2.85 (s, 3H), 3.32 (m, 2H), 6.81 (d, 1H), 8.2 (d, 1H); mp: 182-183 °C; MS (CI) 301 ($MH^+$).

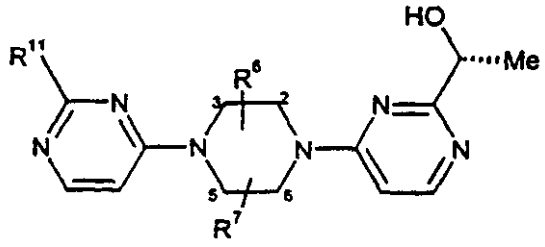
**Step B:** 4-(3R,5S-Dimethyl-piperazin-1-yl)-2-[1,2,4]triazol-1-yl-pyrimidine. To a slurry of sodium hydride (60% dispersion in oil, 0.37 g, 9.4 mmol) in dimethylformamide (5 mL) was added a solution of 1,2,4-triazole (0.67 g, 9.4 mmol) in dimethylformamide (4 mL) at 0 °C under nitrogen atmosphere. After 10 min, a solution of 4-(3R,5S-dimethyl-piperazin-1-yl)-2-methanesulfonyl-pyrimidine (prepared according to the method of Example 188, Step A, 2.54 g, 9.4 mmol) in warm dimethylformamide (5 mL) was added dropwise and stirred at ambient temperature for 2 h then heated to 100 °C for 0.5 h. The mixture was quenched in saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 188, Step B as an oil, 0.50 g (62%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.01 (m, 6H), 2.35-2.88 (m, 5H), 3.32 (m, 1H), 6.81 (d, 1H), 8.16-8.23 (m, 2H), 9.25 (d, 1H); MS (CI) 260 ($MH^+$).

**Step C:** 1R-{4-[2R,6S-Dimethyl-4-(2-[1,2,3]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 4-(3R,5S-dimethyl-piperazin-1-yl)-2-[1,2,4]triazol-1-yl-pyrimidine (prepared according to the method of Example 188, Step B, 0.46 g, 1.8 mmol) in acetonitrile (3 mL) was added (R)-1-(4-methanesulfonyloxy-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Eight, 0.57 g, 2.0 mmol) and heated to reflux for 6 h under nitrogen atmosphere. The mixture was quenched in saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound of Example 188, Step C as an oil, 0.22 g (54%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, 3H), 1.51 (m, 6H), 1.54 (d, 3H), 1.63 (m, 2H), 2.38 (t, 2H), 3.38 (m, 2H), 4.33-4.64 (m, 4H), 5.68 (q, 1H), 6.28 (d, 1H), 6.58 (d, 1H), 8.10 (s, 1H), 8.26-8.32 (m, 2H), 9.10 (d, 1H); MS (CI) 452 ($MH^+$); $[\alpha]_D$ +50.0 (c 1.0, MeOH).

**Step D:** 1R-{4-[2R,6S-Dimethyl-4-(2-[1,2,4]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol. 1R-{4-[2R,6S-Dimethyl-4-(2-[1,2,3]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 188, Step C, 0.18 g, 0.40 mmol) was combined with concentrated hydrochloric acid (2 mL) and stirred at ambient temperature for 4 h. The mixture was quenched in saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound as a white solid, 0.13 g (87%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 6H), 1.51 (d, 3H), 3.42 (m, 2H), 4.42-4.73 (m, 5H), 6.41 (d, 1H), 6.56 (d, 1H), 8.12 (s, 1H), 8.24 (d, 1H), 8.30 (d, 1H), 9.10 (s, 1H); MS (CI) 382 ($MH^+$); $[\alpha]_D$ +18.6 (c 1.0, MeOH).

Examples 189 to 195

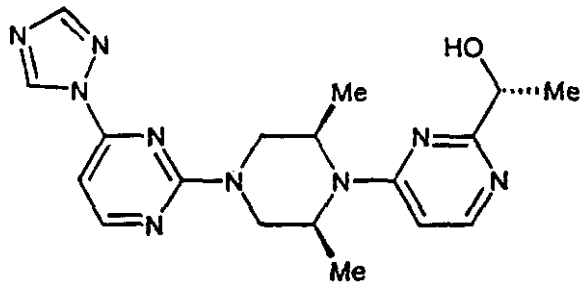
Examples 189 to 195 were prepared from the appropriate starting materials in a manner analogous to the method of Example 188.




| Example | $R^{11}$ | $R^7$ | $R^6$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 189 | 2-hydroxyphenyl | 2R-Me | 6S-Me | 60-70 | 407 |
| 190 | imidazol-1-yl | 2R-Me | 6S-Me | 60-70 | 381 |
| 191 | [1,2,3]triazol-1-yl | 2R-Me | 6S-Me | 70-80 | 382 |
| 192 | pyrrol-1-yl | 2R-Me | 6S-Me | 70-80 | 380 |
| 193 | 4-methylimidazol-1-yl | 2R-Me | 6S-Me | 70-80 | 395 |
| 194 | 2-methylimidazol-1-yl | 2R-Me | 6S-Me | 70-80 | 395 |
| 195 | 2,4-dimethylimidazol-1-yl | 2R-Me | 6S-Me | 70-80 | 409 |

Example 196

1R-[4-[2R,6S-Dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.



Step A: 2-Thiomethyl-4-[1,2,4]triazol-1-yl-pyrimidine. To a slurry of sodium hydride (60% dispersion in oil, 24.2 g, 605 mmol) in dimethylformamide (800 mL) was added a solution of 1,2,4-triazole (0.67 g, 9.4 mmol) in dimethylformamide (4.0 mL) at 0 °C under nitrogen atmosphere. After 10 min, a solution of 4-chloro-2-methylthio-pyrimidine (97.2 g, 605 mmol) in dimethylformamide (200 mL) was added dropwise at 10 °C and stirred at ambient temperature for 14 h. The mixture was quenched in water and the solid precipitate was filtered off and dried under vacuum to give the title compound of Example 196, Step A as a white solid, 113 g (94%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.82 (s, 3H), 6.82 (d, 1H), 8.18 (d, 1H), 8.19 (s, 1H), 9.35 (s, 1H); mp: 125-126 °C; MS (CI) 194 ($MH^+$).

Step B: 2-Methanesulfonyl-4-[1,2,4]triazol-1-yl-pyrimidine. To a mechanically stirred suspension of 3-chloroperoxybenzoic acid (75%, 127 g, 551 mmol) in chloroform (625 mL) was added a solution of 2-thiomethyl-4-[1,2,4]triazol-1-yl-pyrimidine (prepared according to the method of Example 196, Step A, 50.7 g, 262 mmol) in chloroform (625 mL) and stirred at ambient temperature for 16 h. The mixture was filtered and the filtrate was washed six times with saturated aqueous sodium carbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated to give the title compound of Example 196, Step B as a white solid, 37.8 g (64%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.62 (s, 3H), 6.82 (d, 1H), 8.19 (s, 1H), 8.24 (d, 1H), 9.35 (s, 1H); mp: 135-136 °C; MS (CI) 226 ($MH^+$).

**Step C:** 2-(3R,5S-Dimethyl-piperazin-1-yl)-4-[1,2,4]triazol-1-yl-pyrimidine. 2-Methanesulfonyl-4-[1,2,4]triazol-1-yl-pyrimidine (prepared according to the procedure of Example 196, Step B, 32.5 g, 144 mmol) was combined with cis-2,6-dimethylpiperazine (34.5 g, 302 mmol) and heated neat at 135 °C for 1 h, cooled, dissolved in 2 N aqueous hydrochloric acid and washed once with ethyl acetate. The acidic aqueous layer was basified to pH 9 with 6 N aqueous sodium hydroxide at 0 °C then extracted four times with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which crystallized from hexanes to give the title compound of Example 196, Step C as a white solid, 31.8 g (71%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, 6H), 2.38 (m, 4H), 3.30 (s, 2H), 6.82 (d, 1H), 8.18 (d, 1H), 8.19 (s, 1H), 9.35 (s, 1H); mp: 143-145 °C; MS (CI) 260 ($MH^+$).

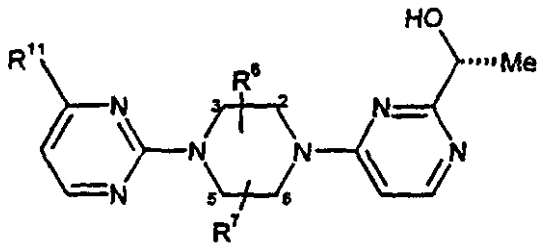
**Step D:** 1R-{4-[2R,6S-Dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 2-(3R,5S-dimethyl-piperazin-1-yl)-4-[1,2,4]triazol-1-yl-pyrimidine (prepared according to the method of Example 196, Step C, 8.33 g, 32.1 mmol) in acetonitrile (30 mL) was added (R)-1-(4-trifluoromethanesulfonyloxy-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Nine, 5.50 g, 16.1 mmol) and heated to reflux for 3 h under nitrogen atmosphere. The cooled mixture was filtered and the solids were washed twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (99:1 dichloromethane:methanol) to give the title compound of Example 196, Step D as an oil, 3.61 g (50%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.91 (d, 6H), 1.26 (t, 3H), 1.59 (d, 3H), 1.69 (q, 2H), 2.40 (m, 2H), 3.40 (d, 2H), 4.60 (m, 4H), 5.70 (q, 1H), 6.39 (d, 1H), 6.58 (d, 1H), 8.12 (s, 1H), 8.25 (d, 1H), 8.31 (d, 1H), 8.35 (s, 1H); MS (CI) 452 ($MH^+$).

**Step E:** 1R-{4-[2R,6S-Dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol. 1R-{4-[2R,6S-Dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 196, Step D, 3.60 g, 8.0 mmol) was combined with concentrated hydrochloric acid (10 mL) and stirred at ambient temperature for 4 h. The mixture was

quenched in saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (99:1 dichloromethane:methanol) to give the title compound as a white solid, 2.35 g (77%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 6H), 1.51 (d, 3H), 3.34 (m, 2H), 4.42 (m, 2H), 4.68-4.82 (m, 3H), 6.42 (d, 1H), 7.11 (d, 1H), 8.11 (s, 1H), 8.23 (d, 1H), 8.49 (d, 1H), 9.12 (s, 1H); $m_p$: 181-182 °C; MS (CI) 382 ($MH^+$).

Examples 197 to 200

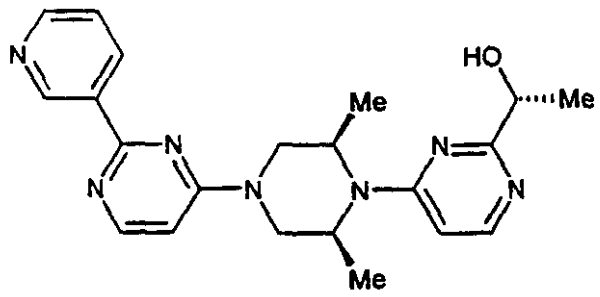
Examples 197 to 200 were prepared from the appropriate starting materials in a manner analogous to the method of Example 196.




| Example | $R^{11}$ | $R^7$ | $R^6$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 197 | imidazol-1-yl | 2R-Me | 6S-Me | 60-70 | 381 |
| 198 | morpholin-4-yl | 2R-Me | 6S-Me | 70-80 | 400 |
| 199 | pyrrolidin-1-yl | 2R-Me | 6S-Me | 70-80 | 384 |
| 200 | 4-methylpiperazin-1-yl | 3R-Me | 5S-Me | 168-170 | 413 |

Example 201

1R-[4-[2R,6S-Dimethyl-4-(2-pyridin-3-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.



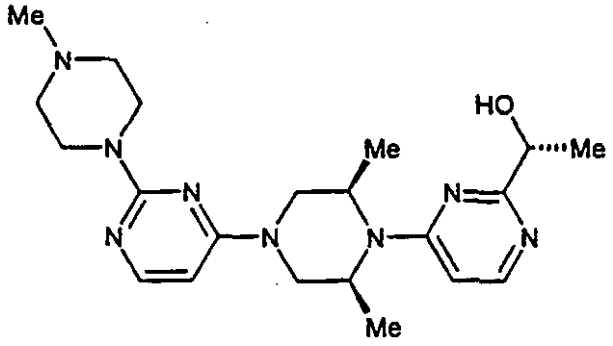
**Step A:** 2-Pyridin-3-yl-pyrimidin-4-yl trifluoromethanesulfonate. To a solution of 2-pyridin-3-yl-3H-pyrimidin-4-one (150 mg, 0.87 mmol; *J. Med. Chem.* 1990, 33, 1230) and triethylamine (0.13 mL, 0.95 mmol) in dichloromethane (3 mL) was added dropwise a solution of trifluoromethanesulfonic anhydride (0.22 mL, 0.91 mmol) in dichloromethane (2 mL) at 0 °C under nitrogen atmosphere. The mixture was allowed to stir for 30 min at 0 °C then diluted with dichloromethane and washed once with water and the aqueous layer was extracted twice with dichloromethane. The organic extracts were combined, washed sequentially with saturated aqueous sodium carbonate and saturated aqueous sodium chloride, dried over sodium sulfate and filtered. The filtrate was evaporated to give the title compound of Example 201, Step A as an orange oil, 0.22 g (95%), that was used without further purification.

**Step B:** 1R-{4-[2R,6S-Dimethyl-4-(2-pyridin-3-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol. A solution of 2-pyridin-3-yl-pyrimidin-4-yl trifluoromethanesulfonate (prepared according to the method of Example 201, Step A, 0.15 g, 0.5 mmol) in tetrahydrofuran (3 mL) at 0 °C was added dropwise to a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1yl)-pyrmidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Four, 0.15 g, 0.45 mmol) in tetrahydrofuran (2 mL) and stirred for 1 h at ambient temperature. The mixture was quenched in saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil and dissolved in concentrated hydrochloric acid (3 mL) and stirred at ambient temperature for 4 h. The mixture was quenched in saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The

filtrate was evaporated to give the title compound as a white foam, 0.091 g (48%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 6H), 1.51 (d, 3H), 3.34 (m, 2H), 4.42-4.70 (m, 4H), 4.71 (q, 1H), 6.40 (d, 1H), 6.56 (d, 1H), 7.37 (m, 1H), 8.22 (d, 1H), 8.36 (d, 1H), 8.62-8.68 (m, 2H), 9.53 (m, 1H); mp: 61-70 °C; MS (CI) 392 ($MH^+$).

Example 202

1R-(4-[2R,6S-Dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl]-pyrimidin-2-yl)-ethanol.



**Step A:** 1R-[4-[4-(2-Methanesulfonyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl]-ethyl butyrate. To a solution of 4-(3R,5S-dimethyl-piperazin-1-yl)-2-methanesulfonyl-pyrimidine (prepared according to the method of Example 188, Step A, 7.70 g, 14.3 mmol) in acetonitrile (30 mL) was added 1R-(4-trifluoromethanesulfonyloxy-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Nine, 5.50 g, 16.1 mmol) and heated to reflux for 3 h under nitrogen atmosphere. The cooled mixture was filtered and the solids were washed twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (98:2 dichloromethane:methanol) to give the title compound of Example 202, Step A as an oil, 4.01 g (62%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3H), 1.21 (d, 6H), 1.55 (d, 3H), 1.64 (q, 2H), 2.36 (t, 2H), 3.25 (s, 3H), 3.37 (m, 2H), 4.5-4.7 (m, 4H), 5.65 (q, 1H), 6.33 (d, 1H), 6.68 (d, 1H), 8.22 (d, 1H), 8.28 (d, 1H); MS (CI) 463 ($MH^+$).

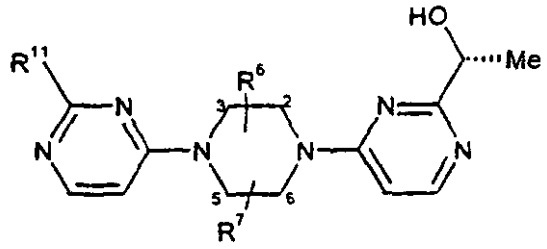
**Step B:** 1R-[4-[4-(2-Methanesulfonyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl]-ethanol. 1R-[4-[4-(2-Methanesulfonyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of

Example 202, Step A, 0.42 g, 0.9 mmol) was combined with concentrated hydrochloric acid (3 mL) and stirred at ambient temperature for 4 h. The mixture was quenched in saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (99:1 dichloromethane:methanol) to give the title compound of Example 202, Step B as a white foam, 0.25 g (71%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 6H), 1.50 (d, 3H), 3.25 (s, 3H), 3.41 (m, 2H), 4.5-4.7 (m, 5H), 6.37 (d, 1H), 6.71 (d, 1H), 8.24 (d, 1H), 8.30 (d, 1H); MS (CI) 393 ($MH^+$).

**Step C:** 1R-(4-{2R,6S-Dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol. 1R-{4-[4-(2-Methanesulfonyl-pyrimidin-4-yl)-2,6-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol (prepared according to the method of Example 202, Step B, 0.25 g, 6.4 mmol) was combined with N-methylpiperazine (2.0 mL) and heated at 80 °C for 1 h under nitrogen atmosphere. The mixture was quenched in water and extracted twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (96:4 chloroform:methanol) to give the title compound as a white foam, 0.11 g (41%). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 6H), 1.51 (d, 3H), 2.47 (s, 3H), 2.63 (m, 4H), 3.23 (m, 2H), 3.94 (m, 4H), 4.33 (m, 2H), 4.57 (m, 2H), 4.71 (q, 1H), 5.96 (d, 1H), 6.46 (d, 1H), 7.98 (d, 1H), 8.23 (d, 1H); mp: 60-70 °C; MS (CI) 413 ($MH^+$).

Examples 203 to 207

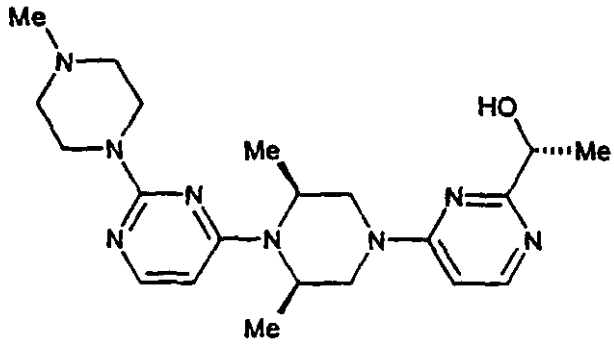
Examples 203 to 207 were prepared from the appropriate starting materials in a manner analogous to the method of Example 202.



| Example | $R^{11}$ | $R^7$ | $R^6$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 203 | morpholin-4-yl | 2R-Me | 6S-Me | 70-80 | 400 |
| 204 | pyrrolidin-1-yl | 2R-Me | 6S-Me | 70-80 | 384 |
| 205 | 2,6-dimethylmorpholin-4-yl | 2R-Me | 6S-Me | | 428 |
| 206 | 3,5-dimethylpiperidin-1-yl | 2R-Me | 6S-Me | | 426 |
| 207 | 5-methyl-furan-2-yl | 2R-Me | 6S-Me | 123-128 | 395 |

Example 208

1R-(4-[3R,5S-Dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl]-pyrimidin-2-yl)-ethanol.



**Step A:** 4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-2-methanesulfonyl-pyrimidine. To a solution of cis-1-benzyl-3,5-dimethylpiperazine (24.9 g, 122 mmol, *Org. Prep. Proceed. Int.* **1976**, *8*, 19) in dimethylacetamide (60 mL) was added 4-chloro-2-methanesulfonyl pyrimidine (11.8 g, 61.3 mmol) and stirred for 16 h at 120 °C. The mixture was partitioned between water and ethyl acetate and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed three times with 1% aqueous copper sulfate, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an orange solid which was slurried in isopropyl ether (100 mL) and filtered to give the title compound of Example 208, Step A as an orange solid, 16.5 g

(75%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.35 (d, 6H), 2.25 (m, 2H), 2.76 (m, 2H), 3.23 (s, 3H), 3.53 (s, 2H), 4.35-4.65 (m, 2H), 6.51 (d, 1H), 7.26 (m, 2H), 7.34 (m, 3H), 8.24 (d, 1H); MS (CI) 361 ($MH^+$).

**Step B:** 4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-2-(4-methylpiperazin-1-yl)-pyrimidine. 4-(4-Benzyl-2R,6S-dimethylpiperazin-1-yl)-2-methanesulfonylpyrimidine (prepared according to the method of Example 208, Step A, 11.5 g, 31.9 mmol) was combined with N-methylpiperazine (15 mL, 128 mmol) and heated to 120 °C for 2 h. The mixture was diluted with ethyl acetate and washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to give the title compound of Example 208, Step B as an orange solid, 14.7 g (84%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.30 (d, 6H), 2.21 (m, 2H), 2.33 (s, 3H), 2.46 (m, 4H), 2.72 (d, 2H), 3.53 (s, 2H), 3.78 (m, 4H), 4.31 (m, 2H), 5.79 (d, 1H), 7.24 (m, 2H), 7.31 (m, 3H), 7.90 (d, 1H); MS (CI) 381 ($MH^+$).

**Step C:** 4-(2R,6S-Dimethyl-piperazin-1-yl)-2-(4-methylpiperazin-1-yl)-pyrimidine. To a solution of 4-(4-benzyl-2R,6S-dimethylpiperazin-1-yl)-2-(4-methyl-piperazin-1-yl)-pyrimidine (prepared according to the method of Example 208, Step B, 9.8 g, 25.8 mmol) in methanol (200 mL) and hydrochloric acid (1 N in ethyl ether, 38.7 mL, 38.7 mmol) was added ammonium formate (16.3 g, 25.8 mmol). After stirring at ambient temperature for 5 min, 10% palladium on carbon (1.96 g, 20 wt% pre-wetted with isopropanol) was added and this mixture was heated to reflux for 2 h. The cooled reaction was filtered and the filtrate was concentrated to a solid, which was diluted with ethyl acetate and washed twice with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to give the title compound of Example 208, Step C as a clear oil, 6.01 g (81%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 6H), 2.31 (s, 3H), 2.24-2.44 (m, 4H), 2.90 (m, 4H), 3.76 (m, 4H), 4.25 (m, 2H), 5.79 (d, 1H), 7.90 (d, 1H); MS (CI) 291 ($MH^+$).

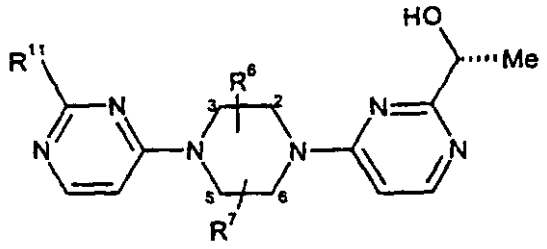
**Step D:** 1R-(4-[3R,5S-Dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl]-pyrimidin-2-yl)-ethyl butyrate. To a solution of 4-(2R,6S-dimethyl-piperazin-1-yl)-2-(4-methyl-piperazin-1-yl)-pyrimidine (prepared according to the method of Example 208, Step C, 9.0 g, 31.1 mmol) and triethylamine (6.5 g, 46.5 mmol) in dimethylformamide (90 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl

butyrate (prepared according to the method of Preparation Seven, 7.78 g, 34.1 mmol) and heated to reflux for 3 h under nitrogen atmosphere. The cooled mixture was filtered and the solids were washed twice with ethyl acetate. The combined extracts were washed once with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil which was purified by flash chromatography (95:5 chloroform:methanol) to give the title compound of Example 208, Step D as an oil, 11.4 g (76%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.18 (d, 6H), 1.54 (d, 3H), 2.23-2.35 (m, 7H), 2.51 (m, 4H), 3.21 (m, 2H), 3.81 (m, 4H), 4.32 (m, 2H), 4.52 (m, 2H), 5.65 (q, 1H), 5.82 (d, 1H), 6.38 (d, 1H), 7.39 (d, 1H), 8.18 (d, 1H); MS (CI) 483 ($MH^+$).

**Step E:** 1R-(4-{3R,5S-Dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol. 1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Example 208, Step D, 11.3 g, 23.5 mmol) was combined with concentrated hydrochloric acid (60 mL) and stirred at ambient temperature for 4 h. The mixture was quenched in saturated aqueous sodium bicarbonate and extracted five times with 10% isopropanol/chloroform. The combined extracts were washed once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was evaporated to an oil and crystallized from isopropanol to give the title compound as a white solid, 7.34 g (76%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, 6H), 1.51 (d, 3H), 2.34 (s, 3H), 2.45 (m, 4H), 3.24 (m, 4H), 3.76 (m, 2H), 4.30-4.53 (m, 4H), 4.68 (q, 1H), 5.82 (d, 1H), 6.42 (d, 1H), 7.94 (d, 1H), 8.21 (d, 1H); mp: 181-182 °C; MS (CI) 413 ($MH^+$).

Examples 209 to 211

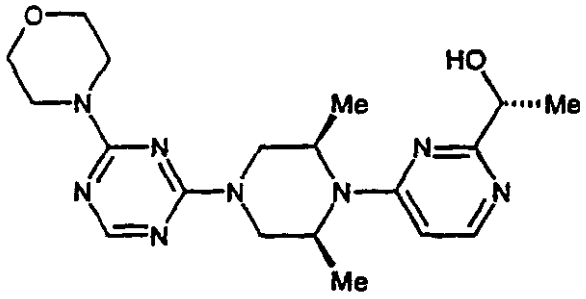
Examples 209 to 211 were prepared from the appropriate starting materials in a manner analogous to the method of Example 208.



| Example | $R^{11}$ | $R^7$ | $R^6$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 209 | 2,6-dimethylmorpholin-4-yl | 3R-Me | 5S-Me | | 428 |
| 210 | 4-ethylpiperazin-1-yl | 3R-Me | 5S-Me | 144-146 | 427 |
| 211 | 4-isopropylpiperazin-1-yl | 3R-Me | 5S-Me | 137-139 | 441 |

Example 212

1R-[4-[2R,6S-Dimethyl-4-(4-morpholino-4-yl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-ethanol.



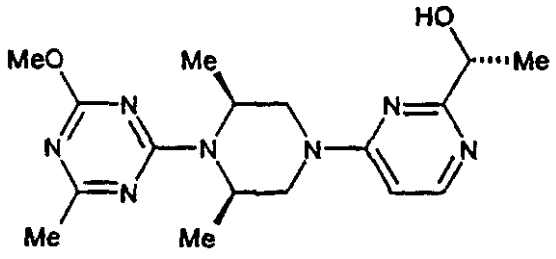
**Step A:** 1R-[4-[4-(4-Chloro-6-morpholino-[1,3,5]triazin-2-yl)-2R,6S-dimethylpiperazin-1-yl]-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Four, 0.31 g, 1.0 mmol) and sodium bicarbonate (0.17 g, 2.0 mmol) in dimethylformamide (3 mL) was added 2,4-dichloro-6-morpholino-[1,3,5]triazine (0.24 g, 1.0 mmol; *Chem. Pharm. Bull.* **1997**, *45*, 291) and stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate and washed twice with water, once with saturated aqueous sodium chloride, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to an oil, which was purified by flash chromatography (99:1 chloroform:methanol) to give the title compound of Example 212, Step A as a white solid, 0.19 g (37%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H), 1.23 (d, 6H), 1.53 (d, 3H), 1.66 (m, 2H), 2.37 (t, 2H), 3.16 (m, 2H), 3.72-

3.78 (m, 10H), 4.12-4.78 (m, 2H), 5.65 (q, 1H), 6.34 (d, 1H), 8.19 (m, 2H); MS (CI) 505, 507 ($MH^+$).

**Step B:** 1R-{4-[2R,6S-Dimethyl-4-(4-morpholino-4-yl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol. To a solution of 1R-{4-[4-(4-chloro-6-morpholino-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 212, Step A, 0.15 g, 0.35 mmol) in ethanol (10 mL) was added 10% palladium on carbon (0.75 g, 500 wt %) and hydrogenated at 45-50 psi using a Parr apparatus for 12 hours. The catalyst was filtered off and the filtrate was concentrated to an oil which was added to concentrated hydrochloric acid (2 mL) and stirred at ambient temperature for 6 hours. The mixture was diluted with chloroform and washed twice with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to give the title compound as a white solid, 0.47 g (40%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, 6H), 1.53 (d, 3H), 3.16 (m, 2H), 3.72-3.78 (m, 10H), 4.12-4.78 (m, 3H), 6.34 (d, 1H), 8.19 (m, 2H); mp: 78-82 °C; MS (CI) 401 ($MH^+$); $[\alpha]_D$ +15.1 (c 1.0, MeOH).

Example 213

1R-{4-[4-(4-Methoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethylpiperazin-1-yl]-pyrimidin-2-yl}-ethanol.



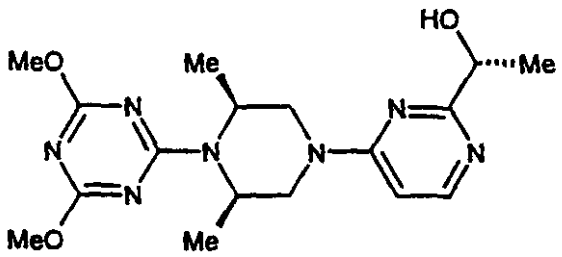

**Step A:** 1R-{4-[4-(4-Chloro-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethylpiperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 1.47 g, 6.43 mmol) and sodium bicarbonate (2.25 g, 26.8 mmol) in dimethylformamide (10 mL) was added 2,4-dichloro-6-methyl-[1,3,5]triazine (0.88 g, 5.3 mmol; *Monatsh. Chem.* **1970**, *101*, 724) and stirred at ambient temperature for 2 h. The mixture was diluted with ethyl acetate (150 mL) and washed twice with water, once with 10% aqueous $CuSO_4$, once with saturated aqueous sodium chloride, and

the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to give the title compound of Example 213, Step A as a tan solid, 2.12 g (91%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H), 1.23 (m, 6H), 1.54 (d, 2H), 1.66 (m, 2H), 2.31 (s, 3H), 2.37 (m, 2H), 2.41 (s, 1H), 3.19 (m, 2H), 4.22-4.55 (m, 2H), 4.91 (m, 2H), 5.65 (q, 1H), 6.40 (d, 1H), 8.20 (d, 1H); MS (CI) 434, 436 ($MH^+$).

**Step B:** 1R-{4-[4-(4-Methoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethylpiperazin-1-yl]-pyrimidin-2-yl}-ethanol. A solution of sodium methoxide in methanol was freshly prepared by allowing sodium metal (0.4 g, 17.3 mmol) to dissolve in methanol (40 mL). To this mixture was added 1R-{4-[4-(4-chloro-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 213, Step A, 1.5 g, 3.46 mmol) which was stirred at ambient temperature for 16 h. The reaction mixture was evaporated to an oil, diluted with chloroform and washed twice with water, once with saturated aqueous sodium chloride, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to a clear oil which was crystallized from isopropyl ether to give the title compound as a white solid, 0.85 g (72%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, 6H), 1.48 (d, 3H), 2.36 (s, 3H), 3.20-3.26 (m, 2H), 3.90 (s, 3H), 4.18-4.43 (m, 2H), 4.63 (m, 2H), 4.68 (q, 1H), 4.85 (d, 1H), 6.42 (d, 1H), 8.18 (d, 1H); mp: 161-162 °C; MS (CI) 360 ($MH^+$); $[\alpha]_D$ +16.8 (c 1.0, MeOH).

Example 214

1R-{4-[4-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



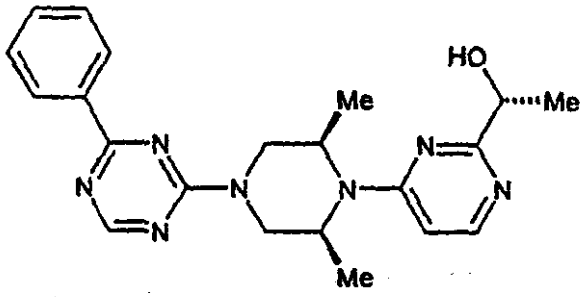

**Step A:** 1R-{4-[4-(4,6-Dichloro-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 1R-[4-(3R,5S-Dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 3.25 g, 10.5 mmol) and sodium bicarbonate (1.01 g, 19.2 mmol) in dimethylformamide (8 mL) was added cyanuric chloride (1.76 g, 9.6 mmol) and stirred

at ambient temperature for 2 h. The mixture was diluted with ethyl acetate and washed twice with water, once with saturated aqueous sodium chloride, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to give the title compound of Example 214, Step A as a white semi-solid, 1.42 g (68%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H), 1.23 (m, 6H), 1.54 (d, 3H), 1.66 (m, 2H), 2.37 (m, 2H), 3.19 (m, 2H), 4.42-4.55 (m, 2H), 4.91 (m, 2H), 5.65 (q, 1H), 6.40 (d, 1H), 8.20 (d, 1H); MS (CI) 446, 448 ($MH^+$).

**Step B:** 1R-{4-[4-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol. A solution of sodium methoxide in methanol was freshly prepared by allowing sodium metal (0.18 g, 8.0 mmol) to dissolve in methanol (16 mL). To this mixture was added 1R-{4-[4-(4,6-dichloro-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 214, Step A, 0.91 g, 2.0 mmol) at 0 °C, then warmed to ambient temperature for 1 h. The mixture was evaporated to an oil, diluted with chloroform and washed once with water, once with saturated aqueous sodium chloride, dried over sodium sulfate and filtered. The filtrate was concentrated to a clear oil which crystallized from isopropyl ether to give the title compound as a white solid, 0.54 g (72%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, 6H), 1.50 (d, 3H), 3.20 (m, 2H), 3.95 (s, 6H), 4.32 (m, 1H), 4.67-4.86 (m, 4H), 6.34 (d, 1H), 8.22 (d, 1H); mp: 187-188 °C; MS (CI) 376 ($MH^+$).

Example 215

1R-[2R,6S-Dimethyl-4-(4-phenyl-[1,3,5]triazin-2yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.




**Step A:** 1R-{4-[4-(4-Chloro-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1yl)-pyrmidin-2yl]-ethyl butyrate (prepared according to the method of Preparation

Four, 2.35 g, 7.67 mmol) and sodium bicarbonate (1.29 g, 15.3 mmol) in dimethylformamide (25 mL) at 0 °C was added 2,4-dichloro-6-phenyl[1,3,5]triazine (1.73 g, 7.67 mmol; *Helv. Chim. Acta* **1950**, 33, 1365) portionwise. The reaction mixture was allowed to warm to room temperature and stir under nitrogen for 4 h, poured into water then filtered to give the title compound of Example 215, Step A as a light tan solid, 1.99 g (51%). 1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, 3H), 1.25 (d, 6H), 1.57 (d, 3H), 1.68 (m, 2H), 2.40 (t, 2H), 3.27 (d, 2H), 4.65 (m, 2H), 4.82 (d, 1H), 5.00 (d, 1H), 5.68 (q, 1H), 6.34 (d, 1H), 7.46 (m, 3H), 8.21 (d, 1H), 8.40 (d, 2H); MS (CI) 496, 498 ($MH^+$).

**Step B:** 1R-{4-[4-(6-Phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. To a solution of 1R-{4-[4-(4-chloro-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 215, Step A, 4.81 g, 9.7 mmol) in methanol (50 mL) was added 10% palladium on carbon (940 mg, 20 wt%), ammonium formate (5.98 g, 97 mmol), and hydrochloric acid (2 M in ethyl ether, 7.1 mL, 14.2 mmol) and refluxed for 1.5 h. The mixture was allowed to cool, then filtered. The filtrate was concentrated and partitioned between chloroform and saturated aqueous sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, filtered, and the filtrate was evaporated to an oil which was purified by flash chromatography (99:1 chloroform:methanol) to give the title compound of Example 215, Step B as a clear oil, 2.69 g (59%). 1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, 3H), 1.25 (d, 6H), 1.57 (d, 3H), 1.68 (m, 2H), 2.40 (t, 2H), 3.27 (d, 2H), 4.65 (m, 2H), 4.82 (d, 1H), 5.00 (d, 1H), 5.68 (q, 1H), 6.34 (d, 1H), 7.46 (m, 3H), 8.21 (d, 1H), 8.40 (d, 2H), 8.66 (s, 1H); MS (CI) 462 ($MH^+$).

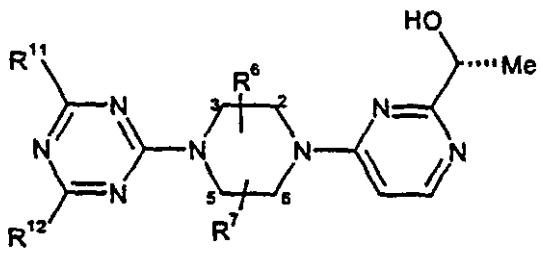
**Step C:** 1R-[2R,6S-Dimethyl-4-(4-phenyl-[1,3,5]triazin-2yl)-piperazin-1-yl]-pyrimidin-2-yl]-ethanol. Concentrated hydrochloric acid (10 mL) was added to 1R-{4-[4-(6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1yl]-pyrimidin-2yl}-ethyl butyrate (prepared according to the method of Example 215, Step B, 2.69 g, 5.8 mmol) and allowed to stir for 5 h at ambient temperature. The reaction mixture was cooled to 0 °C, diluted with chloroform, and 6 M aqueous sodium hydroxide was added slowly until basic (pH 9). The layers were separated and the aqueous layer was extracted twice with chloroform. The combined organic extracts were washed once with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and the filtrate

was concentrated to an oil which was purified by flash chromatography (97:3 chloroform:methanol) to give a white foam that crystallized from isopropyl ether to give the title compound as a white solid, 1.55 g (68%). 1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 6H), 1.54 (d, 3H), 3.31 (d, 2H), 4.63 (m, 2H), 4.77 (q, 1H), 4.85 (d, 1H), 5.50 (d, 1H), 6.42 (d, 1H), 7.50 (m, 3H), 8.25 (d, 1H), 8.41 (d, 2H), 8.68 (s, 1H); mp: 133-134 °C; MS (CI) 392 ($MH^+$); $[\alpha]_D$ +18.7 (c 1.07, MeOH).

Examples 216 to 235

Examples 216 to 235 were prepared from the appropriate starting materials in a manner analogous to the method of Example 215.

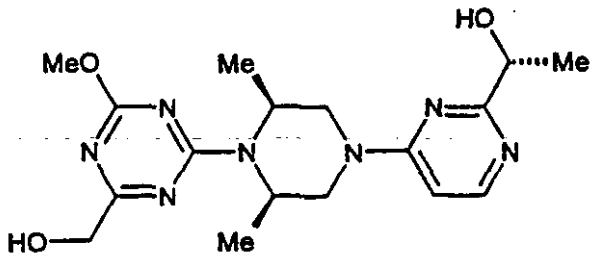
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| Example | $R^{11}$ | $R^{12}$ | $R^6$ | $R^7$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|---|
| 216 | Cl | morpholin-4-yl | 2R-Me | 6S-Me | 138-141 | 435, 437 |
| 217 | H | morpholin-4-yl | 3R-Me | 5S-Me | 152 | 401 |
| 218 | OMe | morpholin-4-yl | 2R-Me | 6S-Me | 176-178 | 431 |
| 219 | Me | 4-methyl-piperazin-1-yl | 3R-Me | 5S-Me | | 428 |
| 220 | Me | H | 2R-Me | 6S-Me | 91-94 | 330 |
| 221 | OMe | OMe | 2R-Me | 6S-Me | 128-129 | 376 |
| 222 | OEt | Me | 3R-Me | 5S-Me | 141-142 | 374 |
| 223 | OiPr | Me | 3R-Me | 5S-Me | 87-91 | 388 |
| 224 | phenyl | H | 3R-Me | 5S-Me | 154-155 | 392 |
| 225 | phenyl | OMe | 3R-Me | 5S-Me | | 422 |
| 226 | phenyl | OMe | 2R-Me | 6S-Me | 135-138 | 422 |
| 227 | iPr | H | 2R-Me | 6S-Me | 122-124 | 358 |
| 228 | iPr | OMe | 3R-Me | 5S-Me | 75-80 | 388 |
| 229 | phenyl | H | H | H | 115-117 | 364 |
| 230 | OMe | Me | H | H | 173-175 | 332 |
| 231 | o-tolyl | H | 3R-Me | 5S-Me | 123-125 | 406 |
| 232 | o-tolyl | OMe | 3R-Me | 5S-Me | 143-145 | 436 |
| 233 | cyclopropyl | H | 3R-Me | 5S-Me | 134-135 | 356 |
| 234 | cyclopropyl | H | 2R-Me | 6S-Me | 133-134 | 356 |
| 235 | OMe | $CH_2OMe$ | 3R-Me | 5S-Me | 104-105 | 390 |

Example 236

1R-{4-[4-(4-Hydroxymethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.

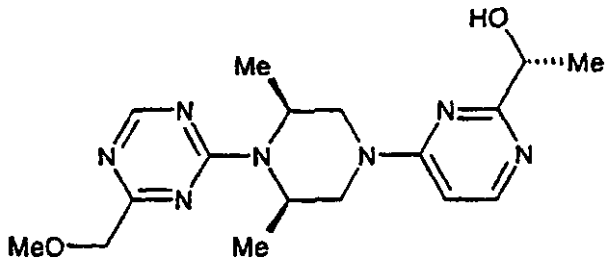


**Step A:** 1R-[4-[4-(4-Chloro-6-diazomethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl)-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 3.06 g, 10.0 mmol) and sodium bicarbonate (1.68 g, 20.0 mmol) in dimethylformamide (10 mL) was added 2,4-dichloro-6-diazomethyl-[1,3,5]triazine (1.90 g, 10.0 mmol; *J. Am. Chem. Soc.* **1957**, *79*, 944) and stirred at ambient temperature for 2 h. The mixture was diluted with ethyl acetate, washed twice with water, once with saturated aqueous sodium chloride, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (ethyl acetate) to give the title compound of Example 236, Step A as a foam, 1.84 g (41%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H), 1.23 (m, 6H), 1.55 (d, 3H), 1.66 (m, 2H), 2.38 (m, 2H), 3.19 (m, 2H), 4.22-4.45 (m, 2H), 4.86 (m, 2H), 5.10 (s, 1H), 5.65 (q, 1H), 6.40 (d, 1H), 8.20 (d, 1H); mp: 106-108 °C; MS (CI) 461, 463 ($MH^+$).

**Step B:** 1R-[4-[4-(4-Hydroxymethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl)-ethanol. 1R-[4-[4-(4-Chloro-6-diazomethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethylpiperazin-1-yl]-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Example 236, Step A, 1.5 g, 3.2 mmol) was dissolved in ethyl acetate (20 mL) and 10% aqueous sulfuric acid (5 mL) was added slowly at ambient temperature, stirred 5 min then basified to pH 9 with 6 N aqueous sodium hydroxide. The separated ethyl acetate layer was washed once with brine, dried over magnesium sulfate, and concentrated to a semi-solid. To a freshly prepared solution of sodium methoxide, generated by dissolving sodium metal (0.92 g, 4.0 mmol) in methanol (6 mL), was added the crude solid (0.89 g, 2.0 mmol). This mixture was stirred for 4 h at ambient temperature then evaporated to dryness. The residue was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound as a white solid, 0.084 g (13%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, 6H), 1.49 (d, 3H), 3.14-3.21 (m, 2H), 3.96 (m, 2H), 3.90 (s, 3H), 4.18-4.38 (m, 2H), 4.69 (q, 1H), 4.97 (m, 2H), 6.44 (d, 1H), 8.20 (d, 1H); mp: 170-171 °C; MS (CI) 376 ($MH^+$); $[\alpha]_D$ +16.6 (c 1.0, MeOH).

## Example 237

1R-[4-[4-(4-Methoxymethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl)-ethanol.



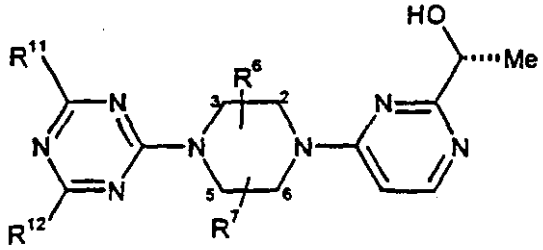

**Step A:** 1R-{4-[4-(4-Chloro-6-methoxymethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate. 1R-{4-[4-(4-Chloro-6-diazomethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethylpiperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 236, Step A, 1.5 g, 3.2 mmol) was dissolved in methanol (10 mL) and 10% aqueous sulfuric acid (3 mL) was added. This mixture was stirred at ambient temperature for 1 h then diluted with ethyl acetate. The separated ethyl acetate layer was washed once with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated to an oil which was purified by flash chromatography (99:1 dichloromethane:methanol) to give the title compound of Example 237, Step A as an oil, 1.02 (60%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.26 (d, 6H), 1.58 (d, 3H), 1.67 (q, 2H), 2.41 (t, 2H), 3.24 (m, 2H), 3.51 (s, 3H), 4.18–4.38 (m, 4H), 4.69 (q, 1H), 4.92 (m, 2H), 6.47 (d, 1H), 8.24 (d, 1H); MS (CI) 464, 466 ($MH^+$).

**Step B:** 1R-{4-[4-(4-Methoxymethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol. To a solution of 1R-{4-[4-(4-chloro-6-methoxymethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethpiperazin-1-yl]- pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 237, Step A, 0.43 g, 0.92 mmol) in methanol (8 mL) and hydrochloric acid (2 M in ethyl ether, 0.7 mL, 1.37 mmol) was added ammonium formate (0.58 g, 9.2 mmol) and 10% palladium on carbon (0.085 g, 20 wt%) and heated to reflux for 3 h. The solvents were removed and concentrated hydrochloric acid (2 mL) was added and stirred at ambient temperature for 16 h, basified to pH 9 with 6 N aqueous sodium hydroxide and diluted with ethyl acetate. The separated ethyl acetate layer was washed once with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated to an oil which was purified by flash chromatography (9:1 dichloromethane:methanol) to give the title compound as a white solid, 0.12 g (36%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, 6H), 1.49 (d,

3H), 3.24 (m, 2H), 3.51 (s, 3H), 4.18-4.38 (m, 4H), 4.72 (q, 1H), 4.97 (m, 2H), 6.47 (d, 1H), 8.22 (d, 1H), 8.57 (s, 1H); MS (CI) 360 ($MH^+$).

Examples 238 to 240

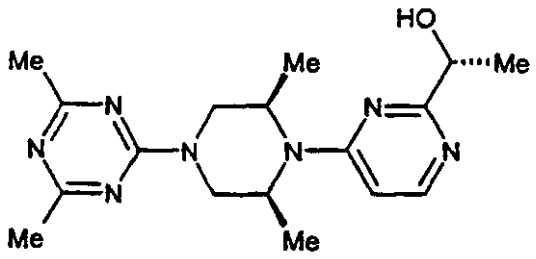
Examples 238 to 240 were prepared from the appropriate starting materials in a manner analogous to the method of Example 237.



| Example | $R^{11}$ | $R^{12}$ | $R^7$ | $R^6$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|---|
| 238 | $CH_2OH$ | H | 3R-Me | 5S-Me | 173-175 | 346 |
| 239 | OMe | $CH_2OMe$ | 3R-Me | 5S-Me | 143-145 | 390 |
| 240 | $CH_2OH$ | phenyl | 2R-Me | 6S-Me | 173-175 | 422 |

Example 241

1R-{4-[4-(4,6-Dimethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethylpiperazin-1-yl]-pyrimidin-2-yl}-ethanol.



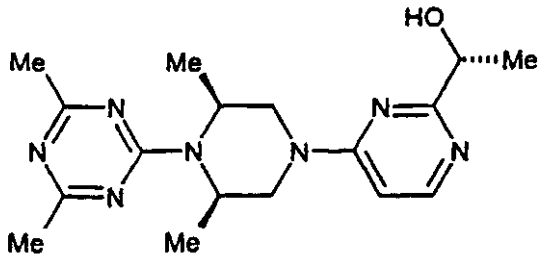
**Step A:** 1R-[4-[4-(4-Methyl-6-trichloromethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate dibenzoyl-L-tartrate salt (prepared according to the method of Preparation Fifteen, 1.33 g, 2.0 mmol) and sodium bicarbonate (0.34 g, 4.0 mmol) in dimethylformamide (5 mL) was added 2-methyl-4,6-

bis-trichloromethyl-[1,3,5]triazine (1.00 g, 3.0 mmol; *Bull. Chem. Soc., Jpn.* **1969**, *42*, 2924) and stirred at ambient temperature for 14 h. The mixture was diluted with ethyl acetate and washed twice with water and the organic layer was dried over magnesium sulfate and concentrated. The crude oil was purified by flash chromatography (95:5 dichloromethane:methanol) to give the title compound of Example 241, Step A as a foam, 0.71 g (69%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.22 (m, 6H), 1.56 (d, 3H), 1.66 (m, 2H), 2.37 (m, 2H), 2.55 (s, 1H), 3.27 (m, 2H), 4.48-4.78 (m, 2H), 4.84 (m, 2H), 5.67 (q, 1H), 6.32 (d, 1H), 8.22 (d, 1H); MS (CI) 517, 519 ($MH^+$).

**Step B:** 1R-{4-[4-(4,6-Dimethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethylpiperazin-1-yl]-pyrimidin-2-yl}-ethanol. A suspension of 1R-{4-[4-(4-methyl-6-trichloromethyl-[1,3,5]triazin-2-yl)-2R,6S dimethyl piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 241, Step A, 0.65 g, 1.2 mmol) and 10% palladium on carbon (0.2 g) in triethylamine (1 mL) and methanol (20 mL) was hydrogenated at 40 psi for 0.5 hours using a Parr apparatus. The catalyst was filtered and the filtrate was concentrated to a solid which was dissolved in concentrated hydrochloric acid (2 mL) and stirred for 6 hours. This mixture was diluted with water, basified to pH 9 with 6 N aqueous sodium hydroxide, and extracted into dichloromethane. The extract was washed twice with water, once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to a clear oil which crystallized from isopropyl ether to give the title compound as a white solid, 0.25 g (58%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, 6H), 1.49 (d, 3H), 2.40 (s, 6H), 3.16 (m, 2H), 4.45-4.68 (m, 2H), 4.71 (q, 1H), 4.84 (m, 2H), 6.42 (d, 1H), 8.20 (d, 1H); mp: 172-173 °C; MS (CI) 344 ($MH^+$); $[\alpha]_D$ +17.2 (c 1.0, MeOH).

## Example 242

1R-{4-[4-(4,6-Dimethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol.



**Step A:** 4-Methyl-6-trichloromethyl-[1,3,5]triazin-2-yl methanesulfonate. To a solution of 2-hydroxy-4-methyl-6-trichloromethyl-[1,3,5]triazine (1.14 g, 5.0 mmol; *J. Amer. Chem. Soc.* **1956**, *78*, 2447) and triethylamine (0.51 g, 5.5 mmol) in dichloromethane was added methanesulfonyl chloride (0.57 g, 5.0 mmol) at 0 °C and stirred for 1 h then quenched in saturated aqueous sodium bicarbonate. The separated organic layer was washed once with saturated sodium chloride, dried over magnesium sulfate and filtered. The filtrate was evaporated to give the title compound of Example 242, Step A as an orange oil, 0.98 g (65%) which was used directly without any further purification. MS (CI) 291,293 ($MH^+$).

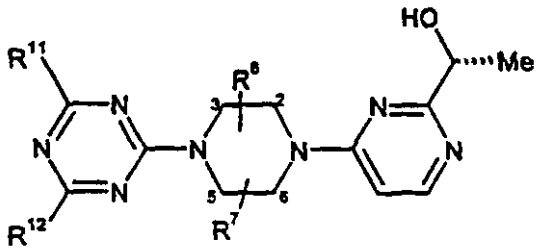
**Step B:** 1R-[4-[3R,5S-Dimethyl-4-(4-methyl-6-trichloromethyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(3R,5S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Three, 0.62 g, 2.0 mmol) and sodium bicarbonate (0.34 g, 4.0 mmol) in dimethylformamide (5 mL) was added 4-methyl-6-trichloromethyl-[1,3,5]triazin-2-yl methanesulfonate (prepared according to the method of Example 242, Step A, 1.00 g, 3.0 mmol) and stirred at ambient temperature for 14 h. The mixture was diluted with ethyl acetate and washed twice with water and the organic layer was dried over magnesium sulfate and concentrated. The crude oil was purified by flash chromatography (ethyl acetate) to give the title compound of Example 242, Step B as a clear oil, 0.41 mg (96%). $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H), 1.22 (m, 6H), 1.56 (d, 3H), 1.66 (m, 2H), 2.37 (m, 2H), 2.55 (s, 3H), 3.27 (m, 2H), 4.48-4.78 (m, 2H), 4.84 (m, 2H), 5.67 (q, 1H), 6.32 (d, 1H), 8.22 (d, 1H); MS (CI) 517, 519 ($MH^+$).

**Step C:** 1R-[4-[4-(4,6-Dimethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl]-ethanol. A suspension of 1R-[4-[3R,5S-dimethyl-4-(4-methyl-6-trichloromethyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 242, Step B, 0.65 g, 1.2 mmol) and 10% palladium on carbon (0.2 g, 30 wt%) in triethylamine (1 mL) and methanol (20

mL) was hydrogenated at 40 psi for 0.5 h using a Parr apparatus. The catalyst was filtered off and the filtrate was concentrated to a solid which was dissolved in concentrated hydrochloric acid (3 mL) and stirred for 6 h. This mixture was diluted with water, basified to pH 9 with 6 N aqueous sodium hydroxide, and extracted into dichloromethane. The extract was washed twice with water and once with saturated aqueous sodium chloride and the organic layer was dried over sodium sulfate and concentrated to a clear oil which crystallized from isopropyl ether to give the title compound as a white solid, 0.25 g (23%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, 6H), 1.49 (d, 3H), 2.40 (s, 6H), 3.16 (m, 2H), 4.45-4.68 (m, 2H), 4.71 (q, 1H), 6.42 (d, 1H), 8.20 (d, 1H); MS (CI) 344 ($MH^+$); mp: 157-159 °C; $[\alpha]_D$ +17.2 (c 1.0, MeOH).

Examples 243 to 246

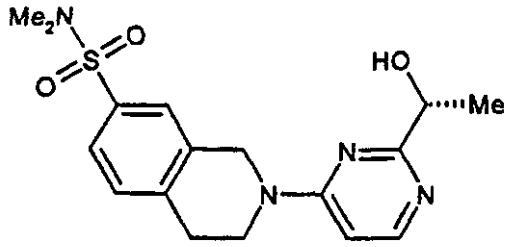
Examples 243 to 246 were prepared from the appropriate starting materials in a manner analogous to the method of Example 242.



| Example | $R^{11}$ | $R^{12}$ | $R^7$ | $R^6$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|---|
| 243 | Me | phenyl | 2R-Me | 6S-Me | | 406 |
| 244 | Me | phenyl | 3R-Me | 5S-Me | 132-134 | 406 |
| 245 | Me | tetrahydrofuran-2-yl | 2R-Me | 6S-Me | | 428 |
| 246 | Me | o-tolyl | 2R-Me | 6S-Me | 148-150 | 436 |

Example 247

(R)-2-[2-(1-Hydroxy-ethyl)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid dimethylamide.



**Step A:** 2-Trifluoroacetyl-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid dimethylamide. A mixture of 2-trifluoroacetyl-1,2,3,4-tetrahydro-isoquinoline-7-sulfonyl chloride (400 mg, 1.22 mmol, *J. Med. Chem.* **1980**, *23*, 837), dimethylamine hydrochloride (150 mg, 1.83 mmol), and triethylamine (0.50 mL, 3.66 mmol) in dioxane (10 mL) was refluxed with stirring for 30 min, cooled to room temperature, concentrated, and purified by flash column chromatography (10→50% ethyl acetate/hexanes) to give 337 mg (82%) of the title compound of Example 247, Step A as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 9:5 mixture of rotamers) δ 7.67-7.52 (c, 2H), 7.36 (t, 1H), 4.87 (s, 1.3H), 4.81 (s, 0.7H), 3.96-3.86 (c, 2H), 3.08-3.02 (c, 2H), 2.72 (s, 6H); MS (TS) 337 ($MH^+$).

**Step B:** 1,2,3,4-Tetrahydro-isoquinoline-7-sulfonic acid dimethylamide. A mixture of 2-trifluoroacetyl-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid dimethylamide (prepared according to the method of Example 247, Step A, 337mg, 1.0 mmol) and potassium carbonate (207 mg, 1.5 mmol) in a 3:1 mixture of methanol/water (10 mL) was stirred at room temperature for 1 h and concentrated. The remaining aqueous residue was extracted with 10% isopropanol/chloroform (7x) and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated to give 214 mg (89%) of the title compound of Example 247, Step B as a white solid. $^1$H NMR ($CD_3OD$, 300 MHz) δ 7.52 (d, 1H), 7.48 (s, 1H), 7.36 (d, 1H), 4.90 (s, 2H), 3.11 (t, 2H), 2.91 (t, 2H), 2.65 (s, 6H); MS ($CI/NH_3$) 241 ($MH^+$).

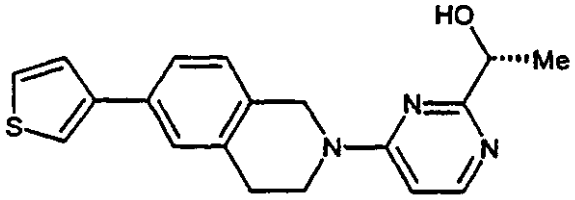
**Step C:** (R)-1-[4-(7-Dimethylsulfamoyl-3,4-dihydro-1H-isoquinolin-2-yl)-pyrimidin-2-yl]-ethyl acetate. To a solution of 1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid dimethylamide (prepared according to the method of Example 247, Step B, 210 mg, 0.88 mmol) in isopropanol (5 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl acetate (prepared according to the method of Preparation Five, 175 mg, 0.88 mmol) followed by triethylamine (0.24 mL, 1.75 mmol). This mixture was stirred at room temperature for 1.75 h then heated to reflux for 1.5 h, cooled to room temperature,

evaporated, and purified by flash column chromatography (1% methanol/chloroform) to give 327 mg (92%) of the title compound of Example 247, Step C as a white solid. $^1$H NMR ($CDCl_3$, 250 MHz) δ 8.28 (d, 1H), 7.68-7.58 (c, 2H), 7.47 (d, 1H), 6.44 (d, 1H), 5.72 (q, 1H), 4.86 (s, 2H), 3.92 (t, 2H), 3.05 (t, 2H), 2.73 (s, 6H), 2.19 (s, 3H), 1.62 (d, 3H); MS (TS) 431 ($MH^+$).

**Step D:** (R)-2-[2-(1-Hydroxy-ethyl)-pyrimidin-4-yl]-1,2,3,4-tetrahydro-isoquinoline-7-sulfonic acid dimethylamide. To a solution of (R)-1-[4-(7-dimethylsulfamoyl-3,4-dihydro-1H-isoquinolin-2-yl)-pyrimidin-2-yl]-ethyl acetate (prepared according to the method of Example 247, Step C, 326 mg, 0.81 mmol) in a 4:1 mixture of methanol/water (8 mL) was added lithium hydroxide hydrate (170 mg, 4.0 mmol). This mixture was stirred at room temperature for 50 min, concentrated, re-suspended in water, and extracted with 10% isopropanol/chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1% methanol/chloroform) to give a white foam which was further purified by recrystallization from ether/methanol to give 90 mg (31%) of the title compound as a white solid. mp: 120.5-122 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.24 (d, 1H), 7.62-7.59 (c, 2H), 7.35 (d, 1H), 6.44 (d, 1H), 4.83 (s, 2H), 4.73 (q, 1H), 4.34 (br s, 1H), 3.93-3.85 (c, 2H), 3.03 (t, 2H), 2.71 (s, 6H), 1.52 (d, 3H); MS (TS) 363 ($MH^+$).

Example 248

1-[4-(6-Thiophen-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-pyrimidin-2-yl]-ethanol.




**Step A:** 6-Thiophen-3-yl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester. A mixture of bis(benzonitrile)palladium(II) chloride (30 mg, 0.079 mmol) and 1,4-bis(diphenylphosphino)butane (33.6 mg, 0.079 mmol) in toluene (3 mL) was stirred at room temperature for 20 min. To this mixture was added 6-trifluoromethanesulfonyloxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (300 mg, 0.79 mmol, *Synth. Commun.* **1995**, 25, 3255), thiophene-3-boronic acid (131 mg, 1.02 mmol), 1 M aqueous sodium carbonate (1.57 mL, 1.57 mmol), and ethanol (2 mL). This dark mixture was heated to reflux with stirring under nitrogen

overnight, cooled to room temperature, diluted with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (4x). The combined organic extracts were dried over sodium sulfate, filtered through Celite, evaporated, and purified by flash column chromatography (hexanes→5% ethyl acetate/hexanes) to give 252 mg (100%) of the title compound of Example 248, Step A as a pale yellow waxy solid. $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.47-7.38 (c, 5H), 7.14 (d, 1H), 4.60 (s, 2H), 3.72-3.64 (c, 2H), 2.95-2.82 (c, 2H), 1.52 (s, 9H); MS (TS) 316 ($MH^+$).

**Step B:** 6-Thiophen-3-yl-3,4-dihydro-1H-isoquinoline hydrochloride. A mixture of 6-(thiophen-3-yl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (prepared according to the method of Example 248, Step A, 250 mg, 0.79 mmol) and hydrochloric acid (4 M in dioxane, 6 mL, 23.8 mmol) was stirred at room temperature for 1 h and concentrated to give 170 mg (86%) of the title compound of Example 248, Step B as a yellow solid that was used without purification in the next step. $^1$H NMR ($CD_3OD$, 250 MHz) δ 7.66 (m, 1H), 7.61-7.53 (c, 2H), 7.51-7.42 (c, 2H), 7.23 (d, 2H), 4.38 (s, 2H), 3.52 (t, 2H), 3.16 (t, 2H); MS (TS) 216 ($MH^+$).

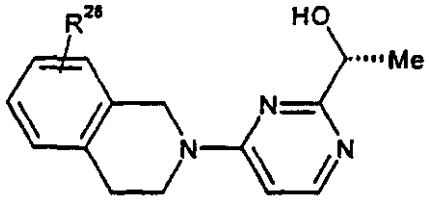
**Step C:** (R)-1-[4-(6-Thiophen-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-pyrimidin-2-yl]-ethyl acetate. To a solution of 6-thiophen-3-yl-3,4-dihydro-1H-isoquinoline hydrochloride (prepared according to the method of Example 248, Step B, 170 mg, 0.68 mmol) in isopropanol (6 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl acetate (prepared according to the method of Preparation Five, 136 mg, 0.68 mmol) followed by triethylamine (0.28 mL, 2.04 mmol). This mixture was stirred at reflux for 7 h, cooled to room temperature overnight, evaporated, and purified by flash column chromatography (0.5→1% methanol/chloroform) to give 253 mg (98%) of the title compound of Example 248, Step C as a yellow solid. $^1$H NMR ($CDCl_3$, 250 MHz) δ 8.26 (d, 1H), 7.52-7.36 (c, 6H), 6.43 (d, 1H), 5.73 (q, 1H), 4.76 (s, 2H), 3.96-3.82 (c, 2H), 3.02 (t, 2H), 2.21 (s, 3H), 1.63 (d, 3H); MS (TS) 380 ($MH^+$).

**Step D:** 1-[4-(6-Thiophen-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-pyrimidin-2-yl]-ethanol. To a solution of (R)-1-[4-(6-thiophen-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-pyrimidin-2-yl]-ethyl acetate (prepared according to the method of Example 248, Step C, 253 mg, 0.67 mmol) in a 3:1:1 mixture of methanol/tetrahydrofuran/water (5 mL) was added lithium hydroxide hydrate (84 mg, 2.0 mmol). This mixture was stirred at room temperature for 1 h, concentrated, re-suspended in water, and extracted with chloroform (4x). The combined organic extracts were dried over sodium sulfate,

filtered, evaporated, and purified by flash column chromatography (2% methanol/chloroform) to give a yellow solid which was further purified by recrystallization from ether/methanol to give 163 mg (72%) of the title compound as a white solid. mp: 125.5-127.5 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, 1H), 7.47-7.35 (c, 5H), 7.22 (d, 1H), 6.42 (d, 1H), 4.78-4.72 (c, 2H), 4.46 (br s, 1H), 3.93-3.84 (c, 2H), 2.99 (t, 2H), 1.54 (d, 3H); MS (APCI) 338 ($MH^+$).

Examples 249 to 252

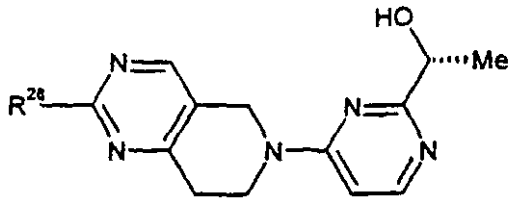
Examples 249 to 252 were prepared from the appropriate starting materials in a manner analogous to the method of Example 248.




| Example | $R^{28}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|
| 249 | 6-thiophen-2-yl | 104-105 | 338 |
| 250 | 6-pyrimidin-5-yl | | 334 |
| 251 | 7-pyrimidin-5-yl | 135-137 | 334 |
| 252 | 6-hydroxy | | 272 |

Examples 253 to 258

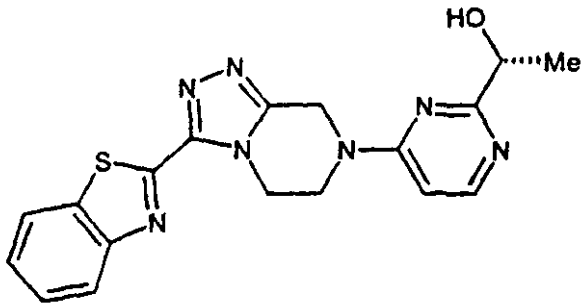
Examples 253 to 258 were prepared from the appropriate starting materials in a manner analogous to the method of Example 86.



| Example | $R^{28}$ | mp (°C) | MS (MH⁺) |
|---|---|---|---|
| 253 | H | 79-82 | 258 |
| 254 | Me | | 272 |
| 255 | $CF_3$ | 130-132 | 326 |
| 256 | $NH_2$ | 208-210 | 273 |
| 257 | Ph | 128-131 | 334 |
| 258 | pyridin-4-yl | 144-148 | 335 |

Example 259

(R)-1-[4-(3-Benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-pyrimidin-2-yl]-ethanol.



**Step A:** 5-Ethoxy-3,6-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester. To a solution of 3-oxo-piperazine-1-carboxylic acid benzyl ester (2.0 g, 8.54 mmol, Maybridge) in dichloromethane (18 mL) at room temperature was added triethyloxonium tetrafluoroborate (4.1 g, 21.3 mmol). This mixture was allowed to stir for about 3 days then quenched by the addition of ice chips followed by saturated aqueous sodium bicarbonate until a neutral pH was obtained. The organic layer was

separated and the aqueous layer was extracted with chloroform (3x). The combined organic extracts were washed with brine (1x), dried over sodium sulfate, and concentrated to give 2.11 g (95%) of the title compound of Example 259, Step A as a slightly yellow oil that was sufficiently pure to carry on to the next step. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.43-6.97 (c, 5H), 5.17 (s, 2H), 4.10 (q, 2H), 3.98 (s, 2H), 3.60-3.40 (c, 4H), 1.27 (t, 3H); MS (APCI) 263 ($MH^+$).

**Step B:** 3-Benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carboxylic acid benzyl ester. A mixture of 5-ethoxy-3,6-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester (prepared according to the method of Example 259, Step A, 490 mg, 1.87 mmol) and benzothiazole-2-carboxylic acid hydrazide (360 mg, 1.87 mmol; *J. Org. Chem.* **1958**, *23*, 1344) in n-butanol (2 mL) was stirred at reflux overnight, cooled to room temperature, concentrated, and purified by flash column chromatography (1% methanol/chloroform) to give 580 mg of the title compound of Example 259, Step B (contaminated with an equimolar amount of benzothiazole-2-carboxylic acid hydrazide which was removed in the subsequent step) as a yellow solid.

**Step C:** 3-Benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine. To a solution of 3-benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-carboxylic acid benzyl ester (prepared according to the method of Example 259, Step B, 580 mg, contaminated with benzothiazole-2-carboxylic acid hydrazide) in dichloromethane (10 mL) at 0 °C was added a solution of boron tribromide (1 M in dichloromethane, 4.45 mL, 4.45 mmol). This mixture was warmed to room temperature overnight, quenched by addition of water, and concentrated. The residual aqueous layer was washed with ether (6x), neutralized with saturated aqueous sodium bicarbonate, and extracted with 10% isopropanol/chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1→10% methanol/chloroform) to give 175 mg (36%, two steps) of the title compound of Example 259, Step C as a white solid. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, 1H), 7.96 (d, 1H), 7.57-7.41 (c, 2H), 4.62 (t, 2H), 4.36 (s, 2H), 3.35 (t, 2H); MS (APCI) 258 ($MH^+$).

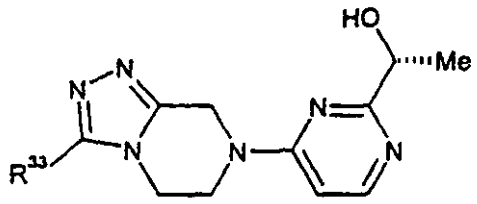
**Step D:** (R)-1-[4-(3-Benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-pyrimidin-2-yl]-ethyl butyrate. A mixture of 3-benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine (prepared according to the method of Example 259, Step C, 170 mg, 0.66 mmol), (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared

according to the method of Preparation Seven, 150 mg, 0.66 mmol), and triethylamine (0.28 mL, 1.98 mmol) in n-butanol (2.2 mL) was heated to reflux overnight, cooled to room temperature, evaporated, and purified by flash column chromatography (1% methanol/chloroform) to give 224 mg (76%) of the title compound of Example 259, Step D as a colorless solid. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.37 (d, 1H), 8.08 (d, 1H), 7.97 (d, 1H), 7.57-7.43 (c, 2H), 6.53 (d, 1H), 5.71 (q, 1H), 5.09 (s, 2H), 4.82 (t, 2H), 4.33-4.26 (c, 2H), 2.42 (t, 2H), 1.78-1.64 (c, 2H), 1.61 (d, 3H), 0.99 (t, 3H); MS (APCI) 450 ($MH^+$).

Step E: (R)-1-[4-(3-Benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-pyrimidin-2-yl]-ethanol. To a solution of (R)-1-[4-(3-benzothiazol-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 259, Step D, 220 mg, 0.49 mmol) in a 3:1:1 mixture of tetrahydrofuran/methanol/water (5 mL) was added lithium hydroxide hydrate (62 mg, 1.47 mmol). This mixture was stirred at room temperature for 3 h, concentrated, and extracted with chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (5% methanol/chloroform) to give 192 mg (100%) of the title compound as a colorless solid. mp: 216.5-218.5 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.37 (d, 1H), 8.06 (d, 1H), 7.97 (d, 1H), 7.56-7.45 (c, 2H), 6.56 (d, 1H), 5.11 (s, 2H), 4.83 (t, 2H), 4.77 (m, 1H), 4.35-4.25 (c, 2H), 4.16 (s, 1H), 1.54 (d, 3H); MS (APCI) 380 ($MH^+$), $[\alpha]_D$ +14.2 (c 1.0, $CHCl_3$).

Examples 260 to 263

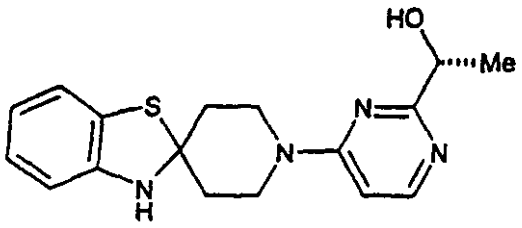
Examples 260 to 263 were prepared from the appropriate starting materials in a manner analogous to the method of Example 259.



| Example | $R^{33}$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|
| 260 | phenyl | 161-164 | 323 |
| 261 | quinoxalin-6-yl | 212-215 | 375 |
| 262 | benzothiophen-2-yl | 224-226 | 379 |
| 263 | biphen-4-yl | 123-125 | 399 |

Example 264

(R)-1-[4-(Spiro[benzothiazoline-2,4'-piperidine])-pyrimidin-2-yl]-ethanol.



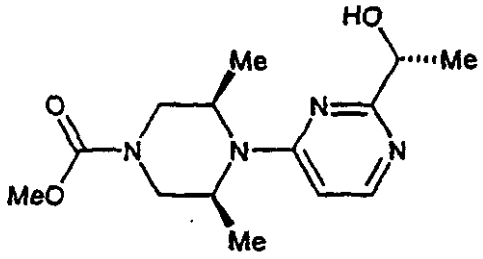
**Step A:** Spiro[benzothiazolin-2,4'-piperidine] hydrochloride. To a solution of 1'-benzylspiro[benzothiazoline-2,4'-piperidine] (500 mg, 1.69 mmol; *Indian J. Chem.* **1976**, *14B*, 984) in acetone (5 mL) at 0 °C was added 1-chloroethyl chloroformate (0.37 mL, 3.38 mmol). This mixture was stirred at 0 °C for 2 h, warmed to room temperature, and concentrated. The residue was purified by flash column chromatography (10→25% ethyl acetate/hexanes) to give the intermediate carbamate which was refluxed in methanol (2 mL) for 30 min. Evaporation of the reaction mixture provided 128 mg (31%) of the title compound of Example 264, Step A as a white solid. $^1H$ NMR ($CD_3OD$, 400 MHz) δ 6.98 (dd, 1H), 6.88 (t, 1H), 6.68-6.64 (c, 2H), 3.48-3.34 (c, 2H), 3.25-3.11 (c, 2H), 2.39-2.20 (c, 4H); MS (APCI) 207 ($MH^+$).

**Step B:** (R)-1-[4-(Spiro[benzothiazoline-2,4'-piperidine])-pyrimidin-2-yl]-ethyl butyrate. To a solution of spiro[benzothiazolin-2,4'-piperidine] hydrochloride (prepared according to the method of Example 264, Step A, 147 mg, 0.60 mmol) in isopropanol (4 mL) was added (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 140 mg, 0.60 mmol) followed by triethylamine (0.25 mL, 1.8 mmol). This mixture was stirred at reflux for 2 h, concentrated, and purified by flash column chromatography (1%→2% methanol/chloroform) to give 210 mg (88%) the title compound of Example 264, Step B as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H), 7.09 (dd, 1H), 6.95 (t, 1H), 6.78 (t, 1H), 6.68 (d, 1H), 6.40 (d, 1H), 5.68 (q, 1H), 4.32-4.18 (c, 2H), 4.02 (s, 1H), 3.38-3.25 (c, 2H), 2.39 (t, 2 h), 2.36-2.25 (c, 2H), 1.99-1.83 (c, 2H), 1.75-1.64 (c, 2H), 1.57 (d, 3H), 0.96 (t, 3H); MS (APCI) 399 ($MH^+$).

**Step C:** (R)-1-[4-(Spiro[benzothiazoline-2,4'-piperidine])-pyrimidin-2-yl]-ethanol. A mixture of (R)-1-[4-(spiro[benzothiazoline-2,4'-piperidine])-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Example 264, Step B, 204 mg, 0.51 mmol) and lithium hydroxide hydrate (65 mg, 1.53 mmol) in a 2:2:1 mixture of tetrahydrofuran/methanol/water (5 mL) was stirred at room temperature for 1 h. The organic solvents were evaporated and the residue was extracted with 10% isopropanol/chloroform (3x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (2% methanol/chloroform, 2x) to give a red foam which was further recyrstallized (ethyl acetate) to give 42 mg (25%) of the title compound as a yellow solid. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, 1H), 7.07 (d, 1H), 6.93 (td, 1H), 6.78 (td, 1H), 6.69 (d, 1H), 6.42 (d, 1H), 4.69 (m, 1H), 4.35-4.16 (c, 3H), 4.02 (s, 1H), 3.41-3.28 (c, 2H), 2.37-2.24 (c, 2H), 1.99-1.85 (c, 2H), 1.49 (d, 3H); MS (APCI) 329 ($MH^+$); $[\alpha]_D$ +17.3 (c 1.0, MeOH).

Example 265

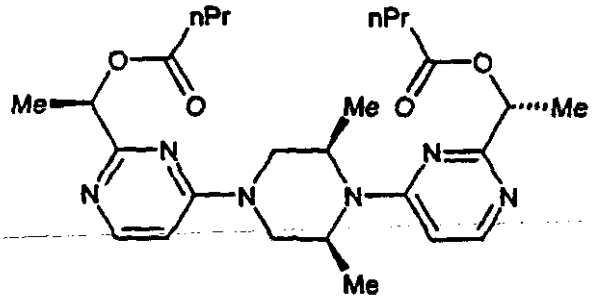
4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazine-1-carboxylic acid methyl ester.



To a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the procedure of Preparation Four, 70 mg, 23 µmol) in tetrahydrofuran (2 mL) at room temperature under nitrogen was added triethylamine (63 µL, 46 µmol) followed by methyl chloroformate (21 µL, 27 µmol). This mixture was stirred for 1 h and concentrated. The residue was dissolved in a 3:1:1 mixture of methanol/tetrahydrofuran/water (2 mL) and lithium hydroxide hydrate (29 mg, 69 µmol) was added. This mixture was stirred for 1 h, concentrated, re-suspended in water, and extracted with 10% isopropanol/chloroform (4x). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (1x), dried over sodium sulfate, filtered, and evaporated to give 50 mg (74%, 2 steps) of the title compound as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, 1H), 6.33 (d, 1H), 4.70 (m, 1H), 4.63-3.92 (c, 5H), 3.76 (s, 3H), 3.20-3.02 (c, 2H), 1.50 (d, 3H), 1.25 (d, 6H); MS (APCI) 295 ($MH^+$); $[\alpha]_D$ +19.0 (c 0.9, MeOH).

Example 266

1R-{4-[4-[2-(1R-Butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate.

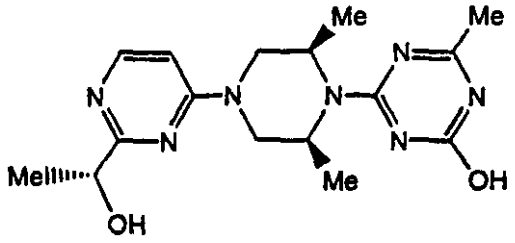


To a solution of 1R-[4-(2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the procedure of Preparation Four, 200 mg, 0.65 mmol) in

isopropanol (2 mL) at room temperature was added triethylamine (0.18 mL, 1.31 mmol) followed by (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the procedure of Preparation Seven, 150 mg, 0.65 mmol). This mixture was heated to reflux for 18 h, cooled to room temperature, concentrated and purified by flash column chromatography (1% methanol/chloroform) to give 321 mg (99%) of the title compound as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, 2H), 6.43 (d, 1H), 6.32 (d, 1H), 5.68 (q, 2H), 4.72-4.24 (c, 4H), 3.30-3.12 (c, 2H), 2.39 (t, 4H), 1.77-1.63 (c, 4H), 1.57 (d, 6H), 1.28-1.17 (c, 6H), 0.96 (t, 6H); MS (APCI) 499 ($MH^+$).

Example 267

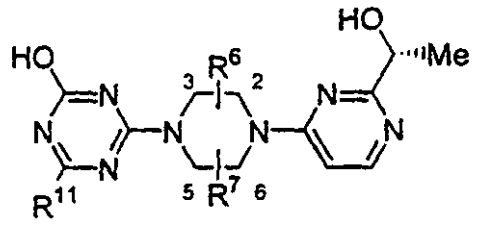
4-{4-[2-(1R-Hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-6-methyl-[1,3,5]triazin-2-ol.




1R-{4-[4-(4-Chloro-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethylpiperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate (prepared according to the method of Example 213, Step A, 0.30 g, 0.70 mmol) was added to concentrated hydrochloric acid (3 mL) and heated to reflux for 12 h. The mixture was neutralized to pH 7 with solid sodium bicarbonate and extracted into chloroform. The organic extract was dried over sodium sulfate and filtered. The filtrate was concentrated to an oil which was purified by flash chromatography (92:8 chloroform:methanol) to give the title compound as a white solid, 0.15 g (64%). $^1$H NMR ($CDCl_3$, 300 MHz) δ1.21 (d, 6H), 1.49 (d, 3H), 2.36 (s, 3H), 3.21-3.27 (m, 2H), 4.22-4.43 (m, 2H), 4.63 (m, 2H), 4.69 (q, 1H), 6.42 (d, 1H), 8.18 (d, 1H); mp: 247-248 °C; MS (CI) 346 ($MH^+$).

Examples 268 to 275

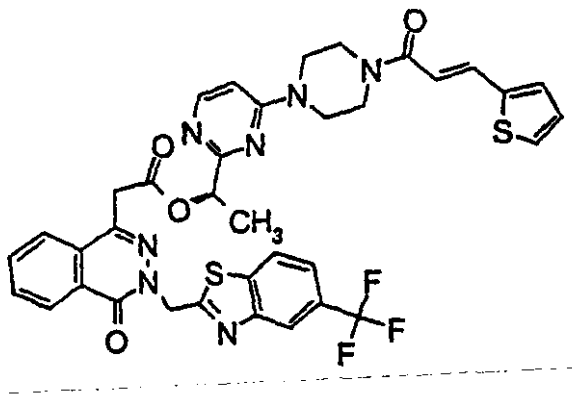
Examples 268 to 275 were prepared from the appropriate starting materials in a manner analogous to the method of Example 267.



| Example | $R^{11}$ | $R^6$ | $R^7$ | mp (°C) | MS ($MH^+$) |
|---|---|---|---|---|---|
| 268 | H | 3R-Me | 5S-Me | > 250 | 332 |
| 269 | isopropyl | 3R-Me | 5S-Me | > 250 | 374 |
| 270 | cyclohexyl | 3R-Me | 5S-Me | > 250 | 414 |
| 271 | phenyl | 3R-Me | 5S-Me | > 250 | 408 |
| 272 | cyclopropyl | 3R-Me | 5S-Me | > 250 | 372 |
| 273 | methyl | 2R-Me | 6S-Me | > 250 | 346 |
| 274 | cyclopropyl | 2R-Me | 6S-Me | > 250 | 372 |
| 275 | phenyl | 2R-Me | 6S-Me | > 250 | 408 |

Example 276

(E)-[4-Oxo-3-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-3,4-dihydro-phthalazin-1-yl]-acetic acid 1R-[4-[4-(3-thiophen-2-yl-acryloyl)-piperazin-1-yl]-pyrimidin-2-yl]-ethyl ester.

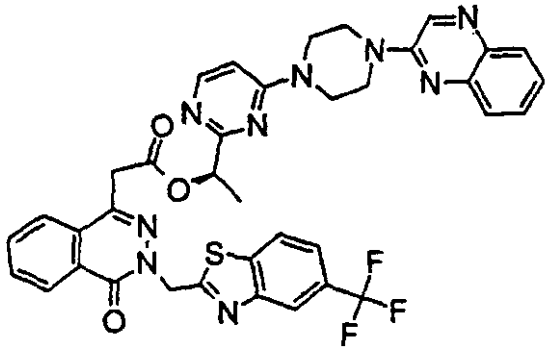


To a solution of [4-oxo-3-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-3,4-dihydro-phthalazin-1-yl]-acetic acid (0.59 g, 1.41 mmol) in dichloromethane (30 mL) and 4-dimethylaminopyridine (0.18 g, 1.41 mmol) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.54 g, 2.82 mmol) followed by (E)-1-[4-[2-(1R-

hydroxy-ethyl)-pyrimidin-4-yl]-piperazin-1-yl}-3-thiophen-2-yl-propenone (prepared according to the method of Example 127, 0.49 g, 1.41 mmol) at ambient temperature and stirred for 20 h. The mixture was washed once with saturated aqueous sodium bicarbonate, once with saturated aqueous sodium chloride, dried over magnesium sulfate and filtered. The filtrate was concentrated to an oil which was purified by flash chromatography (ethyl acetate) to give the title compound as a white foam, 0.65 g (62%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.51 (d, 3H), 3.41-3.77 (m, 8H), 4.28 (m, 2H), 5.18 (q, 1H), 5.79 (d, 1H), 6.35 (d, 1H), 6.68 (d, 1H), 7.05, (m, 1H), 7.32 (d, 1H), 7.68 (m, 1H), 7.71-7.90 (m, 5H), 8.18 (d, 1H), 8.27 (d, 1H), 8.46 (m, 1H); mp: 105-109 °C; MS (CI) 746 ($MH^+$); $[\alpha]_D$ +49.2 (c 1.0, MeOH).

Example 277

(E)-[4-Oxo-3-(5-trifluoromethyl-benzothiazol-2-ylmethyl)-3,4-dihydro-phthalazin-1-yl]-acetic acid 1R-[4-(4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl ester.



Example 277 was prepared from the appropriate starting materials in a manner analogous to the method of Example 276. $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.53 (d, 3H), 3.38-3.87 (m, 8H), 4.28 (m, 2H), 5.18 (q, 1H), 6.35 (d, 1H), 7.68 (m, 1H), 7.68-7.94 (m, 8H), 8.18 (d, 1H), 8.21-8.37 (m, 2H), 8.46 (m, 1H); mp: 108-112 °C; MS (CI) 738 ($MH^+$).

2-Methoxymethyl-4-piperazin-1-yl-pyrimidine.

**Step A:** 2-Methoxymethyl-pyrimidin-4-yl-methanesulfonate. To an ice cold solution of 2-methoxymethyl-3H-pyrimidin-4-one (35.0 g, 250 mmol; US 5,215,990) and triethylamine (25.6 g, 250 mmol) in dichloromethane (250 mL) was added methanesulfonyl chloride (28.6 g, 250 mmol) dropwise. This mixture was allowed to warm slowly to room temperature over 1 h then washed successively with saturated aqueous sodium bicarbonate and water. The organic layer was dried over

magnesium sulfate, filtered, and evaporated to give the title compound of Preparation One, Step A as a tan solid, 49.2 g (90%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.55 (s, 3H), 3.82 (s, 3H), 4.42 (s, 2H), 6.36 (d, 1H), 8.12 (d, 1H); mp: 39-40 °C; MS (TS) 219 ($MH^+$).

**Step B:** 2-Methoxymethyl-4-piperazin-1-yl-pyrimidine. To a solution of 2-methoxymethyl-pyrimidin-4-yl-methanesulfonate (prepared according to the method of Preparation One, Step A, 43.6 g, 200 mmol) in tetrahydrofuran (400 mL) was added piperazine (34.4 g, 400 mmol). This mixture was heated to reflux for 0.5 h, cooled to room temperature, and filtered. The filtrate was concentrated and dried under reduced pressure to give the title compound as a semi-solid, 36.6 g (85%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 2.45 (br s, 1H), 2.88 (m, 4H), 3.45 (s, 3H), 3.72 (m, 4H), 4.46 (s, 2H), 6.38 (d, 1H), 8.22 (d, 1H); MS (TS) 209 ($MH^+$).

Preparation Two

(R)-1-(4-Piperazin-1-yl-pyrimidin-2-yl)-ethyl acetate. A mixture of (R)-1-(4-methanesulfonyloxy-pyrimidin-2-yl)-ethyl acetate (prepared according to the method of Preparation Six, 24.1 g, 92 mmol) and piperazine (16.0 g, 184 mmol) in tetrahydrofuran (200 mL) was heated at reflux for 1 h. This mixture was cooled, filtered, concentrated, and purified by flash column chromatography (9:1 dichloromethane/methanol) to give 24.4 g (88%) of the title compound as an oil. $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, 3H), 2.25 (s, 3H), 2.83 (m, 4H), 3.63 (m, 4H), 5.54 (q, 1H), 6.38 (d, 1H), 8.24 (d, 1H); MS (CI) 251 ($MH^+$).

Preparation Three

1R-[4-(3R,5S-Dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. A mixture of (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 18.5 g, 80.9 mmol) and cis-2,6-dimethylpiperazine (18.6 g, 162 mmol) in tetrahydrofuran (400 mL) was stirred at room temperature overnight, diluted with ether, and washed with saturated aqueous sodium bicarbonate (1x) and water (3x). The combined aqueous extracts were back-extracted with 10% isopropanol/chloroform (6x). The combined organic extracts were dried over sodium sulfate, filtered, evaporated, and purified by flash column chromatography (1→5% methanol/chloroform) to give 20.9 g (64%) of the title compound as a waxy yellow solid. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, 1H), 6.31 (d, 1H), 5.65 (q, 1H), 4.53-4.16

(c, 2H), 2.89-2.78 (c, 2H), 2.47-2.33 (c, 2H), 2.38 (t, 2H), 1.73-1.60 (c, 2H), 1.55 (d, 3H), 1.11 (d, 6H), 0.94 (t, 3H); MS (APCI) 307 ($MH^+$).

Preparation Four

1R-[4-(2R,6S-Dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate.

**Step A:** 1-[4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. A mixture of (R)-1-(4-trifluoromethanesulfonyloxy-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Nine, 84.8 g, 248 mmol) and cis-1-benzyl-3,5-dimethyl-piperazine (101 g, 496 mmol, *Org. Prep. Proceed. Int.* **1976**, *8*, 19) in acetonitrile (310 mL) was stirred at reflux for 15 h, concentrated, and purified by flash column chromatography (15% ethyl acetate/hexanes) to give 52 g (53%) of the title compound of Preparation Four, Step A as an orange oil. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, 1H), 7.39-7.24 (c, 5H), 6.25 (d, 1H), 5.66 (q, 1H), 4.45 (m, 1H), 4.24 (m, 1H), 3.52 (s, 2H), 2.73 (d, 2H), 2.37 (t, 2H), 2.22 (d, 2H), 1.70-1.60 (c, 2H), 1.55 (d, 3H), 1.30 (d, 3H), 1.27 (d, 3H), 0.93 (t, 3H); MS (APCI) 398 ($MH^+$).

**Step B:** 1R-[4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate and 1S-[4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. 1-[4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Four, Step A, 131 g, 79% ee) was purified by chiral HPLC under the following conditions (column: 15 cm id x 25 cm Prochrom column packed with Chiracel AD obtained from Chiral Technologies Inc., 730 Springdale Dr., Exton, Pennsylvania, 19341; mobile phase: 90:10 n-heptane/isopropanol; flow rate: about 1 L/min; loading: 4.2 g/cycle) to provide the title compounds of Preparation Four, Step B (109 g, >98% ee) and (12.6 g, 93% ee), respectively, both as yellow oils. The $^1H$ NMR and MS data for the preceding compounds were in agreement with that for scalemic material of Preparation Four, Step A.

**Step C:** 1R-[4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate hydrochloride. To a solution of 1R-[4-(4-benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate (prepared according to the method of Preparation Four, Step B, 109 g, 275 mmol) in methanol (500 mL) was added hydrogen chloride (5 M in methanol, 56 mL, 278 mmol). This mixture was stirred at room temperature for 5 min and concentrated to give 118 g (99%) of the title compound of Preparation Four, Step C as a slightly yellow foam.

Step D: 1R-[4-(2R,6S-Dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate. To a solution of 1R-[4-(4-benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate hydrochloride (prepared according to the method of Preparation Four, Step C, 54.2 g, 125 mmol) in methanol (200 mL) was added ammonium formate (79 g, 1.25 mol) followed by a slurry of 10% palladium on carbon (13.5 g, 25 wt%) in methanol (200 mL). This mixture was stirred at reflux for 1 h and filtered through Celite. The filtrate was concentrated, diluted with saturated aqueous sodium bicarbonate, and extracted with chloroform (2x). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated to give 40.8 g of the title compound as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, 1H), 6.26 (d, 1H), 5.66 (q, 1H), 4.39 (m, 1H), 4.22 (m, 1H), 2.93 (app s, 4H), 2.38 (t, 2H), 1.71-1.62 (c, 2H), 1.56 (d, 3H), 1.27 (d, 3H), 1.24 (d, 3H), 0.94 (t, 3H); MS (APCI) 307 ($MH^+$).

Preparation Five

(R)-1-(4-Chloro-pyrimidin-2-yl)-ethyl acetate. (R)-2-(1-Acetoxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Thirteen, 3.00 g, 16.5 mmol) was added to phosphorus oxychloride (10 mL) at ambient temperature and stirred for 3 h. Excess phosphorus oxychloride was removed under vacuum and the resulting oil was partitioned between chloroform and saturated aqueous sodium carbonate. The layers were separated and the organic layer was washed twice with water, once with saturated aqueous sodium chloride and dried over magnesium sulfate and filtered. The filtrate was evaporated to give the title compound as an orange oil, 2.88 g (87%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, 3H), 2.18 (s, 3H), 5.68 (q, 1H), 6.32 (d, 1H), 8.21 (d, 1H); MS (CI) 201, 203 ($MH^+$); $[\alpha]_D$ +27.6 (c 1.0, MeOH).

Preparation Six

(R)-1-(4-Methanesulfonyloxy-pyrimidin-2-yl)-ethyl acetate. To an ice cold solution of (R)-2-(1-acetoxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Thirteen, 2.58 g, 14.2 mmol) and triethylamine (1.43 g, 14.2 mmol) in dichloromethane (20 mL) was added methanesulfonyl chloride (1.63 g, 14.2 mmol) dropwise and stirred for 1 h. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, dried over magnesium sulfate and filtered. The filtrate was evaporated to give the title compound as an oil, 3.15 g (85%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, 3H), 2.18 (s, 3H), 3.82 (s, 3H), 5.56 (q, 1H), 6.38 (d, 1H), 8.24 (d, 1H); MS (CI) 261 ($MH^+$); $[\alpha]_D$ +53.8 (c 1.1, MeOH).

Preparation Seven

(R)-1-(4-Chloro-pyrimidin-2-yl)-ethyl butyrate. (R)-2-(1-Butyryloxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Fourteen, 3.00 g, 16.5 mmol) was added to phosphorus oxychloride (10 mL) at ambient temperature and stirred for 3 h. Excess phosphorus oxychloride was removed under vacuum and the resulting oil was partitioned between dichloromethane and saturated aqueous sodium carbonate. The layers were separated and the organic layer was washed once with water, once with saturated aqueous sodium chloride and dried over magnesium sulfate and filtered. The filtrate was evaporated to give the title compound as an orange oil, 3.19 g (85%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H), 1.54 (d, 3H), 1.67 (m, 2H), 2.48 (t, 2H), 5.68 (q, 1H), 6.36 (d, 1H), 8.21 (d, 1H); $[\alpha]_D$ +27.6 (c 1.0, MeOH).

Preparation Eight

(R)-1-(4-Methanesulfonyloxy-pyrimidin-2-yl)-ethyl butyrate. To an ice cold solution of (R)-2-(1-butyryloxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Fourteen, 17.8 g, 97.8 mmol) and triethylamine (9.9 g, 97.8 mmol) in dichloromethane (100 mL) was added methanesulfonyl chloride (11.21 g, 97.8 mmol) dropwise and stirred for 1 h. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, dried over magnesium sulfate and filtered. The filtrate was evaporated to give the title compound as an oil, 24.1 g (94%). $^1$H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H), 1.54 (d, 3H), 1.68 (m, 2H), 2.48 (t, 2H), 3.81 (s, 3H), 5.54 (q, 1H), 6.38 (d, 1H), 8.24 (d, 1H); MS (CI) 261 ($MH^+$); $[\alpha]_D$ +28.8 (c 1.0, MeOH).

Preparation Nine

(R)-1-(4-Trifluoromethanesulfonyloxy-pyrimidin-2-yl)-ethyl butyrate.

**Method 1:** To a solution of (R)-2-(1-butyryloxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Fourteen, 52 g, 248 mmol) and triethylamine (36.2 mL, 260 mmol) in dichloromethane (830 mL) at 0 °C with stirring under nitrogen atmosphere was added a solution of trifluoromethanesulfonic anhydride (44 mL, 260 mmol) in dichloromethane (70 mL) dropwise via addition funnel over 30 min, maintaining an internal temperature of 4-8 °C. This mixture was allowed to stir an additional 15 min at 4 °C, then quenched with water. After stirring for 10 min, the layers were separated and the aqueous layer was extracted with dichloromethane

(3x). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to give 47.2 g (~100%) of the title compound as a dark oil which was used immediately in the next step. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, 1H), 7.03 (d, 1H), 5.82 (q, 1H), 2.41-2.32 (c, 2H), 1.72-1.60 (c, 2H), 1.62 (d, 3H), 0.95 (t, 3H); MS (APCI) 343 ($MH^+$).

**Method 2:** To a solution of (R)-2-(1-butyryloxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Fourteen, 4.20 g, 20.0 mmol) and triethylamine (2.02 g, 20.0 mmol) in dichloromethane (20 mL) was added trifluoromethanesulfonyl chloride (3.37 g, 20.0 mmol) dropwise, maintaining an internal temperature less than -20 °C, and stirred for 0.5 h. The mixture was washed successively with saturated aqueous sodium bicarbonate and water, dried over sodium sulfate and filtered. The filtrate was evaporated to give the title compound as a dark oil, 6.42 g (94%), which was used immediately in the next step. $^1$H NMR and MS data were were in agreement with that from Preparation Nine, Method 1.

Preparation Ten

(R)-1-(4-Chloro-pyrimidin-2-yl)-ethanol. To a solution of (R)-1-(4-chloro-pyrimidin-2-yl)-ethyl butyrate (prepared according to the method of Preparation Seven, 250 mg, 1.1 mmol) in dioxane (0.9 mL) was added concentrated hydrochloric acid (0.9 mL). This mixture was allowed to stir at room temperature for 5 h, quenched with saturated aqueous sodium bicarbonate followed by solid sodium bicarbonate until no more gas evolution was evident. Dichloromethane was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3x) and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated to give 125 mg (71%) of the title compound as a pale yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.59 (d, 1H), 7.25 (d, 1H), 4.92 (q, 1H), 3.81 (br s, 1H), 1.56 (d, 3H); MS (APCI) 159, 161 ($MH^+$).

Preparation Eleven

(R)-(+)-2-(1-Hydroxy-ethyl)-3H-pyrimidin-4-one hydrochloride.

***Step A:*** *R-(+)-2-Hydroxy-propionamidine hydrochloride. To a 22L, 3-neck round* bottom flask equipped with reflux condenser, mechanical stirrer, thermometer and nitrogen inlet was added tetrahydrofuran (7.3 L), R-(+)-2-hydroxy-propionamide (731 g, 8.2 mol) and triethyloxonium tetrafluoroborate (95%, 1.97 kg, 9.8 mol). The resulting yellow solution was allowed to stir at room temperature for 2 h, at which time

an NMR sample indicated consumption of starting material and the presence of the desired imidate. The solution was concentrated under vacuum to provide a yellow oil which was taken up in methanol (2 L). This solution was cooled to 15 °C and anhydrous ammonia was bubbled through the solution for 5 h. The resulting suspension was allowed to stir for 2 h. concentrated to a thick mixture, diluted with ethyl acetate and filtered through Celite. The filtrate was then cooled to 10 °C, anhydrous hydrogen chloride was bubbled through the solution for 2 h, warmed to room temperature, and filtered to provide 418 g (41%) of the title compound of Preparation Eleven, Step A. mp: 134-138 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 1.33 (t, 3H), 4.42 (q, 1H), 6.25-6.88 (br s, 1H), 8.72-9.25 (br s, 3H).

**Step B:** (R)-(+)-2-(1-Hydroxy-ethyl)-3H-pyrimidin-4-one hydrochloride. To a 22 L, 3-neck round bottom flask equipped with a reflux condenser, mechanical stirrer, thermometer and nitrogen inlet was added methanol (8 L), potassium hydroxide (946 g, 14.7 mol), R-(+)-2-hydroxy-propionamidine (prepared according to the method of Preparation Eleven, Step A, 1848 g, 14.7 mol) and ethyl 3-hydroxy-acrylate sodium salt (prepared according to the method of Preparation Twelve, Step C, 2030 g, 14.7 mol). The resulting slurry was stirred at room temperature for 3 h. The pH was adjusted from 12.5 to 7 by the addition of concentrated hydrochloric acid (1.32 L). The solids were filtered off and washed with isopropanol. The filtrate was concentrated to an oil, diluted with isopropanol (4 L), cooled to 10 °C and anhydrous hydrogen chloride was bubbled through the solution for 4 h. The resulting suspension was filtered and the solids were dried to provide 2242 g (87%) of the title compound. mp: 180-184 °C (dec); $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 1.46 (d, 3H), 4.84 (q, 1H), 6.52 (d, 1H), 8.00 (d, 1H).

## Preparation Twelve

2-(1-Hydroxy-ethyl)-3H-pyrimidin-4-one.

**Step A:** 2-Hydroxy-propionimidic acid ethyl ester hydrochloride. A solution of lactonitrile (378 g, 5.32 mol) in ethyl ether (1.46 L) and ethanol (0.34 L) was saturated with hydrogen chloride gas at 0-5 °C for 0.5 h and kept at 5 °C for 60 h. The resulting precipitate was filtered off and washed twice with ethyl ether to give the title compound of Preparation Twelve, Step A as a solid, 815 g (99%). mp: 165-168 °C; $^1$H NMR ($CD_3OD$, 250 MHz) δ 1.45-1.53 (c, 6H), 4.40-4.61 (c, 3H).

**Step B:** 2-Hydroxy-propionamidine hydrochloride. A suspension of 2-hydroxypropionimidic acid ethyl ester hydrochloride (prepared according to the method of Preparation Twelve, Step A, 751 g, 4.87 mol) in ethanol (3.75 L) at 0 °C was saturated with ammonia gas, maintaining an internal temperature < 5 °C, for 1 h then stirred at ambient temperature for 18 h. The solid was filtered off and dried under vacuum at 40 °C to give an initial crop of material. The filtrate was concentrated to one-half volume and a second crop was collected and dried under vacuum. The first and second crops were combined to give the title compound of Preparation Twelve, Step B as a yellow solid, 608 g (99%). mp: 134-138 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 1.30 (d, 3H), 4.38 (q, 1H), 6.23 (br s, 1H), 7.35 (br s, 1H), 8.78 (br s, 3H).

**Step C:** Ethyl 3-hydroxy-acrylate sodium salt. To a suspension of sodium hydride (60% dispersion in oil, 269 g, 16.7 mol) in isopropyl ether (12 L) was added slowly ethyl acetate (1280 g, 14.2 mol) at a rate which maintained an internal temperature of 45 °C. This mixture was stirred for and additional 0.5 h, then ethyl formate (2232 g, 30.1 mol) was added dropwise at 42 °C and stirred at ambient temperature for 18 h. The mixture was filtered and the solids were washed twice with ethyl ether and once with hexanes and dried to give the title compound of Preparation Twelve, Step C as a white solid, 1930 g (99%). $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 1.03 (t, 3H), 3.86 (q, 2H), 4.08 (d, 1H), 8.03 (d, 1H).

**Step D:** 2-(1-Hydroxy-ethyl)-3H-pyrimidin-4-one. To a solution of ethyl 3-hydroxy-acrylate sodium salt (prepared according to the method of Preparation Twelve, Step C, 1301 g, 9.42 mol) in water (1.3 L) was added a solution of 2-hydroxy-propionamidine hydrochloride (prepared according to the method of Preparation Twelve, Step B, 610 g, 4.9 mol) in water (1.3 L) at ambient temperature and stirred for 48 h. The solution was adjusted to pH 7.0 with acetic acid then continuously extracted with chloroform for 48 h. The extract was dried over sodium sulfate and filtered. The filtrate was concentrated to a solid, slurried in ethyl ether, filtered, and dried to give the title compound as a solid, 232 g (38%). mp: 121-124 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 1.30 (d, 3H), 4.46 (q, 1H), 5.62 (br s, 1H), 6.13 (d, 1H), 7.80 (d, 1H).

Preparation Thirteen

(R)-2-(1-Acetoxy-ethyl)-3H-pyrimidin-4-one. To a solution of vinyl acetate (4.3 g, 50 mmol) in dioxane (63 mL) was added 2-(1-hydroxy-ethyl)-3H-pyrimidin-4-one

(prepared according to the method of Preparation Twelve, 2.1 g, 15.1 mmol), and the mixture was heated to 50 °C. To the resulting solution was added lipase P30 (0.21 g, 10 wt%) and the heating was continued for 24 h. The reaction mixture was filtered and the filtrate was evaporated to obtain a thick syrupy liquid residue. The residue was purified by flash column chromatography (95:5 dichloromethane:methanol) to give the title compound as a colorless liquid, 0.97 g (92% of theory). $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.61 (d, 3H), 2.20 (s, 3H), 5.65 (q, 1H), 6.35 (d, 1H), 7.97 (d, 1H), 11.94 (s, 1H); $[\alpha]_D$ +39.9 (c 1.0, MeOH).

Preparation Fourteen

(R)-2-(1-Butyryloxy-ethyl)-3H-pyrimidin-4-one.

**Method 1:** To a solution of vinyl butyrate (17.7 g, 310 mmol) in dioxane (650 mL) was added 2-(1-hydroxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Twelve, 21.8 g, 155 mmol), and the mixture was heated to 50 °C. To the resulting solution was added lipase P30 (4.35 g, 20 wt%) and the heating was continued for 24 h. The reaction mixture was filtered and the filtrate was evaporated to obtain a thick syrupy liquid residue which was partitioned between dichloromethane and water. The layers were separated and the organic layer was dried over sodium sulfate, filtered, and evaporated to give the title compound as a colorless liquid, 9.35 g (86% of theory). $^1$H NMR ($CDCl_3$, 300 MHz) 0.95 (t, 3H), 1.65 (m, 5H), 2.40 (m, 2H), 5.65 (q, 1H), 6.45 (d, 1H), 8.00 (d, 1H); $[\alpha]_D$ +29.5 (c 1.0, MeOH).

**Method 2:** To a chilled (5 °C) solution of (R)-(+)-2-(1-hydroxy-ethyl)-3H-pyrimidin-4-one hydrochloride (prepared according to the method of Preparation Eleven, 750 g, 4.3 mol) in dichloromethane (8 L) was added triethylamine (1216 mL, 8.7 mol) followed by 4-dimethylaminopyridine (25.9 g, 0.21 mol). A solution of butyric anhydride (730 mL, 4.4 mol) in dichloromethane (730 mL) was then slowly added over a period of 5 h, keeping the temperature <3 °C. The mixture was washed twice with half-saturated brine (4 L) and once with saturated aqueous sodium bicarbonate (4 L), dried over sodium sulfate, filtered, and concentrated under vacuum to give 869 g (96%) of the title compound as an oil. The $^1$H NMR and MS data for this compound are in agreement with that of Preparation Fourteen, Method 1.

Preparation Fifteen

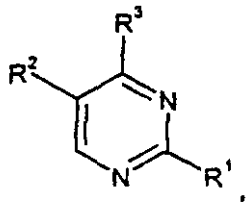
1R-[4-(2R,6S-Dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate dibenzoyl-L-tartrate salt.

**Step A:** 1R-[4-(4-Benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate bis dibenzoyl-L-tartrate salt. To a solution of (R)-2-(1-butyryloxy-ethyl)-3H-pyrimidin-4-one (prepared according to the method of Preparation Fourteen, 254 g, 1.25 mol) and triethylamine (176 mL, 1.3 mol) in dichloromethane (2.3 L) at 5 °C was slowly added a solution of trifluoromethanesulfonic anhydride (211 mL, 1.25 mol) in dichloromethane (355 mL) over a period of 3 h. The reaction was then quenched by the addition of cold water (1.4 L) and the layers were separated. The organic layer was washed once with saturated aqueous sodium bicarbonate (1.5 L), once with saturated aqueous sodium chloride (1 L), and the solvent was removed under vacuum. The resulting oil was dissolved in dimethylacetamide (890 mL) and added slowly to a solution of cis-1-benzyl-3,5-dimethyl-piperazine (735 g, 3.6 mol) in dimethylacetamide (1.3 L) at 80 °C over a 1 h period. Heating at 80 °C was continued for 3.5 h, at which time the reaction was judged complete by gas chromatography. After cooling to room temperature, water (2.5 L) and isopropyl ether (2.5 L) were added, the layers were separated, and the organic layer was washed once with water (2 L). The isopropyl ether layer was then mixed well with a solution of $CuSO_4$ (126 g) in water (3 L) and filtered through a layer of Celite, washing the filter cake with isopropyl ether (1 L). The aqueous layer of the filtrate was drained off, and the remaining organic layer was washed with water (2L) and treated with a solution of dibenzoyl-L-tartaric acid (619 g, 2.4 mol) in isopropyl ether (5.3 L). The resulting thick white slurry was stirred for 16 h and the solids were filtered off, washed with isopropyl ether (2 L), and vacuum dried at
50 °C to yield 854 g (71%) of the title compound of Preparation Fifteen, Step A as a white solid. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 0.89 (t, 3H), 1.23 (d, 3H), 1.25 (d, 3H), 1.48 (d, 3H), 1.54 (dd, 2H), 2.20 (dd, 2H), 2.31 (dt, 2H), 2.77 (d, 2H), 3.57 (s, 1H), 4.45 (m, 1H), 4.24 (m, 1H), 5.51 (q, 1H), 6.60 (d, 1H), 7.30 (m, 1H), 7.39 (m, 4H), 7.64 (m, 7H), 7.77 (m, 4 H), 8.05 (c, 7H), 8.17 (d, 1H).

**Step B:** 1R-[4-(2R,6S-Dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate dibenzoyl-L-tartrate salt. To a mixture of 1R-[4-(4-benzyl-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate bis dibenzoyl-L-tartrate salt (prepared according to the method of Preparation Fifteen, Step A, 50 g, 0.045 mol) and 5% palladium on carbon (50% wet, 10 g, 20 wt%) in methanol (400 mL) under a nitrogen atmosphere was added cyclohexene (4.6 mL, 0.045 mol). This mixture was heated to reflux for 6 h, at which time the reaction was judged complete by TLC. After cooling to 40 °C, the mixture was filtered through Celite and washed with methanol (100 mL). The methanol was gradually displaced with isopropanol by atmospheric pressure distillation until a constant boiling point of 80-82 °C was attained, and the resulting white slurry was cooled to room temperature and stirred for 4 h. The solids were filtered off, washed with isopropanol (100 mL), and vacuum dried at 50 °C to yield 25.7 g (86%) of the title compound as a white solid. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 0.90 (t, 3H), 1.15 (d, 3H), 1.21 (d, 3H), 1.47 (d, 3H), 1.55 (q, 2H), 2.3 (m, 2H), 3.04 (m, 2H), 3.2 (m, 2 H), 4.4 (br s, 1 H), 4.6 (br s, 1 H), 5.5 (q, 1H), 5.74 (s, 2H), 6.6 (d, 1H), 7.5 (t, 4 H), 7.6 (m, 2H), 8.0 (m, 4H), 8.2 (d, 1H).

CLAIMS

1. A compound of the formula I



I

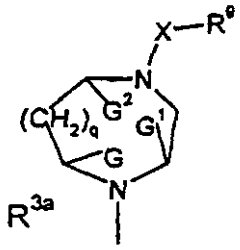
a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

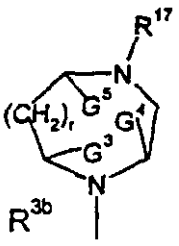
$R^1$ is formyl, acetyl, propionyl, carbamoyl or -C(OH)$R^4R^5$;

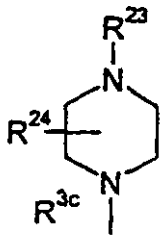
$R^4$ and $R^5$ are each independently hydrogen, methyl, ethyl or hydroxy-($C_1$-$C_3$)alkyl;

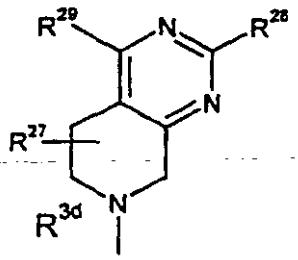
$R^2$ is hydrogen, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy;

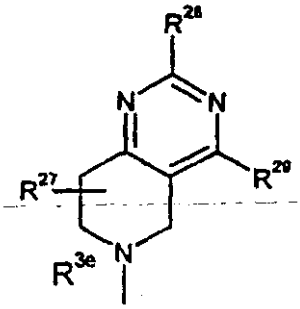
$R^3$ is a radical of the formula

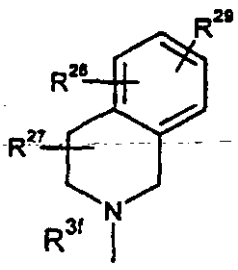


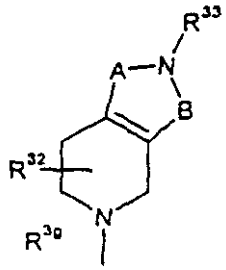


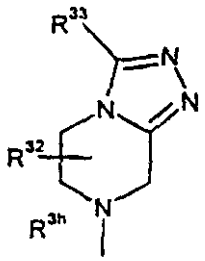


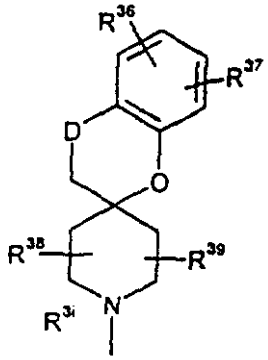


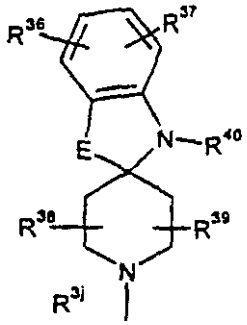


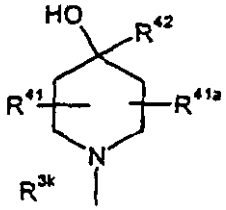


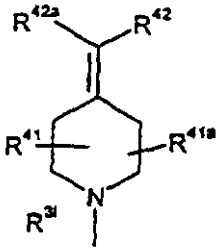


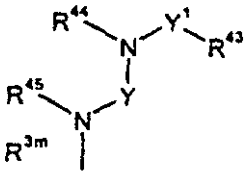


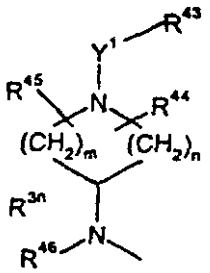




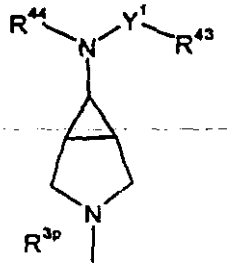




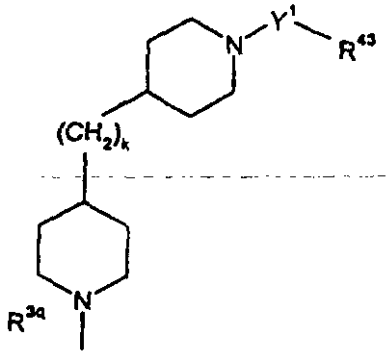








or



wherein said radical of formula $R^{3a}$ is additionally substituted on the ring by $R^6$, $R^7$ and $R^8$;

said radical of formula $R^{3b}$ is additionally substituted on the ring by $R^{18}$, $R^{19}$ and $R^{20}$;

G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or

G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or

$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;

q is 0 or 1;

X is a covalent bond, -(C=$NR^{10}$)-, oxycarbonyl, vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl, vinylenylsulfonyl, sulfinyl-($C_1$-$C_4$)alkylenylcarbonyl, sulfonyl-($C_1$-$C_4$)alkylenylcarbonyl or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl and thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar; said vinylenylsulfonyl and said vinylenylcarbonyl in the definition of X are optionally substituted independently on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; and said carbonyl($C_0$-$C_4$)alkylenylcarbonyl in the definition of X is optionally substituted indepedently with up to three ($C_1$-$C_4$)alkyl, benzyl or Ar;

$R^{10}$ is hydrogen or ($C_1$-$C_4$)alkyl;

$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_3$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro; provided that when q = 0 and X is a covalent bond, oxycarbonyl or ($C_1$-$C_4$)alkylenylcarbonyl, then $R^9$ is not ($C_1$-$C_6$)alkyl;

Ar and $Ar^1$ are independently a fully saturated, partially saturated or fully unsaturated five- to eight-membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two

fused independently partially saturated, fully saturated or fully unsaturated five- to seven-membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five to seven membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially saturated, fully saturated ring or fully unsaturated monocyclic ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

Ar and $Ar^1$ are optionally independently substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to a total of four substituents independently selected from $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$; wherein $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are each taken separately and are each independently halo, formyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)alkylenyloxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, $C(OH)R^{15}R^{16}$, naphthyl, phenyl, imidazolyl, pyridyl, triazolyl, morpholinyl, ($C_0$-$C_4$)alkylsulfamoyl, N-($C_0$-$C_4$)alkylcarbamoyl, N,N-di-($C_1$-$C_4$)alkylcarbamoyl, N-phenylcarbamoyl, N-($C_1$-$C_4$)alkyl-N-phenylcarbamoyl, N,N-diphenyl carbamoyl, ($C_1$-$C_4$)alkylcarbonylamido, ($C_3$-$C_7$)cycloalkylcarbonylamido, phenylcarbonylamido, piperidinyl, pyrrolidinyl, piperazinyl, cyano, benzimidazolyl, amino, anilino, pyrimidyl, oxazolyl, isoxazolyl, tetrazolyl, thienyl, thiazolyl, benzothiazolyl, pyrrolyl, pyrazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, 8-($C_1$-$C_4$)alkyl-3,8-diaza[3.2.1]bicyclooctyl, 3,5-dioxo-1,2,4-triazinyl, phenoxy, thiophenoxy, ($C_1$-$C_4$)alkylsulfanyl, ($C_1$-$C_4$)alkylsulfonyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said naphthyl, phenyl, pyridyl, piperidinyl, benzimidazolyl, pyrimidyl, thienyl, benzothiazolyl, pyrrolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, thiophenoxy, anilino and phenoxy in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of

$R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from ($C_1$-$C_4$)alkyl; said pyrrolidinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from hydroxy, hydroxy-($C_1$-$C_3$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to three substituents independently selected from ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, ($C_0$-$C_4$)alkylsulfamoyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said triazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said tetrazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy-($C_2$-$C_3$)alkyl or ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; and said phenyl and pyridyl which are optionally substituted on piperazine in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

$R^{11}$ and $R^{12}$ are taken together on adjacent carbon atoms and are $-CH_2OC(CH_3)_2OCH_2-$ or $-O-(CH_2)_p-O-$, and $R^{13}$ and $R^{14}$ are taken separately and are each independently hydrogen or ($C_1$-$C_4$)alkyl;

p is 1, 2 or 3;

$R^{15}$ and $R^{16}$ are taken separately and are each independently hydrogen, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; or $R^{15}$ and $R^{16}$ are taken separately and $R^{15}$ is hydrogen and $R^{16}$ is ($C_3$-$C_6$)cycloalkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, imidazolyl, benzothiazolyl or benzoxazolyl; or $R^{15}$ and $R^{16}$ are taken together and are ($C_3$-$C_6$)alkylene;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 0; $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently $(C_1$-$C_4)$alkyl; or

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_1$-$C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1$-$C_6)$alkyl;

$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl and $Ar^2$-$(C_0$-$C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy,

amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$Ar^2$ is independently defined as set forth for Ar and $Ar^1$ above;

said $Ar^2$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{23}$ is $CONR^{25}R^{26}$ or $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen ($C_1$-$C_4$)alkyl or $Ar^3$-($C_0$-$C_4$)alkylenyl and $R^{26}$ is $Ar^3$-($C_0$-$C_4$)alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

$R^{24}$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro;

$Ar^3$ is independently defined as set forth for Ar and $Ar^1$ above;

said $Ar^3$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{27}$ is hydrogen or $(C_1$-$C_4)$alkyl;

$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro, $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$; said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and thiophenoxy in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{30}$ and $R^{31}$ are each independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or

$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

A is N optionally substituted with hydrogen or $(C_1$-$C_4)$alkyl and B is carbonyl; or

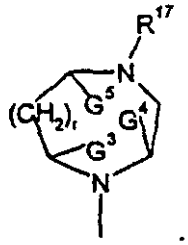
A is carbonyl and B is N optionally substituted with hydrogen or $(C_1$-$C_4)$alkyl;
$R^{32}$ is hydrogen or $(C_1$-$C_4)$alkyl;
$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl; said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl in the definition of $R^{33}$ are optionally substituted with up to three phenyl, phenoxy, $NR^{34}R^{35}$, halo, hydroxy, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{34}$ and $R^{35}$ are each independently hydrogen, $(C_1$-$C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
D is CO, CHOH or $CH_2$;
E is O, NH or S;
$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, $(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, pyrrolidino, piperidino, morpholino, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl, $Ar^4$, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or $(C_1$-$C_4)$-alkyl;
$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or
$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are -O-$(CH_2)_t$-O-;
t is 1, 2 or 3;
Y is $(C_2$-$C_6)$alkylene;
$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl;
m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;
k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;
$R^{43}$ is $(C_3-C_7)$cycloalkyl, $Ar^5$-$(C_0-C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1-C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;
$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1-C_6)$alkyl and $Ar^5$-$(C_0-C_4)$alkylenyl; or
$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;
$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;
$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;
$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3-C_7)$cycloalkyl, $Ar^6$-$(C_0-C_3)$alkylenyl, $Ar^6$-$(C_2-C_4)$alkenyl, $Ar^6$-carbonyl or $(C_1-C_6)$alkyl optionally substituted with up to five fluoro;
$Ar^6$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^6$ is optionally independently substituted as set forth for Ar and $Ar^1$ above; and $R^{41}$ and $R^{41a}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl.

2. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^3$ is



;

substituted by $R^{18}$, $R^{19}$ or $R^{20}$;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen, r is 0 and $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl or phenyl optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; $R^{19}$ and $R^{20}$ are each independently $(C_1$-$C_4)$alkyl;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; and $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl or phenyl optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_1$-$C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1$-$C_6)$alkyl;

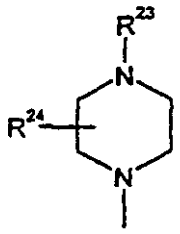
$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl and $Ar^2$-$(C_0$-$C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl,

azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, morpholinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, pyrimidyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro.

3. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^3$ is



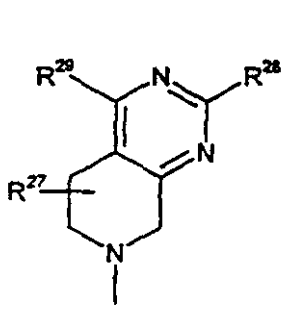
;

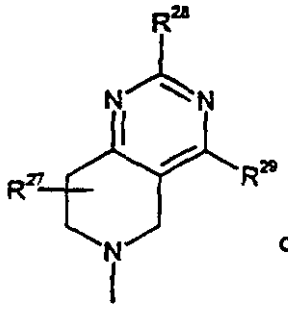
$R^{23}$ is $CONR^{25}R^{26}$, $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen $(C_1\text{-}C_4)$alkyl or $Ar^3\text{-}(C_0\text{-}C_4)$alkylenyl and $R^{26}$ is $Ar^3\text{-}(C_0\text{-}C_4)$alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

$R^{24}$ is hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxycarbonyl or phenyl optionally substituted by up to three $(C_1\text{-}C_4)$alkyl optionally substituted with up to five fluoro, $(C_1\text{-}C_4)$alkoxy optionally substituted with up to five fluoro, hydroxy, halo or hydroxy-$(C_1\text{-}C_3)$alkyl.

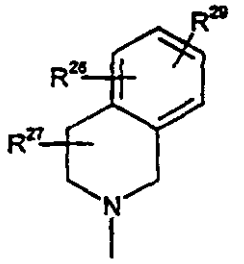
4. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^3$ is





or



$R^{27}$ is hydrogen or $(C_1\text{-}C_4)$alkyl;

$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl optionally substituted with up to five fluoro, $(C_1\text{-}C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$; said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl optionally substituted with up to five fluoro or $(C_1\text{-}C_4)$alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and

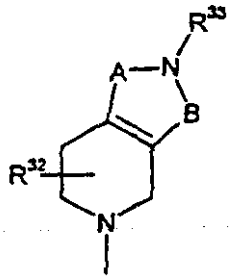
*thiophenoxy in the definition of* $R^{28}$ *and* $R^{29}$ *are optionally* substituted by up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$R^{30}$ and $R^{31}$ are each independently hydrogen, ($C_1$-$C_4$)alkyl, ($C_3$-$C_7$)cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

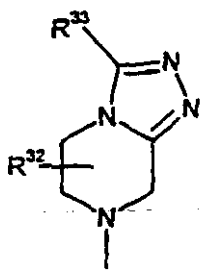
$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, or hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two *substituents independently selected from* hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro.

5. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^3$ is




or




A is N optionally substituted with hydrogen or ($C_1$-$C_4$)alkyl and B is carbonyl; or

A *is carbonyl and* B *is N optionally substituted with* hydrogen or ($C_1$-$C_4$)alkyl;

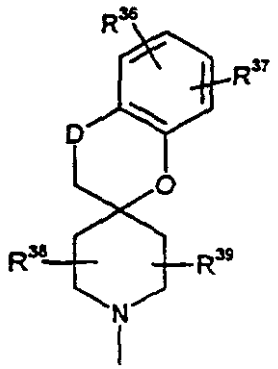
$R^{32}$ is hydrogen or ($C_1$-$C_4$)alkyl;

$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl; said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl in the definition of $R^{33}$ are optionally substituted with up to three phenyl, phenoxy, $NR^{34}R^{35}$, halo, hydroxy, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

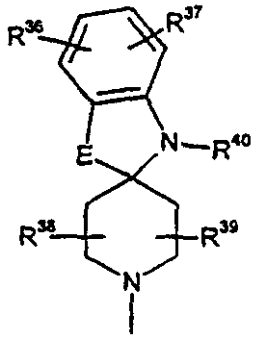
$R^{34}$ and $R^{35}$ are each independently hydrogen, ($C_1$-$C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro.

6. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^3$ is




or




D is CO, CHOH or $CH_2$;

E is O, NH or S;

$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, ($C_1$-$C_6$)alkylamino, di-($C_1$-$C_6$)alkylamino, pyrrolidino, piperidino, morpholino, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl, $Ar^4$, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or ($C_1$-$C_4$)-alkyl;

$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, halo,

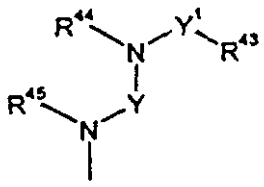
hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

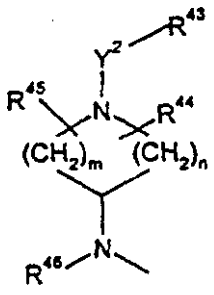
$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are -O-$(CH_2)_t$-O-;

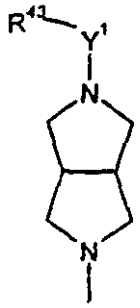
t is 1, 2 or 3.

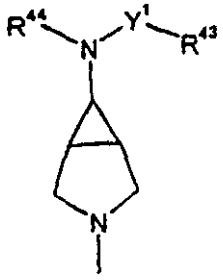
7. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^3$ is

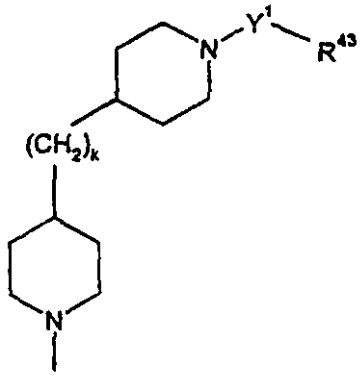








or



;

Y is ($C_2$-$C_6$)alkylene;

$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or ($C_1$-$C_4$)alkyl;

m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;

k is 0 to 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is ($C_3$-$C_7$)cycloalkyl, $Ar^5$-($C_0$-$C_4$)alkylenyl, $NR^{47}R^{48}$ or ($C_1$-$C_6$)alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1$-$C_6)$alkyl and $Ar^5$-$(C_0$-$C_4)$alkylenyl; or

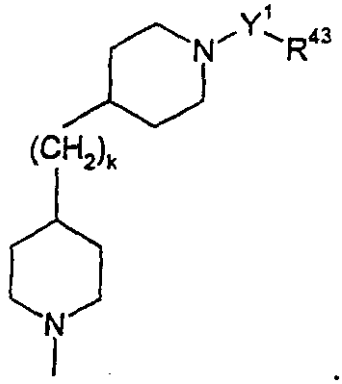
$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro.

8. A compound of claim 7, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^2$ is hydrogen;

$R^3$ is



;

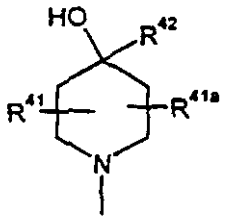
k is 0;

$Y^1$ is a covalent bond; and

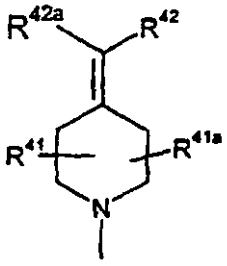
$R^{43}$ is 4-pyrimidinyl substituted at the 2-position with 1-hydroxymethyl.

9. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^3$ is



or



$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3\text{-}C_7)$cycloalkyl, $Ar^6\text{-}(C_0\text{-}C_3)$alkylenyl, $Ar^6\text{-}(C_2\text{-}C_4)$alkenyl, $Ar^6$-carbonyl or $(C_1\text{-}C_6)$alkyl optionally substituted with up to five fluoro; and

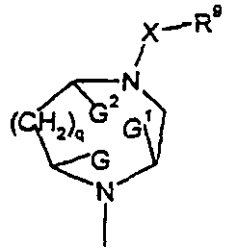
$R^{41}$ and $R^{41a}$ are independently is hydrogen or $(C_1\text{-}C_4)$alkyl.

10. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^1$ is $C(OH)R^4R^5$, where $R^4$ and $R^5$ are each independently hydrogen or methyl;

$R^2$ is hydrogen;

$R^3$ is



wherein said $R^3$ is substituted by $R^6$, $R^7$ or $R^8$;

G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen or ($C_1$-$C_4$)alkyl; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or

G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or

$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;

q is 0 or 1;

X is a covalent bond, oxycarbonyl,vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl or vinylenylsulfonyl; said vinylenylcarbonyl and said vinylenylsulfonyl in the definition of X are optionally substituted on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; said oxy($C_1$-$C_4$)alkylenylcarbonyl and said thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are optionally substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar;

$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_4$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro;

$Ar^1$ is phenyl, naphthyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, furopyrazinyl,

thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, furopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; and

said $Ar^1$ is optionally substituted as set forth in claim 1.

11. A compound of claim 10, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

X is a covalent bond, oxycarbonyl or vinylenylcarbonyl optionally substituted on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar;

$R^9$ is $Ar^1$-($C_0$-$C_4$)alkylenyl;

$Ar^1$ is phenyl, naphthyl, pyridyl, pyrimidyl, pyrazinyl, triazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, furanyl, thienyl, indolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, furopyridyl, oxazolopyridyl, thiazolopyridyl, thienopyridyl, furopyrimidyl, thienopyrimidyl, oxazolopyrimidyl or thiazolopyrimidyl; and

said $Ar^1$ is optionally substituted as set forth in claim 1.

12. A compound of claim 11, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

$R^2$ is hydrogen;

$R^4$ is hydrogen or methyl;

$R^5$ is methyl;

G, $G^1$ and $G^2$ are hydrogen;

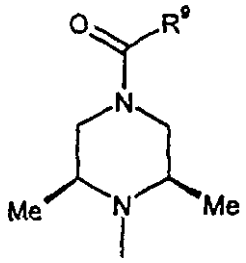
$R^6$ and $R^7$ are each independently hydrogen or methyl;

$R^8$ is hydrogen.

13. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is



14. The compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein: $R^9$ is 2-furo[3,2-c]pyridyl; 2-(4-chloro-furo[3,2-c]pyridyl); 2-(4-pyrrolidin-1-yl-furo[3,2-c]pyridyl); 2-(4-morpholin-4-yl-furo[3,2-c]pyridyl); or 2-imidazo[1,2-a]pyridyl.

15. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, selected from 1R-(4-{1'-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-[4,4']bipiperidinyl-1-yl}-pyrimidin-2-yl)-ethanol; furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone; (4-chloro-furo[3,2-c]pyridin-2-yl)-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-pyrrolidin-1-yl-furo[3,2-c]pyridin-2-yl)-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-morpholin-4-yl-furo[3,2-c]pyridin-2-yl)-methanone; {4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-imidazo[1,2-a]pyridin-2-yl-methanone; furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-methanone; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid pyridin-3-yl ester; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 2-methyl-pyridin-3-yl ester; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1- carboxylic acid 5-chloro-pyridin-3-yl ester; 4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 6-methyl-pyridin-3-yl ester; (E)-1-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-3-thiophen-2-yl-propenone; 1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(4-

ethyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-{3R,5S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{3R,5S-dimethyl-4-[2-(2-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(4-isopropyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{3R,5S-dimethyl-4-[4-methyl-6-(4-methyl-piperazin-1-yl)-[1,3,5]triazin-2-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-ethoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[3R,5S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropoxy-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-isopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[3R,5S-dimethyl-4-(4-methyl-6-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-ethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]- pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2,6-dimethyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1S-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1-{4-[4-(2-acetyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-

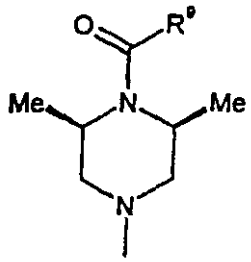
ethanone; 1RS-(4-{4-[2-(1RS-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; (4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone; 1R-{4-[2R,6S-dimethyl-4-(2-morpholin-4-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[2R,6S-dimethyl-4-(2-[1,2,4]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6R-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(4-ethyl-piperazin-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxy-6-methoxymethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-methyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl-ethanol; 1R-(4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-morpholin-4-yl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-methoxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl)-ethanol; 1R-{4-[2R,6S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2-hydroxymethyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol; 1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-py-rimidin-2-yl}-ethanol; 1R-[4-(3S-methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; 1R-[4-(3S-methyl-4-oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; 1R-[4-(3S-methyl-4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol; (4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1R-(4-{4-[2-(1R-

hydroxy-ethyl)-pyrimidin-4-yl]-2R-methyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; 1-{4-[4-(2-acetyl-pyrimidin-4-yl)-2R*,6S*-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanone or 1-(-4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone.

16. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is

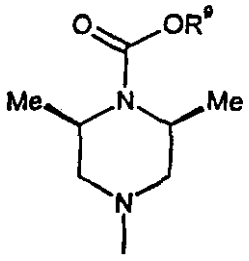


17. The compound of claim 16, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2-furo[3,2-c]pyridyl.

18. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is

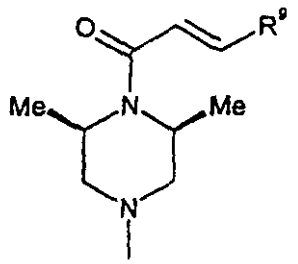


19. The compound of claim 18, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 3-pyridyl; 3-(2-methylpyridyl); 3-(5-chloropyridyl); or 3-(6-methylpyridyl).

20. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

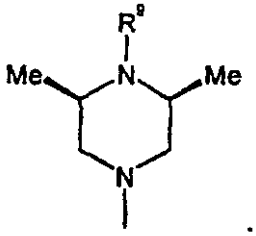
$R^1$ is (R)-1-hydroxy-ethyl; and

$R^3$ is



21. The compound of compound of claim 20, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2-thienyl.

22. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:
$R^1$ is (R)-1-hydroxy-ethyl;
$R^3$ is



; and

$R^9$ is pyrimidyl or triazinyl; said pyrimidyl or triazinyl is optionally substituted with up to two hydroxy, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_4)$alkoxy, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkylenyl, phenyl, piperazinyl optionally substituted with $(C_1$-$C_4)$alkyl, or imidazolyl optionally substituted with up to two $(C_1$-$C_4)$alkyl.

23. A compound of claim 22, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is pyrimid-2-yl optionally substituted with up to two $(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl.

24. The compound of claim 23, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 4,6-dimethylpyrimid-2-yl; 4-methoxymethyl-6-methylpyrimid-2-yl; or 4-hydroxymethyl-6-methylpyrimid-2-yl.

25. A compound of claim 22, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is pyrimid-4-yl optionally substituted with up to two $(C_1$-$C_4)$alkylpiperazin-1-yl or imidazolyl; and said imidazolyl is optionally substituted with up to two $(C_1$-$C_4)$alkyl.

26. The compound of claim 25, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2-(4-methylpiperazin-1-yl)-pyrimid-4-yl; 2-(4-ethylpiperazin-1-yl)- pyrimid-4-yl; 2-(4-methylimidazol-1-yl)- pyrimid-4-yl; 2-(2-methylimidazol-1-yl)- pyrimid-4-yl; 2-(2,4-dimethylimidazol-1-yl)- pyrimid-4-yl; or 2-(4-isopropylpiperazin-1-yl)-pyrimid-4-yl.

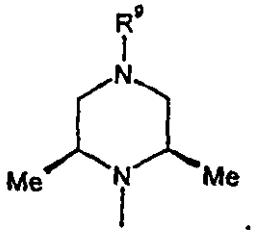
27. A compound of claim 22, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is [1,3,5]-triazin-2-yl optionally substituted with up to two $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkylpiperazin-1-yl or phenyl.

28. The compound of claim 27, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 4-methyl-6-(4-methylpiperazin-1-yl)-[1,3,5]-triazin-2-yl; 4-methoxy-6-methyl-[1,3,5]-triazin-2-yl; 4,6-dimethyoxy-[1,3,5]-triazin-2-yl; 4-ethoxy-6-methyl-[1,3,5]-triazin-2-yl; 4-isopropoxy-6-methyl-[1,3,5]-triazin-2-yl; 4-phenyl-[1,3,5]-triazin-2-yl; 4-hydroxymethyl-6-methoxy-[1,3,5]-triazin-2-yl; 4-isopropoxy-6-methoxy-[1,3,5]-triazin-2-yl; 4-isopropyl-[1,3,5]-triazin-2-yl; 4-ethyl-6-methoxy-[1,3,5]-triazin-2-yl; 4-cyclopropyl-[1,3,5]-triazin-2-yl; 4,6-dimethyl-[1,3,5]-triazin-2-yl; or 4-methyl-6-phenyl-[1,3,5]-triazin-2-yl.

29. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is




; and

$R^9$ is pyrimidyl or triazinyl, said pyrimidyl and triazinyl optionally substituted with up to two hydroxy, $(C_1-C_4)$alkyl, $(C_3-C_7)$cycloalkyl, $(C_1-C_4)$alkoxy, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, triazolyl, acetyl, morpholinyl, $(C_1-C_4)$alkylpiperazinyl, phenyl or imidazolyl optionally substituted with up to two $(C_1-C_4)$alkyl.

30. A compound of claim 29, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is pyrimid-2-yl optionally substituted with up to two $(C_1-C_4)$alkyl, hydroxy-$(C_1-C_4)$alkyl or triazolyl.

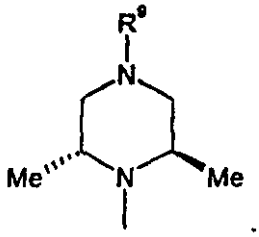
31. The compound of claim 30, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 4,6-dimethyl-pyrimid-2-yl; 4-hydroxymethyl-6-methylpyrimid-2-yl; or 4-[1,2,4]-triazol-1-yl-pyrimid-2-yl.

32. A compound of claim 29, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is pyrimid-4-yl optionally substituted with up to two ($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl, acetyl, morpholinyl, ($C_1$-$C_4$)alkylpiperazinyl, triazolyl or imidazolyl optionally substituted with up to two ($C_1$-$C_4$)alkyl.

33. The compound of claim 32, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2,6-dimethyl-pyrimid-4-yl; 2-hydroxymethyl-6-methyl-pyrimid-4-yl; 2-acetyl-pyrimid-4-yl; 2-morpholin-4-yl-pyrimid-4-yl; 2-(4-methylpiperazin-1-yl)-pyrimid-4-yl; 2-[1,2,4]-triazol-1-yl-pyrimid-4-yl; 2-(1S-hydroxyethyl)-pyrimid-4-yl; 2-(1R-hydroxyethyl)-pyrimid-4-yl; 2-(4-ethylpiperazin-1-yl)-pyrimid-4-yl; 2-(4-methylimidazol-1-yl)-pyrimid-4-yl; or 2-(2,4-dimethylimidazol-1-yl)-pyrimid-4-yl.

34. A compound of claim 12 wherein

$R^1$ is (R)-1-hydroxyethyl; $R^3$ is




; and

$R^9$ is 2-(1R-hydroxyethyl-pyrimid-4-yl, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

35. A compound of claim 29, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein $R^9$ is [1,3,5]-triazin-2-yl optionally substituted with up to two hydroxy, ($C_1$-$C_4$)alkyl, ($C_3$-$C_7$)cycloalkyl, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, morpholinyl or phenyl.

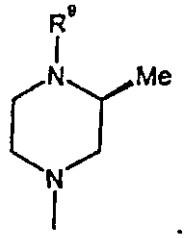
36. The compound of claim 35, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 4-morpholin-4-yl-[1,3,5]-triazin-2-yl; 4-methoxy-6-methyl-[1,3,5]-triazin-2-yl; 4,6-dimethoxy-[1,3,5]-triazin-2-yl; 4-phenyl-[1,3,5]-triazin-2-yl; 4-cyclopropyl-[1,3,5]-triazin-2-yl; 4,6-dimethyl-[1,3,5]-triazin-2-yl; 4-hydroxymethyl-6-phenyl-[1,3,5]-triazin-2-yl; 4-methoxy-6-

methoxymethyl-[1,3,5]-triazin-2-yl; 4-methyl-[1,3,5]-triazin-2-yl; or 4-methoxymethyl-6-phenyl-[1,3,5]triazin-2-yl.

37. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is



; and

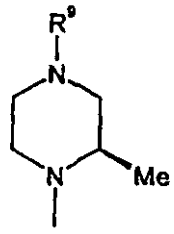
$R^9$ is pyrimidyl, quinoxalyl or oxazolopyridyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy or hydroxy-($C_1$-$C_4$)alkyl.

38. The compound of claim 37, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 4-hydroxymethyl-6-methyl-pyrimid-2-yl; 2-hydroxymethyl-pyrimid-4-yl; 2-hydroxymethyl-6-methyl-pyrimid-4-yl; 2-(oxazolo[5,4-b]pyridyl; or 2-(oxazolo[4,5-b]pyridyl; 2-quinoxalyl.

39. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is



; and

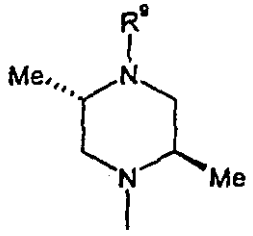
$R^9$ is pyrimidyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, hydroxy-($C_1$-$C_4$)alkyl.

40. The compound of claim 39, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2-(1R-hydroxyethyl)-pyrimid-4-yl.

41. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (R)-1-hydroxy-ethyl;

$R^3$ is



; and

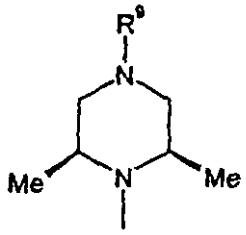
$R^9$ is pyrimidyl optionally substituted with up to two $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, hydroxy-$(C_1\text{-}C_4)$alkyl.

42. The compound of claim 41, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2-(1R-hydroxyethyl)-pyrimid-4-yl.

43. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is (S)-1-hydroxy-ethyl;

$R^3$ is



; and

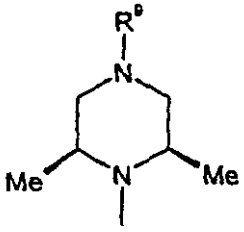
$R^9$ is pyrimidyl optionally substituted with up to two $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or hydroxy-$(C_1\text{-}C_4)$alkyl.

44. The compound of claim 43, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2-(1R-hydroxy-ethyl)-pyrimid-4-yl.

45. A compound of claim 12, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

$R^1$ is acetyl;

$R^3$ is



; and

$R^9$ is pyrimidyl optionally substituted with up to two ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, acetyl or hydroxy-($C_1$-$C_4$)alkyl.

46. The compound of claim 45, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein: $R^9$ is 2-acetyl-pyrimid-4-yl; or

2-(1R-hydroxyethyl)-pyrimid-4-yl.

47. A pharmaceutical composition comprising a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a pharmaceutically acceptable carrier or diluent.

48. A method of inhibiting sorbitol dehydrogenase in a mammal in need of such inhibition comprising administering to said mammal a sorbitol dehydrogenase inhibiting amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

49. A method of treating diabetes in a mammal suffering from diabetes comprising administering to said mammal an effective amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

50. A method of treating or preventing diabetic complications in a mammal comprising administering to said mammal an effective amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug.

51. A pharmaceutical composition comprising a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and an aldose reductase inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said aldose reductase inhibitor or said prodrug.

52. A method of treating diabetes in a mammal suffering from diabetes comprising administering to said mammal an effective amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said

prodrug and an aldose reductase inhibitor, a prodrug of said aldose reductase inhibitor or a pharmaceutically acceptable salt of said aldose reductase inhibitor or said prodrug.

53. A method of treating or preventing diabetic complications in a mammal comprising administering to said mammal an effective amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable of said compound or said prodrug and an aldose reductase inhibitor, a prodrug of said aldose reductase inhibitor or a pharmaceutically acceptable salt of said aldose reductase inhibitor or said prodrug thereof.

54. A pharmaceutical composition comprising a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug of said NHE-1 inhibitor or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug thereof.

55. A method of treating or preventing diabetic complications in a mammal comprising administering to said mammal an effective amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug of said NHE-1 inhibitor or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug.

56. A method of treating diabetes in a mammal suffering from diabetes comprising administering to said mammal an effective amount of a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, and a sodium hydrogen ion exchange (NHE-1) inhibitor, a prodrug of said NHE-1 inhibitor or a pharmaceutically acceptable salt of said NHE-1 inhibitor or said prodrug.

57. A method of inhibiting sorbitol dehydrogenase in a mammal in need thereof comprising administering to said mammal a pharmaceutical composition of claim 47.

58. A method of treating ischemia in a mammal suffering from ischemia comprising administering to said mammal a pharmaceutical composition of claim 54.

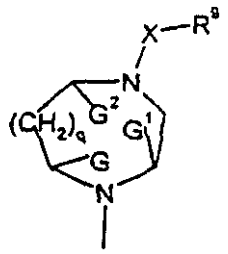
59. A method of treating or preventing diabetic complications in a mammal comprising administering to said mammal a pharmaceutical composition of claim 47.

60. A compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, wherein:

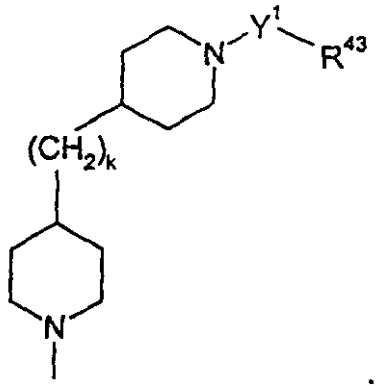
$R^1$ is $C(OH)R^4R^5$, where $R^4$ and $R^5$ are each independently hydrogen or methyl;

$R^2$ is hydrogen;

$R^3$ is



or



;

wherein said piperazinyl $R^3$ is substituted by $R^6$, $R^7$ or $R^8$;

G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen or ($C_1$-$C_4$)alkyl; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or

G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or

$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;

q is 0 or 1;

X is a covalent bond, oxycarbonyl,vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl or vinylenylsulfonyl; said vinylenylcarbonyl and said vinylenylsulfonyl in the definition of X are optionally substituted on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; said oxy($C_1$-$C_4$)alkylenylcarbonyl and said thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are optionally substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar;

$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_4$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro;

$Ar^1$ is phenyl, naphthyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxalyl, phthalazinyl, cinnolinyl, naphthyridinyl, pteridinyl, pyrazinopyrazinyl, pyrazinopyridazinyl, pyrimidopyridazinyl, pyrimidopyrimidyl, pyridopyrimidyl, pyridopyrazinyl, pyridopyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl,

oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, pyrrolopyridyl, furopyridyl, thienopyridyl, imidazolopyridyl, oxazolopyridyl, thiazolopyridyl, pyrazolopyridyl, isoxazolopyridyl, isothiazolopyridyl, pyrrolopyrimidyl, furopyrimidyl, thienopyrimidyl, imidazolopyrimidyl, oxazolopyrimidyl, thiazolopyrimidyl, pyrazolopyrimidyl, isoxazolopyrimidyl, isothiazolopyrimidyl, pyrrolopyrazinyl, furopyrazinyl, thienopyrazinyl, imidazolopyrazinyl, oxazolopyrazinyl, thiazolopyrazinyl, pyrazolopyrazinyl, isoxazolopyrazinyl, isothiazolopyrazinyl, pyrrolopyridazinyl, furopyridazinyl, thienopyridazinyl, imidazolopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, pyrazolopyridazinyl, isoxazolopyridazinyl or isothiazolopyridazinyl; and

said $Ar^1$ is optionally substituted as set forth above;

k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is $(C_3\text{-}C_7)$cycloalkyl, $Ar^5\text{-}(C_0\text{-}C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1\text{-}C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1\text{-}C_6)$alkyl and $Ar^5\text{-}(C_0\text{-}C_4)$alkylenyl; or

$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl optionally substituted with up to five fluoro or $(C_1\text{-}C_4)$alkoxy optionally substituted with up to fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl optionally substituted with up to five fluoro or $(C_1\text{-}C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl optionally

substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above.

61. A compound selected from:

1R-(4-{1'-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-[4,4']bipiperidinyl-1-yl}-pyrimidin-2-yl)-ethanol;

furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone;

(4-chloro-furo[3,2-c]pyridin-2-yl)-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-methanone;

{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-pyrrolidin-1-yl-furo[3,2-c]pyridin-2-yl)-methanone;

{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-(4-morpholin-4-yl-furo[3,2-c]pyridin-2-yl)-methanone;

{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-imidazo[1,2-a]pyridin-2-yl-methanone;

furo[3,2-c]pyridin-2-yl-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-methanone;

4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid pyridin-3-yl ester;

4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 2-methyl-pyridin-3-yl ester;

4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1- carboxylic acid 5-chloro-pyridin-3-yl ester;

4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazine-1-carboxylic acid 6-methyl-pyridin-3-yl ester;

(E)-1-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-3-thiophen-2-yl-propenone;

1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-methoxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-(4-{4-[2-(4-ethyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-(4-{3R,5S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-(4-{3R,5S-dimethyl-4-[2-(2-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-(4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-(4-{4-[2-(4-isopropyl-piperazin-1-yl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-(4-{3R,5S-dimethyl-4-[4-methyl-6-(4-methyl-piperazin-1-yl)-[1,3,5]triazin-2-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-ethoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-isopropoxy-6-methyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[3R,5S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-hydroxymethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-isopropoxy-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-isopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-ethyl-6-methoxy-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4,6-dimethyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]- pyrimidin-2-yl}-ethanol;

1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[2R,6S-dimethyl-4-(4-[1,2,4]triazol-1-yl-pyrimidin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[4-(2,6-dimethyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-(4-{4-[2-(1S-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

1-{4-[4-(2-acetyl-pyrimidin-4-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanone;

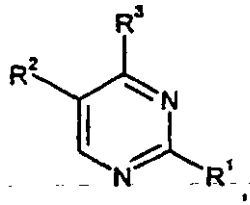
1RS-(4-{4-[2-(1RS-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;

(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone;

1R-{4-[2R,6S-dimethyl-4-(2-morpholin-4-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;
1R-{4-[2R,6S-dimethyl-4-(2-[1,2,4]triazol-1-yl-pyrimidin-4-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6R-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;
1R-(4-{4-[2-(4-ethyl-piperazin-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;
1R-(4-{2R,6S-dimethyl-4-[2-(4-methyl-imidazol-1-yl)-pyrimidin-4-yl]-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;
1R-(4-{4-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol;
1R-{4-[2R,6S-dimethyl-4-(4-morpholin-4-yl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4-methoxy-6-methyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[2R,6S-dimethyl-4-(4-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4-hydroxymethyl-6-methyl-pyrimidin-2-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(2-hydroxymethyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(2-hydroxymethyl-6-methyl-pyrimidin-4-yl)-3S-methyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-[4-(3S-methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol;
1R-[4-(3S-methyl-4-oxazolo[4,5-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol;
1R-[4-(3S-methyl-4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethanol;
1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;

1R-{4-[3R,5S-dimethyl-4-(4-methyl-6-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4-hydroxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[4-(4-methoxy-6-methoxymethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
1R-{4-[2R,6S-dimethyl-4-(4-methyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl-ethanol;
1-{4-[4-(2-acetyl-pyrimidin-4-yl)-2R*,6S*-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanone;
1-(-4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanone;
1R-{4-[4-(4-methoxymethyl-6-phenyl-[1,3,5]-triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethanol;
(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol; and
1S-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethanol.

62. A compound of the formula $I^A$,



$I^A$

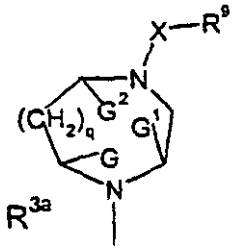
wherein:

$R^1$ is C-($OR^{80}$)$R^4R^5$, where $R^{80}$ is independently ($C_1$-$C_4$)alkyl, benzyl, ($C_1$-$C_6$)alkylcarbonyl or phenylcarbonyl, where said benzyl and said phenyl are optionally substituted with up to three ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, halo or nitro;

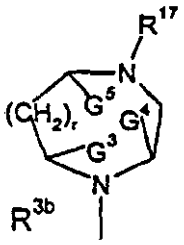
$R^4$ and $R^5$ are each independently hydrogen, methyl, ethyl or hydroxy-($C_1$-$C_3$)alkyl;

$R^2$ is hydrogen, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy;

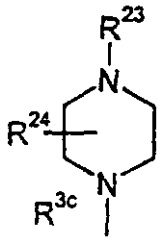
$R^3$ is a radical of the formula



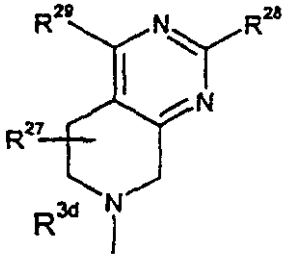
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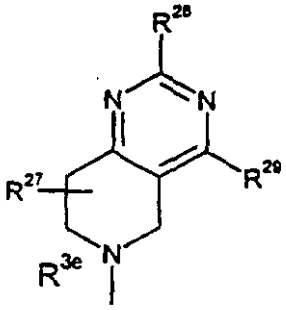
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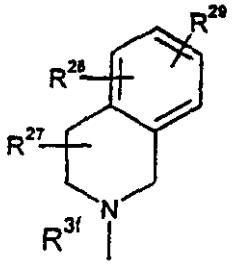
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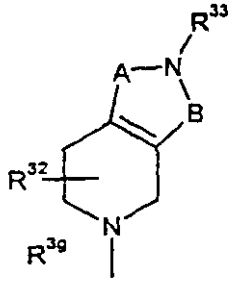
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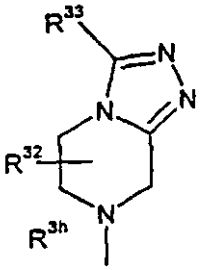


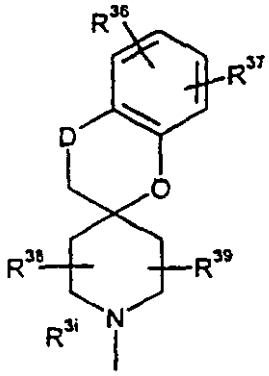
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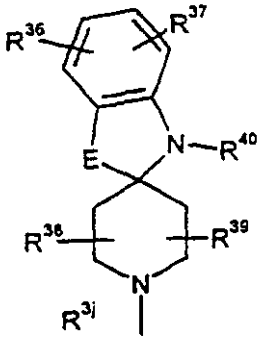


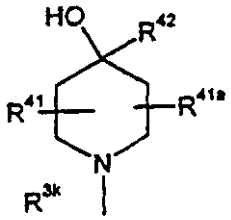
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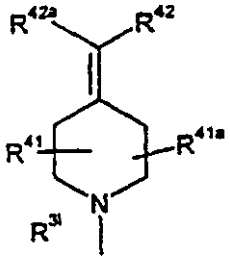


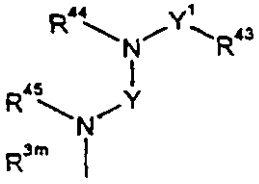


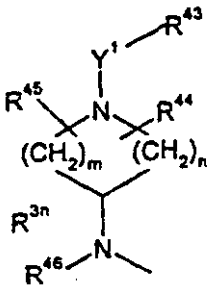




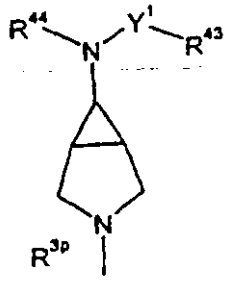




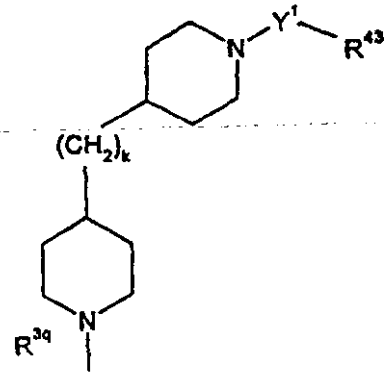








or



wherein said radical of formula $R^{3a}$ is substituted by $R^6$, $R^7$ and $R^8$;
said radical of formula $R^{3b}$ is substituted by $R^{18}$, $R^{19}$ and $R^{20}$;
G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or
G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or
$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;
q is 0 or 1;
X is a covalent bond, -(C=$NR^{10}$)-, oxycarbonyl, vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl, vinylenylsulfonyl, sulfinyl-($C_1$-$C_4$)alkylenylcarbonyl, sulfonyl-($C_1$-$C_4$)alkylenylcarbonyl or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl and thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar; said vinylenylsulfonyl and said vinylenylcarbonyl in the definition of X are optionally substituted independently on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; and said carbonyl($C_0$-$C_4$)alkylenylcarbonyl in the definition of X is optionally substituted indepedently with up to three ($C_1$-$C_4$)alkyl, benzyl or Ar;
$R^{10}$ is hydrogen or ($C_1$-$C_4$)alkyl;
$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_3$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro; provided that when q = 0 and X is a covalent bond, oxycarbonyl or ($C_1$-$C_4$)alkylenylcarbonyl, then $R^9$ is not ($C_1$-$C_6$)alkyl;
Ar and $Ar^1$ are independently a fully saturated, partially saturated or fully unsaturated five- to eight-membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two

fused independently partially saturated, fully saturated or fully unsaturated five- to seven-membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five to seven membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially saturated, fully saturated ring or fully unsaturated monocyclic ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

Ar and $Ar^1$ are optionally independently substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to a total of four substituents independently selected from $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$; wherein $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are each taken separately and are each independently halo, formyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)alkylenyloxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, $C(OH)R^{15}R^{16}$, naphthyl, phenyl, imidazolyl, pyridyl, triazolyl, morpholinyl, ($C_0$-$C_4$)alkylsulfamoyl, N-($C_0$-$C_4$)alkylcarbamoyl, N,N-di-($C_1$-$C_4$)alkylcarbamoyl, N-phenylcarbamoyl, N-($C_1$-$C_4$)alkyl-N-phenylcarbamoyl, N,N-diphenyl carbamoyl, ($C_1$-$C_4$)alkylcarbonylamido, ($C_3$-$C_7$)cycloalkylcarbonylamido, phenylcarbonylamido, piperidinyl, pyrrolidinyl, piperazinyl, cyano, benzimidazolyl, amino, anilino, pyrimidyl, oxazolyl, isoxazolyl, tetrazolyl, thienyl, thiazolyl, benzothiazolyl, pyrrolyl, pyrazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, 8-($C_1$-$C_4$)alkyl-3,8-diaza[3.2.1]bicyclooctyl, 3,5-dioxo-1,2,4-triazinyl, phenoxy, thiophenoxy, ($C_1$-$C_4$)alkylsulfanyl, ($C_1$-$C_4$)alkylsulfonyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said naphthyl, phenyl, pyridyl, piperidinyl, benzimidazolyl, pyrimidyl, thienyl, benzothiazolyl, pyrrolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, thiophenoxy, anilino and phenoxy in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of

$R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from ($C_1$-$C_4$)alkyl; said pyrrolidinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from hydroxy, hydroxy-($C_1$-$C_3$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to three substituents independently selected from ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, ($C_0$-$C_4$)alkylsulfamoyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said triazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said tetrazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy-($C_2$-$C_3$)alkyl or ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; and said phenyl and pyridyl which are optionally substituted on piperazine in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

$R^{11}$ and $R^{12}$ are taken together on adjacent carbon atoms and are $-CH_2OC(CH_3)_2OCH_2-$ or $-O-(CH_2)_p-O-$, and $R^{13}$ and $R^{14}$ are taken separately and are each independently hydrogen or ($C_1$-$C_4$)alkyl;

p is 1, 2 or 3;

$R^{15}$ and $R^{16}$ are taken separately and are each independently hydrogen, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; or $R^{15}$ and $R^{16}$ are taken separately and $R^{15}$ is hydrogen and $R^{16}$ is ($C_3$-$C_6$)cycloalkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, imidazolyl, benzothiazolyl or benzoxazolyl; or $R^{15}$ and $R^{16}$ are taken together and are ($C_3$-$C_6$)alkylene;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 0; $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently $(C_1$-$C_4)$alkyl; or

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_1$-$C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1$-$C_6)$alkyl;

$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl and $Ar^2$-$(C_0$-$C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy,

amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, pyrimidyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$Ar^2$ is independently defined as set forth for Ar and $Ar^1$ above;

said $Ar^2$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{23}$ is $CONR^{25}R^{26}$ or $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen ($C_1$-$C_4$)alkyl or $Ar^3$-($C_0$-$C_4$)alkylenyl and $R^{26}$ is $Ar^3$-($C_0$-$C_4$)alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

$R^{24}$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro;

$Ar^3$ is independently defined as set forth for Ar and $Ar^1$ above;
said $Ar^3$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;
$R^{27}$ is hydrogen or $(C_1$-$C_4)$alkyl;
$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro, $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$; said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and thiophenoxy in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{30}$ and $R^{31}$ are each independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or
$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
A is N optionally substituted with hydrogen or $(C_1$-$C_4)$alkyl and B is carbonyl; or

A is carbonyl and B is N optionally substituted with hydrogen or $(C_1$-$C_4)$alkyl;

$R^{32}$ is hydrogen or $(C_1$-$C_4)$alkyl;

$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl;

said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl in the definition of $R^{33}$ are optionally substituted with up to three phenyl, phenoxy, $NR^{34}R^{35}$, halo, hydroxy, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{34}$ and $R^{35}$ are each independently hydrogen, $(C_1$-$C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

D is CO, CHOH or $CH_2$;

E is O, NH or S;

$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, $(C_1$-$C_6)$alkylamino, di-$(C_1$-$C_6)$alkylamino, pyrrolidino, piperidino, morpholino, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl, $Ar^4$, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;

$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or $(C_1$-$C_4)$-alkyl;

$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or

$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are -O-$(CH_2)_t$-O-;

t is 1, 2 or 3;

Y is $(C_2$-$C_6)$alkylene;

$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl;

m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;

k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is $(C_3-C_7)$cycloalkyl, $Ar^5$-$(C_0-C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1-C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1-C_6)$alkyl and $Ar^5$-$(C_0-C_4)$alkylenyl; or

$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;

$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

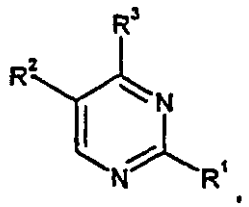
$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3-C_7)$cycloalkyl, $Ar^6$-$(C_0-C_3)$alkylenyl, $Ar^6$-$(C_2-C_4)$alkenyl, $Ar^5$-carbonyl or $(C_1-C_6)$alkyl optionally substituted with up to five fluoro;

$Ar^6$ is independently defined as set forth for Ar and $Ar^1$ above;

$Ar^6$ is optionally independently substituted as set forth for Ar and $Ar^1$ above; and $R^{41}$ and $R^{41a}$ are each independently hydrogen or $(C_1-C_4)$alkyl.

63. A compound of claim 62 selected from 1R-(4-{4-[2-(1R-butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl)-pyrimidin-2-yl)-ethyl butyrate; 1R-(4-{4-[2-(1S-butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; 1S-(4-{4-[2-(1R-butyryloxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; (E)-1R-{4-[4-(2-methyl-32-phenyl-acryloyl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl acetate; (R)-1-[4-(4-quinoxalin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl acetate; 1R-(4-{4-[2-(1RS-hydroxy-ethyl)-pyrimidin-4-yl]-2R,6S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; 1RS-(4-{4-[2-(1R-hydroxy-ethyl)-pyrimidin-4-yl]-3R,5S-dimethyl-piperazin-1-yl}-pyrimidin-2-yl)-ethyl butyrate; 1R-[4-(3S-methyl-4-oxazolo[5,4-b]pyridin-2-yl-piperazin-1-yl)-pyrimidin-2-yl]-ethyl butyrate; 1R-{4-[3R,5S-dimethyl-4-(4-methyl-6-phenyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-3R,5S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-cyclopropyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4,6-dimethyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-hydroxymethyl-6-phenyl-[1,3,5]triazin-2-yl)-2R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; 1R-{4-[4-(4-methoxy-6-methoxymethyl-[1,3,5]triazin-2-yl)-R,6S-dimethyl-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate; and 1R-{4-[2R,6S-dimethyl-4-(4-methyl-[1,3,5]triazin-2-yl)-piperazin-1-yl]-pyrimidin-2-yl}-ethyl butyrate.

64. A compound of the formula $I^B$,



$I^B$

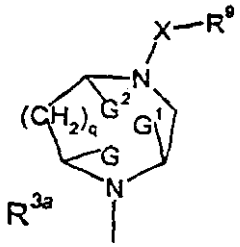
wherein:

$R^1$ is C-$(OR^{61})R^4R^5$, where $R^{61}$ is an acyl radical of a carboxylic acid aldose reductase inhibitor;

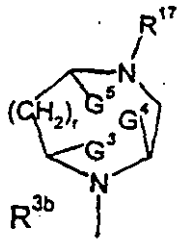
$R^4$ and $R^5$ are each independently hydrogen, methyl, ethyl or hydroxy-$(C_1-C_3)$alkyl;

$R^2$ is hydrogen, $(C_1-C_4)$alkyl or $(C_1-C_4)$alkoxy;

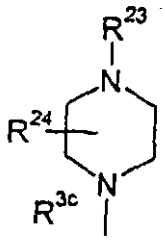
$R^3$ is a radical of the formula



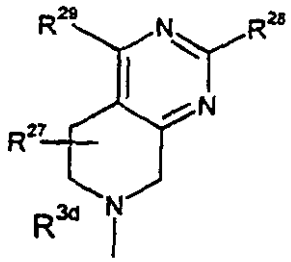

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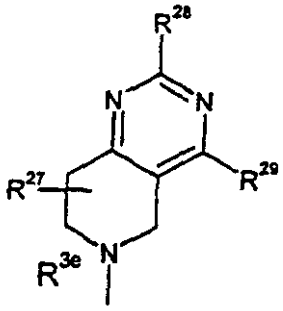

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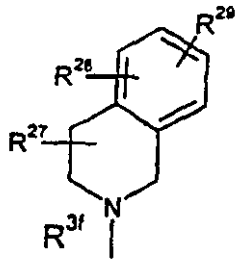

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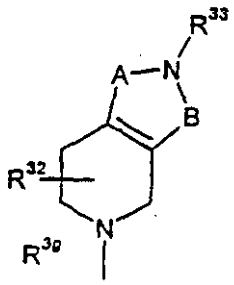

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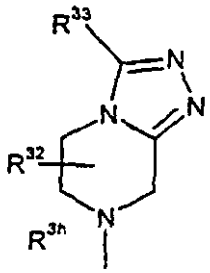


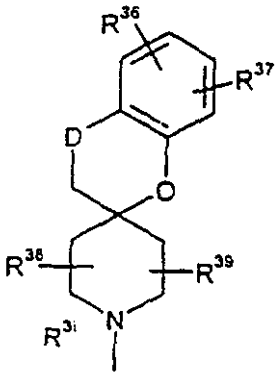

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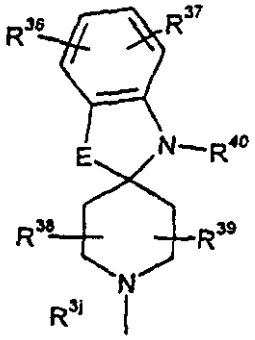


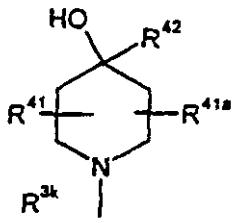

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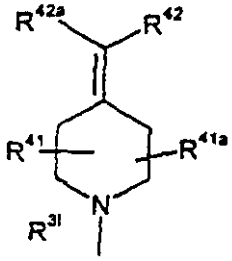


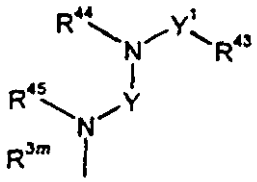


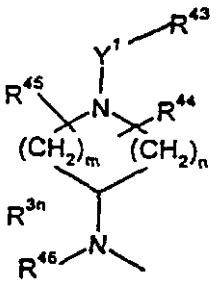




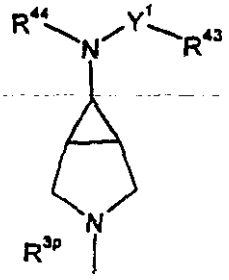




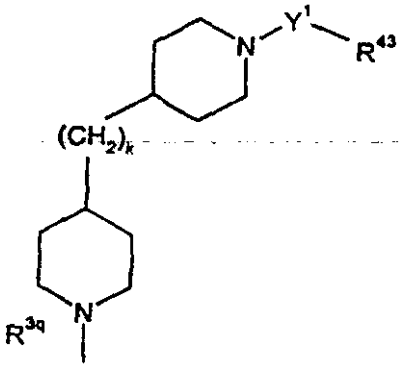








or



wherein said radical of formula $R^{3a}$ is substituted by $R^6$, $R^7$ and $R^8$;
said radical of formula $R^{3b}$ is substituted by $R^{18}$, $R^{19}$ and $R^{20}$;
G, $G^1$ and $G^2$ are taken separately and are each hydrogen and $R^6$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; $R^7$ and $R^8$ are each independently hydrogen or ($C_1$-$C_4$)alkyl; or
G and $G^1$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and $G^2$ are hydrogen; or
$G^1$ and $G^2$ are taken together and are ($C_1$-$C_3$)alkylene and $R^6$, $R^7$, $R^8$ and G are hydrogen;
q is 0 or 1;
X is a covalent bond, -(C=$NR^{10}$)-, oxycarbonyl, vinylenylcarbonyl, oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl, thio($C_1$-$C_4$)alkylenylcarbonyl, vinylenylsulfonyl, sulfinyl-($C_1$-$C_4$)alkylenylcarbonyl, sulfonyl-($C_1$-$C_4$)alkylenylcarbonyl or carbonyl($C_0$-$C_4$)alkylenylcarbonyl; wherein said oxy($C_1$-$C_4$)alkylenylcarbonyl, ($C_1$-$C_4$)alkylenylcarbonyl, ($C_3$-$C_4$)alkenylcarbonyl and thio($C_1$-$C_4$)alkylenylcarbonyl in the definition of X are each optionally and independently substituted with up to two ($C_1$-$C_4$)alkyl, benzyl or Ar; said vinylenylsulfonyl and said vinylenylcarbonyl in the definition of X are optionally substituted independently on one or two vinylenyl carbons with ($C_1$-$C_4$)alkyl, benzyl or Ar; and said carbonyl($C_0$-$C_4$)alkylenylcarbonyl in the definition of X is optionally substituted indepedently with up to three ($C_1$-$C_4$)alkyl, benzyl or Ar;
$R^{10}$ is hydrogen or ($C_1$-$C_4$)alkyl;
$R^9$ is ($C_3$-$C_7$)cycloalkyl, $Ar^1$-($C_0$-$C_3$)alkylenyl or ($C_1$-$C_6$)alkyl optionally substituted with up to five fluoro; provided that when q = 0 and X is a covalent bond, oxycarbonyl or ($C_1$-$C_4$)alkylenylcarbonyl, then $R^9$ is not ($C_1$-$C_6$)alkyl;
Ar and $Ar^1$ are independently a fully saturated, partially saturated or fully unsaturated five- to eight-membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two

fused independently partially saturated, fully saturated or fully unsaturated five- to seven-membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated five to seven membered rings, taken independently, optionally having up to four heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially saturated, fully saturated ring or fully unsaturated monocyclic ring, bicyclic ring or tricyclic ring optionally having one or two oxo groups substituted on carbon or one or two oxo groups substituted on sulfur;

Ar and $Ar^1$ are optionally independently substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to a total of four substituents independently selected from $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$; wherein $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are each taken separately and are each independently halo, formyl, ($C_1$-$C_6$)alkoxycarbonyl, ($C_1$-$C_6$)alkylenyloxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, $C(OH)R^{15}R^{16}$, naphthyl, phenyl, imidazolyl, pyridyl, triazolyl, morpholinyl, ($C_0$-$C_4$)alkylsulfamoyl, N-($C_0$-$C_4$)alkylcarbamoyl, N,N-di-($C_1$-$C_4$)alkylcarbamoyl, N-phenylcarbamoyl, N-($C_1$-$C_4$)alkyl-N-phenylcarbamoyl, N,N-diphenyl carbamoyl, ($C_1$-$C_4$)alkylcarbonylamido, ($C_3$-$C_7$)cycloalkylcarbonylamido, phenylcarbonylamido, piperidinyl, pyrrolidinyl, piperazinyl, cyano, benzimidazolyl, amino, anilino, pyrimidyl, oxazolyl, isoxazolyl, tetrazolyl, thienyl, thiazolyl, benzothiazolyl, pyrrolyl, pyrazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, 8-($C_1$-$C_4$)alkyl-3,8-diaza[3.2.1]bicyclooctyl, 3,5-dioxo-1,2,4-triazinyl, phenoxy, thiophenoxy, ($C_1$-$C_4$)alkylsulfanyl, ($C_1$-$C_4$)alkylsulfonyl, ($C_3$-$C_7$)cycloalkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said naphthyl, phenyl, pyridyl, piperidinyl, benzimidazolyl, pyrimidyl, thienyl, benzothiazolyl, pyrrolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzoxazolyl, pyridazinyl, pyridyloxy, pyridylsulfanyl, furanyl, thiophenoxy, anilino and phenoxy in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said imidazolyl, oxazolyl, isoxazolyl, thiazolyl and pyrazolyl in the definition of

$R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to two substituents independently selected from hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from ($C_1$-$C_4$)alkyl; said pyrrolidinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to two substituents independently selected from hydroxy, hydroxy-($C_1$-$C_3$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with up to three substituents independently selected from ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, ($C_0$-$C_4$)alkylsulfamoyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said triazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said tetrazolyl in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ is optionally substituted with hydroxy-($C_2$-$C_3$)alkyl or ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; and said phenyl and pyridyl which are optionally substituted on piperazine in the definition of $R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are optionally substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or

$R^{11}$ and $R^{12}$ are taken together on adjacent carbon atoms and are $-CH_2OC(CH_3)_2OCH_2-$ or $-O-(CH_2)_p-O-$, and $R^{13}$ and $R^{14}$ are taken separately and are each independently hydrogen or ($C_1$-$C_4$)alkyl;

p is 1, 2 or 3;

$R^{15}$ and $R^{16}$ are taken separately and are each independently hydrogen, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; or $R^{15}$ and $R^{16}$ are taken separately and $R^{15}$ is hydrogen and $R^{16}$ is ($C_3$-$C_8$)cycloalkyl, hydroxy-($C_1$-$C_3$)alkyl, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, imidazolyl, benzothiazolyl or benzoxazolyl; or $R^{15}$ and $R^{16}$ are taken together and are ($C_3$-$C_8$)alkylene;

$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 0; $R^{18}$ is hydrogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently $(C_1$-$C_4)$alkyl; *or*

*$G^3$, $G^4$ and $G^5$ are taken separately and are each hydrogen; r is 1; $R^{18}$ is hydrogen,* $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, hydroxy-$(C_1$-$C_4)$alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy, wherein said $(C_1$-$C_4)$alkyl in the definition of $R^6$ and said $(C_1$-$C_4)$alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro; and $R^{19}$ and $R^{20}$ are each independently hydrogen or $(C_1$-$C_4)$alkyl; or

$G^3$ and $G^4$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^5$ are hydrogen; or

$G^4$ and $G^5$ are taken together and are $(C_1$-$C_3)$alkylene; r is 0 or 1; and $R^{18}$, $R^{19}$, $R^{20}$ and $G^3$ are hydrogen;

$R^{17}$ is $SO_2NR^{21}R^{22}$, $CONR^{21}R^{22}$, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkylcarbonyl, $Ar^2$-carbonyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_1$-$C_6)$alkylsulfinyl, $Ar^2$-sulfonyl, $Ar^2$-sufinyl and $(C_1$-$C_6)$alkyl;

$R^{21}$ and $R^{22}$ are taken separately and are each independently selected from hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl and $Ar^2$-$(C_0$-$C_4)$alkylenyl; or

$R^{21}$ and $R^{22}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl, 1,2,3,4-tetrahydro-isoquinolyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with one substituent selected from hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl, azepinyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to two substituents independently selected from hydroxy,

amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to two substituents independently selected from hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said piperazinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted independently with up to three substituents independently selected from phenyl, pyridyl, pyrimidyl, ($C_1$-$C_4$)alkoxycarbonyl and ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro; said 1,2,3,4-tetrahydro-isoquinolyl and said 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl in the definition of $R^{21}$ and $R^{22}$ are optionally substituted independently with up to three substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to four substituents independently selected from hydroxy, amino, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; said pyrimidyl, pyridyl and phenyl which are optionally substituted on said piperazine in the definition of $R^{21}$ and $R^{22}$ is optionally substituted with up to three substituents selected from hydroxy, amino, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro and ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;

$Ar^2$ is independently defined as set forth for Ar and $Ar^1$ above;

said $Ar^2$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{23}$ is $CONR^{25}R^{26}$ or $SO_2R^{25}R^{26}$, wherein $R^{25}$ is hydrogen ($C_1$-$C_4$)alkyl or $Ar^3$-($C_0$-$C_4$)alkylenyl and $R^{26}$ is $Ar^3$-($C_0$-$C_4$)alkylenyl; provided that when $Ar^3$ is phenyl, naphthyl or biphenyl, then $R^{23}$ cannot be $CONR^{25}R^{26}$ where $R^{25}$ is hydrogen or $Ar^3$ and $R^{26}$ is $Ar^3$;

$R^{24}$ is hydrogen, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxycarbonyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl or phenyl optionally independently substituted with up to three hydroxy, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, wherein said ($C_1$-$C_4$)alkyl in the definition of $R^6$ and said ($C_1$-$C_4$)alkoxy in the definition of $R^6$ are optionally and independently substituted with up to five fluoro;

$Ar^3$ is independently defined as set forth for Ar and $Ar^1$ above;
said $Ar^3$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;
$R^{27}$ is hydrogen or $(C_1$-$C_4)$alkyl;
$R^{28}$ and $R^{29}$ are each independently hydrogen, hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro, $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro, phenyl, pyridyl, pyrimidyl, thienyl, furanyl, thiazolyl, oxazolyl, phenoxy, thiophenoxy, $SO_2NR^{30}R^{31}$, $CONR^{30}R^{31}$ or $NR^{30}R^{31}$; said thienyl, pyrimidyl, furanyl, thiazolyl and oxazolyl in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to two hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said phenyl, pyridyl, phenoxy and thiophenoxy in the definition of $R^{28}$ and $R^{29}$ are optionally substituted by up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
$R^{30}$ and $R^{31}$ are each independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_3$-$C_7)$cycloalkyl or phenyl, said phenyl is optionally substituted with up to three hydroxy, halo, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; or
$R^{30}$ and $R^{31}$ are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl; said pyrrolidinyl and piperidinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said indolinyl and piperazinyl in the definition of $R^{30}$ and $R^{31}$ are optionally substituted with up to three hydroxy, amino, hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxycarbonyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro or $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{30}$ and $R^{31}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkyl optionally substituted with up to five fluoro and $(C_1$-$C_4)$alkoxy optionally substituted with up to five fluoro;
A is N optionally substituted with hydrogen or $(C_1$-$C_4)$alkyl and B is carbonyl; or

A is carbonyl and B is N optionally substituted with hydrogen or ($C_1$-$C_4$)alkyl;
$R^{32}$ is hydrogen or ($C_1$-$C_4$)alkyl;
$R^{33}$ is phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl or benzothienyl; said phenyl, pyridyl, pyrimidyl, thiazolyl, oxazolyl, benzyl, quinolyl, isoquinolyl, phthalizinyl, quinoxanlyl, benzothiazoyl, benzoxazolyl, benzofuranyl and benzothienyl in the definition of $R^{33}$ are optionally substituted with up to three phenyl, phenoxy, $NR^{34}R^{35}$, halo, hydroxy, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;
$R^{34}$ and $R^{35}$ are each independently hydrogen, ($C_1$-$C_4$ alkyl), phenyl or phenylsulfonyl; said phenyl and phenylsulfonyl in the definition of $R^{34}$ and $R^{35}$ are optionally substituted with up to three halo, hydroxy, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;
D is CO, CHOH or $CH_2$;
E is O, NH or S;
$R^{36}$ and $R^{37}$ are taken separately and are each independently hydrogen, halo, cyano, hydroxy, amino, ($C_1$-$C_6$)alkylamino, di-($C_1$-$C_6$)alkylamino, pyrrolidino, piperidino, morpholino, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, hydroxy-($C_1$-$C_4$)alkyl, $Ar^4$, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro;
$R^{38}$, $R^{39}$ and $R^{40}$ are each independently hydrogen or ($C_1$-$C_4$)-alkyl;
$Ar^4$ is phenyl, furanyl, thienyl, pyridyl, pyrimidyl, pyrazinyl or pyridazinyl; said $Ar^4$ being optionally substituted with up to three hydroxy, ($C_1$-$C_4$)alkoxy-($C_1$-$C_4$)alkyl, halo, hydroxy-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl optionally substituted with up to five fluoro or ($C_1$-$C_4$)alkoxy optionally substituted with up to five fluoro; or
$R^{36}$ and $R^{37}$ are taken together on adjacent carbon atoms and are -O-($CH_2$)$_t$-O-;
t is 1, 2 or 3;
Y is ($C_2$-$C_6$)alkylene;
$R^{44}$, $R^{45}$ and $R^{46}$ are each independently hydrogen or ($C_1$-$C_4$)alkyl;
m and n are each independently 1, 2 or 3, provided that the sum of m and n is 2, 3 or 4;
k is 0, 1, 2, 3 or 4;

$Y^1$ is a covalent bond, carbonyl, sulfonyl or oxycarbonyl;

$R^{43}$ is $(C_3-C_7)$cycloalkyl, $Ar^5$-$(C_0-C_4)$alkylenyl, $NR^{47}R^{48}$ or $(C_1-C_6)$alkyl optionally substituted with one to five fluoro; provided that when $Y^1$ is a covalent bond or oxycarbonyl, then $R^{43}$ is not $NR^{47}R^{48}$;

$R^{47}$ and $R^{48}$ are taken separately and are each independently selected from hydrogen, $Ar^5$, $(C_1-C_6)$alkyl and $Ar^5$-$(C_0-C_4)$alkylenyl; or

$R^{47}$ and $R^{48}$ are taken together with the nitrogen atom to which they are attached to form azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepinyl, azabicyclo[3.2.2]nonanyl, azabicyclo[2.2.1]heptyl, 1,2,3,4-tetrahydroisoquinolyl, 6,7-dihydro-5H-dibenzo[c,e]azepinyl or 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidyl; said azetidinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with one hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said pyrrolidinyl, piperidinyl and azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to two hydroxy, amino, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said morpholinyl in the definition of $R^{47}$ and $R^{48}$ is optionally substituted with up to two substituents independently selected from hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro and $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; said piperazinyl, 1,2,3,4-tetrahydroisoquinolyl and 5,6,7,8-tetrahydro[4,3-d]pyrimidyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to three hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro; and said 6,7-dihydro-5H-dibenzo[c,e]azepinyl in the definition of $R^{47}$ and $R^{48}$ are optionally substituted with up to four hydroxy, amino, halo, hydroxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy-$(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl optionally substituted with up to five fluoro or $(C_1-C_4)$alkoxy optionally substituted with up to five fluoro;

$Ar^5$ is independently defined as set forth for Ar and $Ar^1$ above;

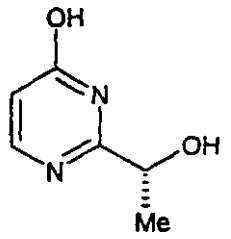
$Ar^5$ is optionally independently substituted as set forth for Ar and $Ar^1$ above;

$R^{42}$ and $R^{42a}$ are independently hydrogen, $(C_3-C_7)$cycloalkyl, $Ar^6$-$(C_0-C_3)$alkylenyl, $Ar^6$-$(C_2-C_4)$alkenyl, $Ar^6$-carbonyl or $(C_1-C_6)$alkyl optionally substituted with up to five fluoro;

$Ar^6$ is independently defined as set forth for Ar and $Ar^1$ above;

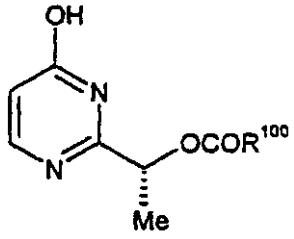
$Ar^6$ is optionally independently substituted as set forth for Ar and $Ar^1$ above; and $R^{41}$ and $R^{41a}$ are each independently hydrogen or $(C_1\text{-}C_4)$alkyl.

65. A compound of the formula Z



Z

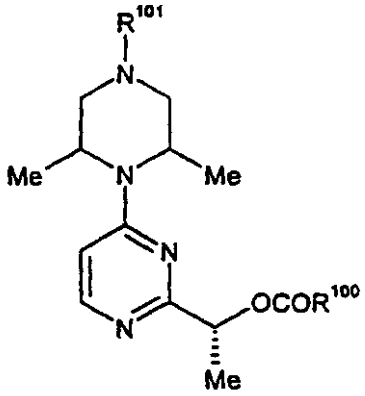
66. A compound of the formula ZZ,



ZZ

wherein $R^{100}$ is $(C_1\text{-}C_8)$alkyl, benzyl or phenyl wherein said benzyl and phenyl are optionally substituted with up to three halo or $(C_1\text{-}C_4)$alkyl.

67. A compound of the formula III,



III

wherein:

$R^{100}$ is $(C_1\text{-}C_8)$alkyl, benzyl or phenyl wherein said benzyl and phenyl are optionally substituted with up to three halo or $(C_1\text{-}C_4)$alkyl; and

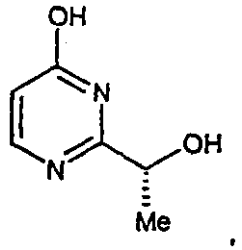
$R^{101}$ is hydrogen or a suitable amine protecting group.

68. A compound of claim 67 wherein $R^{100}$ is ($C_1$-$C_4$)alkyl and $R^{101}$ is benzyl or tert-butyloxycarbonyl.

69. A compound of claim 68 wherein $R^{100}$ is n-butyl or ethyl and $R^{101}$ is benzyl.

70. A compound of claim 68 wherein $R^{100}$ is n-butyl or ethyl and $R^{101}$ is tert-butyloxycarbonyl.

71. A process for preparing a compound of the formula Z,



Z

comprising:

a) reacting R-(+)-2-hydroxy-propionamide with triethyloxonium tetrafluoroborate in a reaction inert solvent for 10 minutes to 24 hours at 0 °C to ambient temperature to form the corresponding imidate;

b) reacting said corresponding imidate with anhydrous ammonia in a reaction inert solvent for 2 hours to 24 hours at 0 °C to ambient temperature to form R-(+)-2-hydroxy-propionamidine hydrochloride; and

c) reacting said R-(+)-2-hydroxy-propionamidine hydrochloride with ethyl 3-hydroxy-acrylate sodium salt and a suitable base in a reaction inert solvent to form said compound of formula Z.

72. A pharmaceutical composition comprising a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said prodrug or said compound, and a glycogen phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

73. A method of treating or preventing diabetic complications in a mammal comprising administering to said mammal a pharmaceutical composition of claim 181.

74. A method of treating diabetic complications in a mammal comprising adminstering to said mammal a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a glycogen

phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

75. A method of treating diabetes in a mammal comprising administering to said mammal a compound of claim 1, a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug and a glycogen phosphorylase inhibitor (GPI), a prodrug of said GPI or a pharmaceutically acceptable salt of said GPI or said prodrug.

# INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/IB 00/00296

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61P3/10 C07D241/44 C07D498/04 C07D401/14
C07D239/42 C07D451/02 C07D451/14 C07D471/04 C07D491/10
C07D487/08 C07D409/12 C07D405/12 C07D491/04 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K C06D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 94 07867 A (PFIZER INC.)<br>14 April 1994 (1994-04-14)<br>cited in the application<br>claims 1-37 | 1-75 |
| Y | EP 0 384 370 A (HOECHST AG)<br>29 August 1990 (1990-08-29)<br>cited in the application<br>claims 1-6 | 1-75 |
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| Y | DE 39 05 364 A (HOECHST AG)<br>23 August 1990 (1990-08-23)<br>claims 1-6 | 1-75 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 June 2000 | 26/06/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Herz, C |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/00296

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 C07D409/14 C07D487/04 C07D513/10 C07D417/14
//(C07D498/04,213:00,263:00),(C07D471/04,221:00,231:00),
(C07D491/10,221:00,311:00),(C07D471/04,221:00,239:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | K. GEISEN ET AL.: "Sorbitol-accumulating Pyrimidine Derivatives" ARZNEIM. FORSCH., vol. 44, no. 9, 1994, pages 1032-1043, XP000910176 page 1032, right-hand column ----- | 1-75 |

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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I. ational Application No
PCT/IB 00/00296

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D487/08,209:00,209:00),(C07D491/04,221:00,307:00), (C07D487/04,241:00,251:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ' | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| | | |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

' Special categories of cited documents :

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 June 2000 | |

| Name and mailing address of the ISA | Authorized officer |
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Ir. ational Application No
PCT/IB 00/00296

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Information on patent family members

In tional Application No
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
-A61K 31/505
A61P 3/10 C07D241/44
C07D498/04 C07D401/14
C07D239/42 C07D451/02
C07D451/14 C07D471/04
C07D491/10 C07D487/08
C07D409/12 C07D405/12

# [12]发明专利申请公开说明书

[21]申请号 00807825.4

[43]公开日 2002年5月29日

[11]公开号 CN 1351497A

[22]申请日 2000.3.16 [21]申请号 00807825.4

[30]优先权

[32]1999.4.1 [33]US [31]60/127,437

[86]国际申请 PCT/IB00/00296 2000.3.16

[87]国际公布 WO00/59510 英 2000.10.12

[85]进入国家阶段日期 2001.11.20

[71]申请人 辉瑞产品公司

地址 美国康涅狄格

[72]发明人 M·Y·朱-莫伊尔 J·A·姆利

B·L·米拉里

W·J·赞布罗斯吉

[74]专利代理机构 中国国际贸易促进委员会专利商标事务所

代理人 唐晓峰

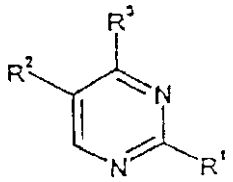
H01L087

权利要求书69页 说明书263页 附图页数0页

[54]发明名称 用作山梨醇脱氢酶抑制剂的氨基嘧啶类化合物

[57]摘要

本发明涉及式(I)的山梨醇脱氢酶抑制剂化合物,其中$R^1$、$R^2$和$R^3$如说明书中所定义。本发明还涉及含有这些化合物的药物组合物以 及通过向患有糖尿病因而有发生并发症的危险性的哺乳动物施用所述 化合物来治疗或预防糖尿病并发症、特别是糖尿病性神经病、糖尿病 性肾病、糖尿病性微血管病、糖尿病性大血管病和糖尿病性心肌病的 方法。本发明还涉及含有本发明式(I)化合物与醛糖还原酶抑制剂的联 合形式的药物组合物以及用该组合物治疗或预防糖尿病并发症的方 法。本发明还涉及含有本发明式(I)化合物与NHE-1抑制剂的联合形 式的药物组合物以及用该组合物治疗心肌病和其它与心脏有关的问题 的方法。本发明还涉及用于合成本发明式(I)化合物的某些中间体以及 制备这些中间体的方法。

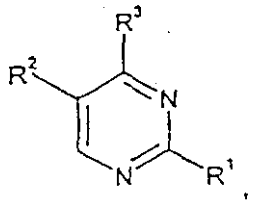


(I)

ISSN1008-4274

# 权 利 要 求 书

1、 式 I 化合物



I

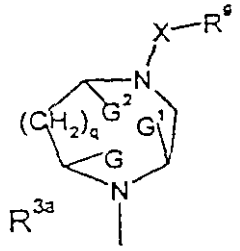
其前药或所述化合物或所述前药的可药用盐，其中：

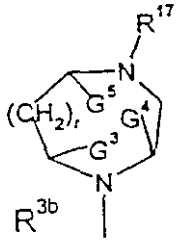
$R^1$是甲酰基、乙酰基、丙酰基、氨基甲酰基或-C(OH)$R^4R^5$；

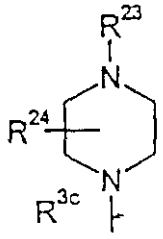
$R^4$和$R^5$彼此独立地是氢、甲基、乙基或羟基-($C_1$-$C_3$)烷基；

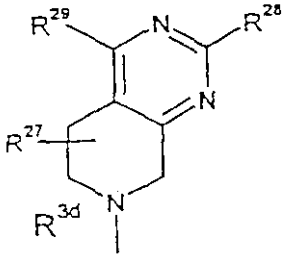
$R^2$是氢、($C_1$-$C_4$)烷基或($C_1$-$C_4$)烷氧基；

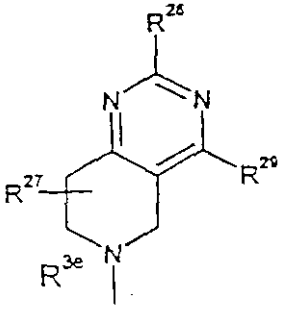
$R^3$是下式的基团

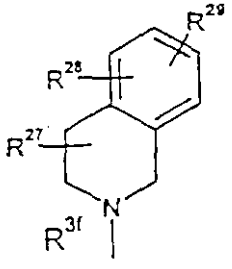


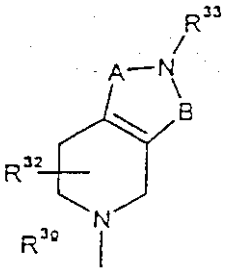


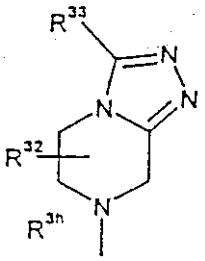


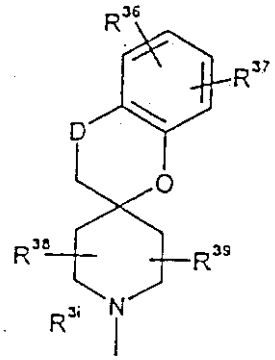


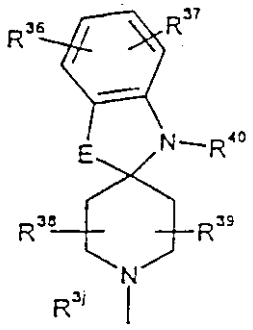


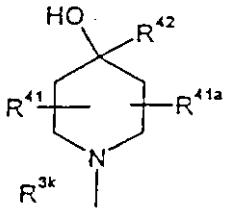


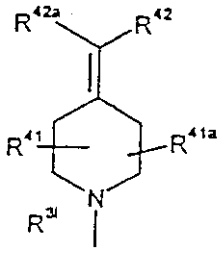


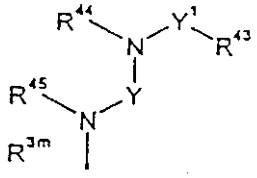


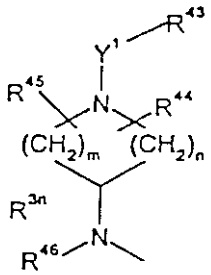


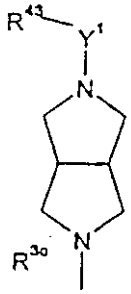


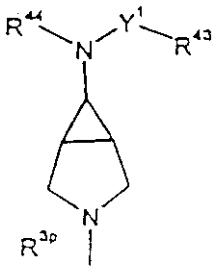




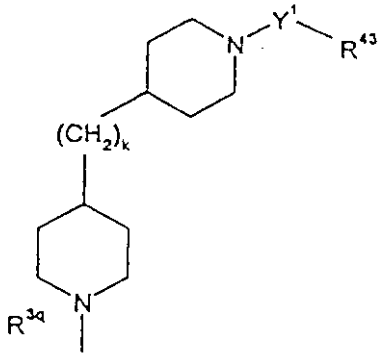








或



;

其中所述式 $R^{3a}$ 的基团还在环上被 $R^6$、$R^7$ 和 $R^8$ 所取代；

所述式 $R^{3b}$ 的基团还在环上被 $R^{18}$、$R^{19}$ 和 $R^{20}$ 所取代；

G、$G^1$ 和 $G^2$ 彼此独立地是氢并且 $R^6$ 是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多三个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$ 的定义中的所述$(C_1-C_4)$烷基和 $R^6$ 定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^7$ 和 $R^8$ 彼此独立地是氢或$(C_1-C_4)$烷基；或者

G 和 $G^1$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 $G^2$ 是氢；或者

$G^1$ 和 $G^2$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 G 是氢；

q 是 0 或 1；

X 是共价键、$-(C=NR^{10})-$、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基、硫$(C_1-C_4)$二价烷基羰基、亚乙烯基磺酰基、亚磺酰基-$(C_1-C_4)$二价烷基羰基、磺酰基-$(C_1-C_4)$二价烷基羰基或羰基$(C_0-C_4)$二价烷基羰基；其中，在 X 的定义中的所述氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基和硫$(C_1-C_4)$二价烷基羰基选择性地并且彼此独立地被最多两个$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述亚乙烯基磺酰基和所述亚乙烯基羰基选择性地并且彼此独立地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述羰基$(C_0-C_4)$二价烷基羰基选择性地并且彼此独立地被最多三个$(C_1-C_4)$烷基、苄基或 Ar 所取代；

$R^{10}$ 是氢或$(C_1-C_4)$烷基；

$R^9$ 是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_3)$二价烷基或选择性地被最多 5 个氟取代的 $(C_1-C_6)$烷基；条件是，当 q=0 并且 X 是共价键、氧羰基或$(C_1-C_4)$二价烷基羰基时，则 $R^9$ 不是$(C_1-C_6)$烷基；

Ar 和 $Ar^1$ 彼此独立地是完全饱和的、部分饱和的或完全不饱和的 5 至 8 元环，其选择性地含有最多 4 个彼此独立地选自氧、硫和氮的

杂原子；或是由两个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的二环，所述的两个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；或是由三个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的三环，所述的三个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；所述部分饱和的、完全饱和的环或完全不饱和的单环、二环或三环选择性地带有一个或两个取代在碳上的氧代基团或一个或两个取代在硫上的氧代基团；

Ar 和 $Ar^1$ 选择性地并且彼此独立地在碳或氮上被最多共 4 个彼此独立地选自 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的取代基所取代，如果该部分是单环，则在一个环上被取代，如果该部分是二环，则在一个或同时在两个环上被取代，如果该部分是三环，则在一个、两个或三个环上被取代；其中 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$彼此独立地是卤素、甲酰基、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$二价烷基氧羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$C(OH)R^{15}R^{16}$、萘基、苯基、咪唑基、吡啶基、三唑基、吗啉基、$(C_0-C_4)$烷基氨磺酰基、N-$(C_0-C_4)$烷基氨基甲酰基、N,N-二-$(C_1-C_4)$烷基氨基甲酰基、N-苯基氨基甲酰基、N-$(C_1-C_4)$烷基-N-苯基氨基甲酰基、N,N-二苯基氨基甲酰基、$(C_1-C_4)$烷基羰基氨基、$(C_3-C_7)$环烷基羰基氨基、苯基羰基氨基、哌啶基、吡咯烷基、哌嗪基、氰基、苯并咪唑基、氨基、苯氨基、嘧啶基、噁唑基、异噁唑基、四唑基、噻吩基、噻唑基、苯并噻唑基、吡咯基、吡唑基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、8-$(C_1-C_4)$烷基-3,8-二氮杂[3.2.1]二环辛基、3,5-二氧代-1,2,4-三嗪基、苯氧基、噻吩氧基、$(C_1-C_4)$烷硫基、$(C_1-C_4)$烷基磺酰基、$(C_3-C_7)$环烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述萘基、苯基、吡啶基、哌啶基、苯并咪唑基、嘧啶基、噻吩基、苯并噻唑基、吡咯基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、噻吩氧基、苯氨基和苯氧基选择性地

被最多 3 个取代基所取代，所述取代基彼此独立地选自羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述咪唑基、噁唑基、异噁唑基、噻唑基和吡唑基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述吗啉基选择性地被最多两个彼此独立地选自($C_1$-$C_4$)烷基的取代基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述吡咯烷基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、羟基-($C_1$-$C_3$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、羟基-($C_1$-$C_3$)烷基、苯基、吡啶基、($C_0$-$C_4$)烷基氨磺酰基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述三唑基选择性地被羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述四唑基选择性地被羟基-($C_2$-$C_3$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的哌嗪上选择性取代的所述苯基和吡啶基选择性地被最多 3 个羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

或者 $R^{11}$ 和 $R^{12}$ 与相邻的碳原子合在一起是-$CH_2OC(CH_3)_2OCH_2$-或-O-$(CH_2)_p$-O-，并且 $R^{13}$ 和 $R^{14}$ 彼此独立地是氢或($C_1$-$C_4$)烷基；

p 是 1、2 或 3；

$R^{15}$和 $R^{16}$彼此独立地是氢、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基；或者 $R^{15}$是氢而 $R^{16}$是$(C_3-C_6)$环烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、咪唑基、苯并噻唑基或苯并噁唑基；或者 $R^{15}$和 $R^{16}$合在一起是$(C_3-C_6)$亚烷基；

$G^3$、$G^4$和 $G^5$分别是氢；r 是 0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和 $R^{20}$彼此独立地是$(C_1-C_4)$烷基；或者

$G^3$、$G^4$和 $G^5$分别是氢；r 是 1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和 $R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和 $G^4$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和 $G^5$是氢；或者

$G^4$和 $G^5$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和 $G^3$是氢；

$R^{17}$是 $SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

$R^{21}$和 $R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和 $Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和 $R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、

氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、1,2,3,4-四氢-异喹啉基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基的取代基所取代；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 1,2,3,4-四氢-异喹啉基和所述 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多 3 个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

$Ar^2$彼此独立地如以上 Ar 和 $Ar^1$所定义；

所述 $Ar^2$选择性地如以上 Ar 和 $Ar^1$中所述被取代；

$R^{23}$是 $CONR^{25}R^{26}$或 $SO_2R^{25}R^{26}$，其中 $R^{25}$是氢、$(C_1-C_4)$烷基或 $Ar^3-(C_0-C_4)$二价烷基，$R^{26}$是 $Ar^3-(C_0-C_4)$二价烷基；条件是当 $Ar^3$是苯基、萘基或联苯基时，则 $R^{23}$不能是 $CONR^{25}R^{26}$，其中 $R^{25}$是氢或 $Ar^3$，$R^{26}$是 $Ar^3$；

$R^{24}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$的定义中的所述$(C_1-C_4)$烷基和 $R^6$定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；

$Ar^3$彼此独立地如以上 Ar 和 $Ar^1$所定义；

所述 $Ar^3$选择性地如以上 Ar 和 $Ar^1$中所述被取代；

$R^{27}$是氢或$(C_1-C_4)$烷基；

$R^{28}$和 $R^{29}$彼此独立地是氢、羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$或 $NR^{30}R^{31}$；在 $R^{28}$和 $R^{29}$的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{28}$和 $R^{29}$的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

$R^{30}$和 $R^{31}$彼此独立地是氢、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基或苯基，所述苯基选择性地被最多 3 个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$

烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；或者

$R^{30}$和 $R^{31}$与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌啶基、哌嗪基或吗啉基；在 $R^{30}$和 $R^{31}$的定义中的所述吡咯烷基和哌啶基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$和 $R^{31}$的定义中的所述二氢吲哚基和哌嗪基选择性地被最多 3 个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基羰基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$和 $R^{31}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

A 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N，B 是羰基；或者

A 是羰基而 B 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N；

$R^{32}$是氢或($C_1$-$C_4$)烷基；

$R^{33}$是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基或苯并噻吩基；在 $R^{33}$的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多 3 个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{34}$和 $R^{35}$彼此独立地是氢、($C_1$-$C_4$ 烷基)、苯基或苯基磺酰基；在 $R^{34}$和 $R^{35}$的定义中的所述苯基和苯基磺酰基选择性地被最多 3 个卤素、羟基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

D 是 CO、CHOH 或 $CH_2$；

E 是 O、NH 或 S；

$R^{36}$ 和 $R^{37}$ 彼此独立地是氢、卤素、氰基、羟基、氨基、$(C_1-C_6)$烷基氨基、二-$(C_1-C_6)$烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、$Ar^4$、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；

$R^{38}$、$R^{39}$和 $R^{40}$彼此独立地是氢或$(C_1-C_4)$-烷基；

$Ar^4$ 是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述 $Ar^4$ 选择性地被最多 3 个羟基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、卤素、羟基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{36}$和 $R^{37}$与相邻的碳原子合在一起是-O-$(CH_2)_t$-O-；

t 是 1、2 或 3；

Y 是$(C_2-C_6)$亚烷基；

$R^{44}$、$R^{45}$和 $R^{46}$彼此独立地是氢或$(C_1-C_4)$烷基；

m 和 n 彼此独立地是 1、2 或 3，条件是 m 和 n 的总和是 2、3 或 4；

k 是 0、1、2、3 或 4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是$(C_3-C_7)$环烷基、$Ar^5$-$(C_0-C_4)$二价烷基、$NR^{47}R^{48}$或选择性地被最多 5 个氟取代的$(C_1-C_6)$烷基；条件是当 $Y^1$ 是共价键或氧羰基时，则 $R^{43}$不能是 $NR^{47}R^{48}$；

$R^{47}$ 和 $R^{48}$ 彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$烷基和 $Ar^5$-$(C_0-C_4)$二价烷基；或者

$R^{47}$和 $R^{48}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-

$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个羟基、氨基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个羟基、氨基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

$Ar^5$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

所述 $Ar^5$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{42}$ 和 $R^{42a}$ 彼此独立地是氢、$(C_3-C_7)$环烷基、$Ar^6$-$(C_0-C_3)$二价烷基、$Ar^6$-$(C_2-C_4)$链烯基、$Ar^6$-羰基或选择性地被最多 5 个氟取代的$(C_1-C_6)$烷基；

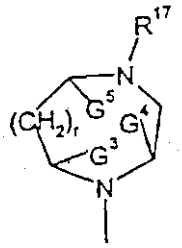
$Ar^6$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

$Ar^6$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{41}$ 和 $R^{41a}$ 彼此独立地是氢或$(C_1-C_4)$烷基。

2. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^3$是



；

其被$R^{18}$、$R^{19}$或$R^{20}$所取代；

$G^3$、$G^4$和$G^5$分别是氢；r是0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基取代的苯基；$R^{19}$和$R^{20}$彼此独立地是$(C_1-C_4)$烷基；

$G^3$、$G^4$和$G^5$分别是氢；r是1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基取代的苯基；$R^{19}$和$R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和$G^4$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^5$是氢；或者

$G^4$和$G^5$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^3$是氢；

$R^{17}$是$SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

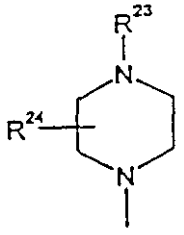
$R^{21}$和$R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和$Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和$R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、

氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、1,2,3,4-四氢-异喹啉基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基的取代基所取代；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、嘧啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 1,2,3,4-四氢-异喹啉基和所述 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多 3 个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基。

3. 权利要求1的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^3$是



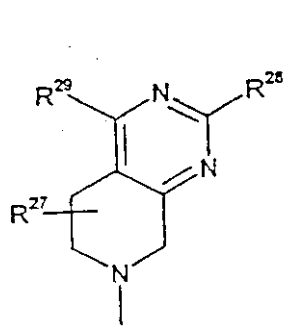
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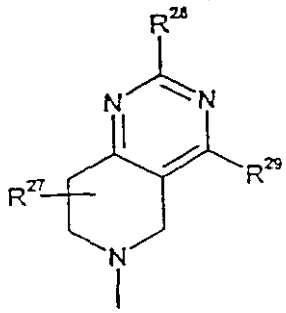
$R^{23}$是$CONR^{25}R^{26}$、$SO_2R^{25}R^{26}$，其中$R^{25}$是氢、$(C_1-C_4)$烷基或$Ar^3-(C_0-C_4)$二价烷基，$R^{26}$是$Ar^3-(C_0-C_4)$二价烷基；条件是当$Ar^3$是苯基、萘基或联苯基时，则$R^{23}$不能是$CONR^{25}R^{26}$，其中$R^{25}$是氢或$Ar^3$，$R^{26}$是$Ar^3$；

$R^{24}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基或选择性地被最多3个选择性地被最多5个氟取代的$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基、羟基、卤素或羟基-$(C_1-C_3)$烷基取代的苯基。

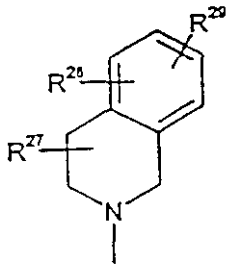
4. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^3$是





或



$R^{27}$是氢或$(C_1-C_4)$烷基；

$R^{28}$和$R^{29}$彼此独立地是氢、羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基、苯基、吡啶基、嘧啶

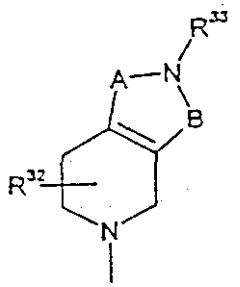
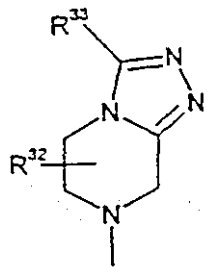
基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$或$NR^{30}R^{31}$；在$R^{28}$和$R^{29}$的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{28}$和$R^{29}$的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；

$R^{30}$和$R^{31}$彼此独立地是氢、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基或苯基，所述苯基选择性地被最多3个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{30}$和$R^{31}$与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌啶基、哌嗪基或吗啉基；在$R^{30}$和$R^{31}$的定义中的所述吡咯烷基和哌啶基选择性地被最多两个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{30}$和$R^{31}$的定义中的所述二氢吲哚基和哌嗪基选择性地被最多3个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{30}$和$R^{31}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基。

5. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^3$是


或


A是选择性地被氢或($C_1$-$C_4$)烷基取代的N，B是羰基；或者

A是羰基而B是选择性地被氢或($C_1$-$C_4$)烷基取代的N；

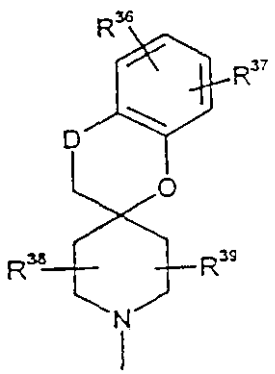
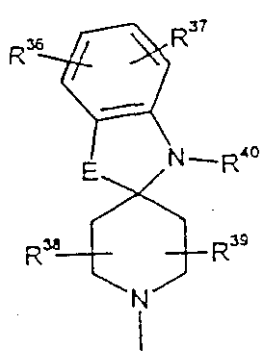
$R^{32}$是氢或($C_1$-$C_4$)烷基；

$R^{33}$是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基或苯并噻吩基；在$R^{33}$的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多3个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{34}$和$R^{35}$彼此独立地是氢、($C_1$-$C_4$烷基)、苯基或苯基磺酰基；在$R^{34}$和$R^{35}$的定义中的所述苯基和苯基磺酰基选择性地被最多3个卤素、羟基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代。

6. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^3$是


或


D是CO、CHOH或$CH_2$；

E是O、NH或S；

$R^{36}$和$R^{37}$彼此独立地是氢、卤素、氰基、羟基、氨基、$(C_1-C_6)$烷基氨基、二-$(C_1-C_6)$烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、$Ar^4$、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；

$R^{38}$、$R^{39}$和$R^{40}$彼此独立地是氢或$(C_1-C_4)$-烷基；

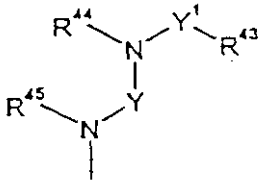
$Ar^4$是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述$Ar^4$选择性地被最多3个羟基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、卤素、羟基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；或者

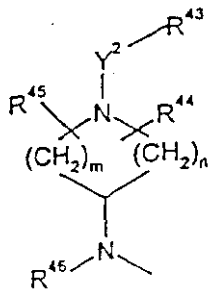
$R^{36}$和$R^{37}$与相邻的碳原子合在一起是-O-$(CH_2)_t$-O-；

t是1、2或3。

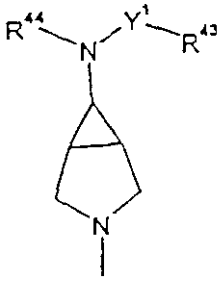
7. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^3$是

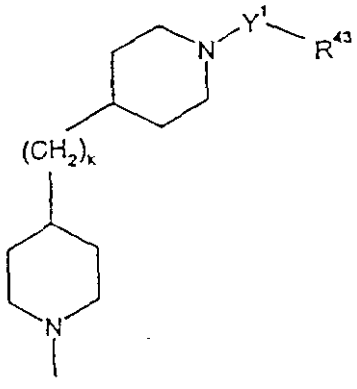








或



;

Y是($C_2$-$C_6$)亚烷基；

$R^{44}$、$R^{45}$和$R^{46}$彼此独立地是氢或($C_1$-$C_4$)烷基；

m和n彼此独立地是1、2或3，条件是m和n的总和是2、3或4；

k是0至4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是($C_3$-$C_7$)环烷基、$Ar^5$-($C_0$-$C_4$)二价烷基、$NR^{47}R^{48}$或选择性地被最多5个氟取代的($C_1$-$C_6$)烷基；条件是当$Y^1$是共价键或氧羰基时，则$R^{43}$不能是$NR^{47}R^{48}$；

$R^{47}$和$R^{48}$彼此独立地选自氢、$Ar^5$、($C_1$-$C_6$)烷基和$Ar^5$-($C_0$-$C_4$)二价烷基；或者

$R^{47}$和$R^{48}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在$R^{47}$和$R^{48}$的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{47}$和$R^{48}$的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多3个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地

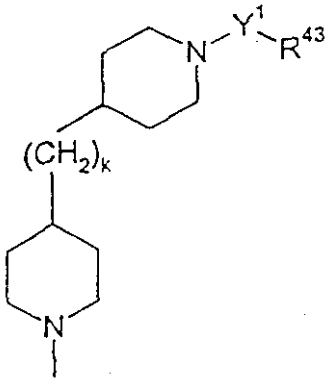
被最多4个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代。

8. 权利要求 7 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^2$是氢；

$R^3$是



；

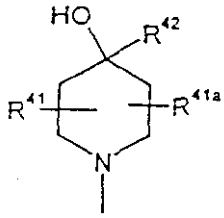
k是0；

$Y^1$是共价键；

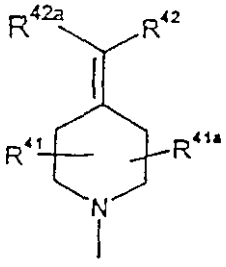
$R^{43}$是在2位被1-羟甲基取代的4-嘧啶基。

9. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^3$是



或



$R^{42}$和$R^{42a}$彼此独立地是氢、$(C_3-C_7)$环烷基、$Ar^6-(C_0-C_3)$二价烷基、$Ar^6-(C_2-C_4)$链烯基、$Ar^6-$羰基或选择性地被最多5个氟取代的$(C_1-C_6)$烷基；

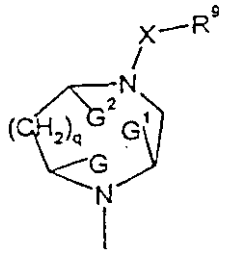
$R^{41}$和$R^{41a}$彼此独立地是氢或$(C_1-C_4)$烷基。

10. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是$C(OH)R^4R^5$，其中$R^4$和$R^5$彼此独立地是氢或甲基；

$R^2$是氢；

$R^3$是




其中所述的$R^3$被$R^6$、$R^7$或$R^8$取代；

G、$G^1$和$G^2$彼此独立地是氢并且$R^6$是氢或$(C_1-C_4)$烷基；$R^7$和$R^8$彼此独立地是氢或$(C_1-C_4)$烷基；或者

G和$G^1$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和$G^2$是氢；或者

$G^1$和$G^2$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和G是氢；

q是0或1；

X是共价键、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、硫$(C_1-C_4)$二价烷基羰基或亚乙烯基磺酰基；在X的定义中的所述亚乙烯基羰基和所述亚乙烯基磺酰基选择性地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或Ar所取代；在X的定义中的所述氧$(C_1-C_4)$二价烷基羰基和所述硫$(C_1-C_4)$二价烷基羰基选择性地被最多两个$(C_1-C_4)$烷基、苄基或Ar所取代；

$R^9$是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_4)$二价烷基或选择性地被最多5个

氟取代的 ($C_1$-$C_6$)烷基；

$Ar^1$是苯基、萘基、吡啶基、嘧啶基、吡嗪基、哒嗪基、三嗪基、喹啉基、异喹啉基、喹唑啉基、喹喔啉基、酞嗪基、噌啉基、蝶啶基、吡嗪并吡嗪基、吡嗪并哒嗪基、嘧啶并哒嗪基、嘧啶并嘧啶基、吡啶并嘧啶基、吡啶并吡嗪基、吡啶并哒嗪基、吡咯基、呋喃基、噻吩基、咪唑基、噁唑基、噻唑基、吡唑基、异噁唑基、异噻唑基、三唑基、噁二唑基、噻二唑基、四唑基、吲哚基、苯并呋喃基、苯并噻吩基、苯并咪唑基、苯并噁唑基、苯并噻唑基、吲唑基、苯并异噁唑基、苯并异噻唑基、吡咯并吡啶基、呋喃并吡啶基、噻吩并吡啶基、咪唑并吡啶基、噁唑并吡啶基、噻唑并吡啶基、吡唑并吡啶基、异噁唑并吡啶基、异噻唑并吡啶基、吡咯并嘧啶基、呋喃并嘧啶基、噻吩并嘧啶基、咪唑并嘧啶基、噁唑并嘧啶基、噻唑并嘧啶基、吡唑并嘧啶基、异噁唑并嘧啶基、异噻唑并嘧啶基、吡咯并吡嗪基、呋喃并吡嗪基、噻吩并吡嗪基、咪唑并吡嗪基、噁唑并吡嗪基、噻唑并吡嗪基、吡唑并吡嗪基、异噁唑并吡嗪基、异噻唑并吡嗪基、吡咯并哒嗪基、呋喃并哒嗪基、噻吩并哒嗪基、咪唑并哒嗪基、噁唑并哒嗪基、噻唑并哒嗪基、吡唑并哒嗪基、异噁唑并哒嗪基或异噻唑并哒嗪基；

所述$Ar^1$选择性地按照权利要求1所述被取代。

11. 权利要求 10 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

X是共价键、氧羰基或选择性地在一个或两个亚乙烯基碳原子上被($C_1$-$C_4$)烷基、苄基或Ar取代的亚乙烯基羰基；

$R^9$是$Ar^1$-($C_0$-$C_4$)二价烷基；

$Ar^1$是苯基、萘基、吡啶基、嘧啶基、吡嗪基、三嗪基、喹啉基、异喹啉基、喹唑啉基、喹喔啉基、呋喃基、噻吩基、吲哚基、苯并呋喃基、苯并噻吩基、苯并噁唑基、苯并噻唑基、呋喃并吡啶基、噁唑并吡啶基、噻唑并吡啶基、噻吩并吡啶基、呋喃并嘧啶基、噻吩并嘧

啶基、噁唑并嘧啶基或噻唑并嘧啶基；

所述$Ar^1$选择性地按照权利要求1所述被取代。

12. 权利要求 11 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^2$是氢；

$R^4$是氢或甲基；

$R^5$是甲基；

G、$G^1$和$G^2$是氢；

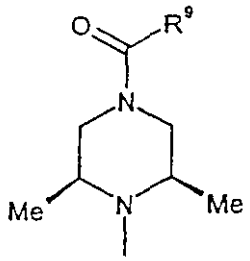
$R^6$和$R^7$彼此独立地是氢或甲基；

$R^8$是氢。

13. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




14. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 2-呋喃并[3,2-c]吡啶基；2-(4-氯-呋喃并[3,2-c]吡啶基)；2-(4-吡咯烷-1-基-呋喃并[3,2-c]吡啶基)；2-(4-吗啉-4-基-呋喃并[3,2-c]吡啶基)；或 2-咪唑并[1,2-a]吡啶基。

15. 权利要求 1 的化合物、其前药或所述化合物或所述前药的可

药用盐，选自：1R-(4-{1'-[2-(1R-羟基-乙基)-嘧啶-4-基]-[4,4']联哌啶-1-基}-嘧啶-2-基)-乙醇；呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-甲酮；(4-氯呋喃并[3,2-c]吡啶-2-基)-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-甲酮；{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-(4-吡咯烷-1-基-呋喃并[3,2-c]吡啶-2-基)-甲酮；{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-(4-吗啉-4-基-呋喃并[3,2c]吡啶-2-基)-甲酮；{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-咪唑并[1,2-a]吡啶-2-基-甲酮；呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 2-甲基-吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 5-氯-吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 6-甲基-吡啶-3-基酯；(E)-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-3-噻吩-2-基-丙烯酮；1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(2-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(2,4-二甲基-咪唑-1-基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-

{4-[2-(4-异丙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇; 1R-(4-{3R,5S-二甲基-4-[4-甲基-6-(4-甲基-哌嗪-1-基)-[1,3,5]三嗪-2-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇; 1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4,6-二甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4-乙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4-异丙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]嘧啶-2-基}-乙醇; 1R-{4-[3R,5S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4-羟甲基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4-异丙氧基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4-异丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[3R,5S-二甲基-4-(4-甲基-6-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4-乙基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基)-乙醇; 1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-{4-[4-(2,6-二甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇; 1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-(4-{4-[2-(1S-羟基-乙基)-

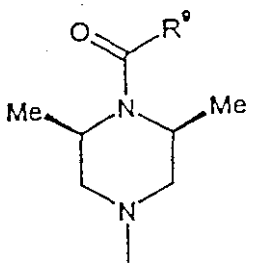
嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮；1RS-(4-{4-[2-(1RS-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇；(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮；1R-{4-[2R,6S-二甲基-4-(2-吗啉-4-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-{4-[2R,6S-二甲基-4-(2-[1,2,4]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]嘧啶-2-基}-乙醇；1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6R-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基-6-甲氧基甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[2R,6S-二甲基-4-(4-甲基-[1,3,5]三嗪-2-基)哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-(4-{4-[2-(2,4-二甲基-咪唑-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-{4-[2R,6S-二甲基-4-(4-吗啉-4-基-[1,3,5]三嗪-2-基)哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲氧基[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧

啶-2-基}-乙醇；1R-{4-[2R,6S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3S-甲基-哌嗪-1-基]嘧啶-2-基}-乙醇；1R-{4-[4-(2-羟甲基-嘧啶-4-基)-3S-甲基哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-[4-(3S-甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇；1R-[4-(3S-甲基-4-噁唑并[4,5-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇；1R-[4-(3S-甲基-4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇；(4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R-甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R*,6S*-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮；或 1-(4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮。

16. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是

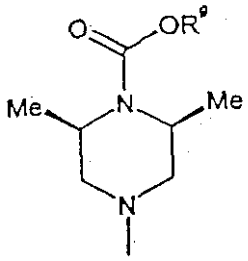



17. 权利要求 16 的化合物、其前药或所述化合物或所述前药的可药用盐，其中 $R^9$是 2-呋喃并[3,2-c]吡啶基。

18. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是

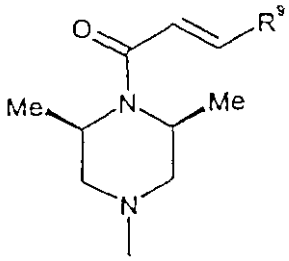



19. 权利要求 18 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 3-吡啶基；3-(2-甲基吡啶基)；3-(5-氯吡啶基)或 3-(6-甲基吡啶基)。

20. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是

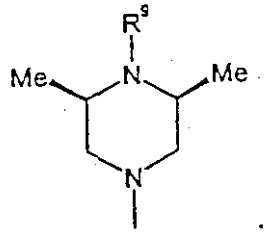



21. 权利要求 20 的化合物、其前药或所述化合物或所述前药的可药用盐，其中 $R^9$是 2-噻吩基。

22. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是



；和

$R^9$是嘧啶基或三嗪基；所述嘧啶基或三嗪基选择性地被最多两个羟基、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基、$(C_1-C_4)$烷氧基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$二价烷基、苯基、被$(C_1-C_4)$烷基选择性取代的哌嗪基或被最多两个$(C_1-C_4)$烷基选择性取代的咪唑基所取代。

23. 权利要求 22 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多两个$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基取代的嘧啶-2-基。

24. 权利要求 23 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 4,6-二甲基嘧啶-2-基；4-甲氧基甲基-6-甲基嘧啶-2-基或 4-羟甲基-6-甲基嘧啶-2-基。

25. 权利要求 22 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多两个$(C_1-C_4)$烷基哌嗪-1-基或咪唑基取代的嘧啶-4-基；所述咪唑基选择性地被最多两个$(C_1-C_4)$烷基取代。

26. 权利要求 25 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 2-(4-甲基哌嗪-1-基)-嘧啶-4-基；2-(4-乙

基哌嗪-1-基)-嘧啶-4-基；2-(4-甲基咪唑-1-基)-嘧啶-4-基；2-(2-甲基咪唑-1-基)-嘧啶-4-基；2-(2,4-二甲基咪唑-1-基)-嘧啶-4-基或2-(4-异丙基哌嗪-1-基)-嘧啶-4-基。

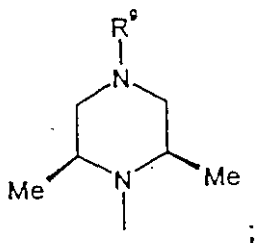
27. 权利要求22的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷基哌嗪-1-基或苯基取代的[1,3,5]-三嗪-2-基。

28. 权利要求27的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是4-甲基-6-(4-甲基哌嗪-1-基)-[1,3,5]-三嗪-2-基；4-甲氧基-6-甲基-[1,3,5]-三嗪-2-基；4,6-二甲氧基-[1,3,5]-三嗪-2-基；4-乙氧基-6-甲基-[1,3,5]-三嗪-2-基；4-异丙氧基-6-甲基-[1,3,5]-三嗪-2-基；4-苯基-[1,3,5]-三嗪-2-基；4-羟甲基-6-甲氧基-[1,3,5]-三嗪-2-基；4-异丙氧基-6-甲氧基-[1,3,5]-三嗪-2-基；4-异丙基-[1,3,5]-三嗪-2-基；4-乙基-6-甲氧基-[1,3,5]-三嗪-2-基；4-环丙基-[1,3,5]-三嗪-2-基；4,6-二甲基-[1,3,5]-三嗪-2-基或4-甲基-6-苯基-[1,3,5]-三嗪-2-基。

29. 权利要求12的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




；和

$R^9$是嘧啶基或三嗪基，所述嘧啶基和三嗪基选择性地被最多两个羟基、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基、$(C_1-C_4)$烷氧基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、三唑基、乙酰基、吗啉基、$(C_1-C_4)$烷基哌嗪基、苯基或选择性地被最多两个$(C_1-C_4)$烷基取代的咪唑基所取代。

30. 权利要求 29 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多两个$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或三唑基取代的嘧啶-2-基。

31. 权利要求 30 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 4,6-二甲基-嘧啶-2-基；4-羟甲基-6-甲基嘧啶-2-基或 4-[1,2,4]-三唑-1-基-嘧啶-2-基。

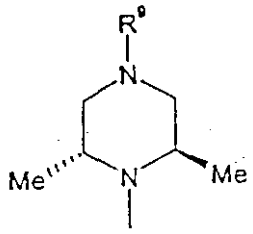
32. 权利要求 29 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多两个$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、乙酰基、吗啉基、$(C_1-C_4)$烷基哌嗪基、三唑基或选择性地被最多两个$(C_1-C_4)$烷基取代的咪唑基取代的嘧啶-4-基。

33. 权利要求 32 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 2,6-二甲基-嘧啶-4-基；2-羟甲基-6-甲基-嘧啶-4-基；2-乙酰基-嘧啶-4-基；2-吗啉-4-基嘧啶-4-基；2-(4-甲基哌嗪-1-基)-嘧啶-4-基；2-[1,2,4]-三唑-1-基-嘧啶-4-基；2-(1S-羟基乙基)-嘧啶-4-基；2-(1R-羟基乙基)-嘧啶-4-基；2-(4-乙基哌嗪-1-基)-嘧啶-4-基；2-(4-甲基咪唑-1-基)-嘧啶-4-基或 2-(2,4-二甲基咪唑-1-基)-嘧啶-4-基。

34. 权利要求 12 的化合物，其中：

$R^1$是(R)-1-羟基乙基；

$R^3$是




；和

$R^9$是 2-(1R-羟基乙基-嘧啶-4-基)、其前药或所述化合物或所述前药的可药用盐。

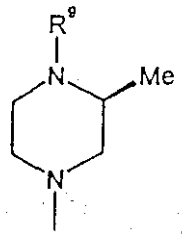
35. 权利要求 29 的化合物、其前药或所述化合物或所述前药的可药用盐，其中 $R^9$是选择性地被最多两个羟基、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基、吗啉基或苯基取代的[1,3,5]-三嗪-2-基。

36. 权利要求 35 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 4-吗啉-4-基-[1,3,5]-三嗪-2-基；4-甲氧基-6-甲基-[1,3,5]-三嗪-2-基；4,6-二甲氧基[1,3,5]-三嗪-2-基；4-苯基-[1,3,5]-三嗪-2-基；4-环丙基-[1,3,5]-三嗪-2-基；4,6-二甲基[1,3,5]-三嗪-2-基；4-羟甲基-6-苯基-[1,3,5]-三嗪-2-基；4-甲氧基-6-甲氧基甲基-[1,3,5]-三嗪-2-基；4-甲基-[1,3,5]-三嗪-2-基或 4-甲氧基甲基-6-苯基-[1,3,5]三嗪-2-基。

37. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




；和

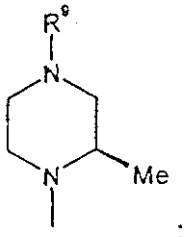
$R^9$ 是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基或羟基-($C_1$-$C_4$)烷基取代的嘧啶基、喹喔啉基或噁唑并吡啶基。

38. 权利要求 37 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$ 是 4-羟甲基-6-甲基-嘧啶-2-基；2-羟甲基-嘧啶-4-基；2-羟甲基-6-甲基-嘧啶-4-基；2-(噁唑并[5,4-b]吡啶基)或2-(噁唑并[4,5-b]吡啶基)；2-喹喔啉基。

39. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$ 是(R)-1-羟基-乙基；

$R^3$ 是




；和

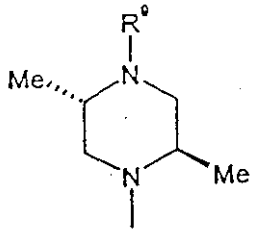
$R^9$ 是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

40. 权利要求 39 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$ 是 2-(1R-羟基乙基)-嘧啶-4-基。

41. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




；和

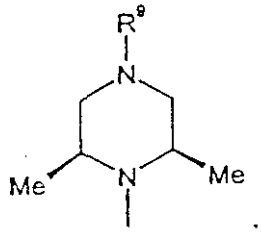
$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

42. 权利要求 41 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 2-(1R-羟基乙基)-嘧啶-4-基。

43. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是(S)-1-羟基-乙基；

$R^3$是




；和

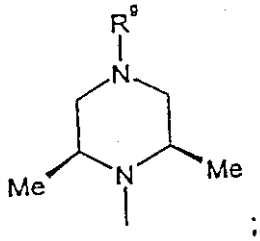
$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基或羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

44. 权利要求 43 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 2-(1R-羟基-乙基)-嘧啶-4-基。

45. 权利要求 12 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：

$R^1$是乙酰基；

$R^3$是



；和

$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、乙酰基或羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

46. 权利要求 45 的化合物、其前药或所述化合物或所述前药的可药用盐，其中：$R^9$是 2-乙酰基-嘧啶-4-基或 2-(1R-羟基乙基)-嘧啶-4-基。

47. 一种药物组合物，其含有权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐以及可药用载体或稀释剂。

48. 在需要抑制山梨醇脱氢酶的哺乳动物中抑制山梨醇脱氢酶的方法，该方法包括，向所述哺乳动物施用山梨醇脱氢酶抑制量的权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐。

49. 在患有糖尿病的哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用有效量的权利要求 1 的化合物、其前药或所

述化合物或所述前药的可药用盐。

50. 在哺乳动物中治疗或预防糖尿病并发症的方法，该方法包括，向所述哺乳动物施用有效量的权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐。

51. 一种药物组合物，其含有权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和醛糖还原酶抑制剂、其前药或所述醛糖还原酶抑制剂或所述前药的可药用盐。

52. 在患有糖尿病的哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用有效量的权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和醛糖还原酶抑制剂、所述醛糖还原酶抑制剂的前药或所述醛糖还原酶抑制剂或所述前药的可药用盐。

53. 在哺乳动物中治疗或预防糖尿病并发症的方法，该方法包括，向所述哺乳动物施用有效量的权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和醛糖还原酶抑制剂、所述醛糖还原酶抑制剂的前药或所述醛糖还原酶抑制剂或所述前药的可药用盐。

54. 一种药物组合物，其含有权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和钠氢离子交换(NHE-1)抑制剂、所述 NHE-1 抑制剂的前药或所述 NHE-1 抑制剂或所述前药的可药用盐。

55. 在哺乳动物中治疗或预防糖尿病并发症的方法，该方法包括，向所述哺乳动物施用有效量的权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和钠氢离子交换(NHE-1)抑制剂、所述 NHE-1 抑制剂的前药或所述 NHE-1 抑制剂或所述前药的可药用盐。

56. 在患有糖尿病的哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用有效量的权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和钠氢离子交换(NHE-1)抑制剂、所述 NHE-1 抑制剂的前药或所述 NHE-1 抑制剂或所述前药的可药用盐。

57. 在需要抑制山梨醇脱氢酶的哺乳动物中抑制山梨醇脱氢酶的方法，该方法包括，向所述哺乳动物施用权利要求 47 的药物组合物。

58. 在患有局部缺血的哺乳动物中治疗局部缺血的方法，该方法包括，向所述哺乳动物施用权利要求 54 的药物组合物。

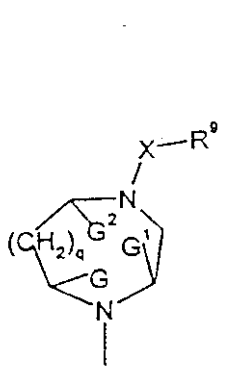
59. 在哺乳动物中治疗或预防糖尿病并发症的方法，该方法包括，向所述哺乳动物施用权利要求 47 的药物组合物。

60. 利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐， 其中：

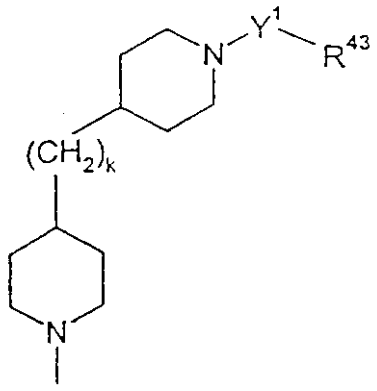
$R^1$是$-C(OH)R^4R^5$，其中$R^4$和$R^5$彼此独立地是氢或甲基；

$R^2$是氢；

$R^3$是




或




；

其中所述的哌嗪基$R^3$被$R^6$、$R^7$或$R^8$取代；

G、$G^1$和$G^2$彼此独立地是氢并且$R^6$是氢或$(C_1-C_4)$烷基；$R^7$和$R^8$彼此

独立地是氢或($C_1$-$C_4$)烷基；或者

G和$G^1$合在一起是($C_1$-$C_3$)亚烷基并且$R^6$、$R^7$、$R^8$和$G^2$是氢；或者

$G^1$和$G^2$合在一起是($C_1$-$C_3$)亚烷基并且$R^6$、$R^7$、$R^8$和G是氢；

q是0或1；

X是共价键、氧羰基、亚乙烯基羰基、氧($C_1$-$C_4$)二价烷基羰基、硫($C_1$-$C_4$)二价烷基羰基或亚乙烯基磺酰基；在X的定义中的所述亚乙烯基羰基和所述亚乙烯基磺酰基选择性地在一个或两个亚乙烯基碳原子上被($C_1$-$C_4$)烷基、苄基或Ar所取代；在X的定义中的所述氧($C_1$-$C_4$)二价烷基羰基和所述硫($C_1$-$C_4$)二价烷基羰基选择性地被最多两个($C_1$-$C_4$)烷基、苄基或Ar所取代；

$R^9$是($C_3$-$C_7$)环烷基、$Ar^1$-($C_0$-$C_4$)二价烷基或选择性地被最多5个氟取代的 ($C_1$-$C_6$)烷基；

$Ar^1$是苯基、萘基、吡啶基、嘧啶基、吡嗪基、哒嗪基、三嗪基、喹啉基、异喹啉基、喹唑啉基、喹喔啉基、酞嗪基、噌啉基、蝶啶基、吡嗪并吡嗪基、吡嗪并哒嗪基、嘧啶并哒嗪基、嘧啶并嘧啶基、吡啶并嘧啶基、吡啶并吡嗪基、吡啶并哒嗪基、吡咯基、呋喃基、噻吩基、噁唑基、噻唑基、吡唑基、异噁唑基、异噻唑基、三唑基、噁二唑基、噻二唑基、四唑基、吲哚基、苯并呋喃基、苯并噻吩基、苯并咪唑基、苯并噁唑基、苯并噻唑基、吲唑基、苯并异噁唑基、苯并异噻唑基、吡咯并吡啶基、呋喃并吡啶基、噻吩并吡啶基、咪唑并吡啶基、噁唑并吡啶基、噻唑并吡啶基、吡唑并吡啶基、异噁唑并吡啶基、异噻唑并吡啶基、吡咯并嘧啶基、呋喃并嘧啶基、噻吩并嘧啶基、咪唑并嘧啶基、噁唑并嘧啶基、噻唑并嘧啶基、吡唑并嘧啶基、异噁唑并嘧啶基、异噻唑并嘧啶基、吡咯并吡嗪基、呋喃并吡嗪基、噻吩并吡嗪基、咪唑并吡嗪基、噁唑并吡嗪基、噻唑并吡嗪基、吡唑并吡嗪基、异噁唑并吡嗪基、异噻唑并吡嗪基、吡咯并哒嗪基、呋喃并哒嗪基、噻吩并哒嗪基、咪唑并哒嗪基、噁唑并哒嗪基、噻唑并哒嗪基、吡唑并哒嗪基、异噁唑并哒嗪基或异噻唑并哒嗪基；

所述$Ar^1$选择性地按照以上描述被取代；

k是0、1、2、3或4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是$(C_3-C_7)$环烷基、$Ar^5-(C_0-C_4)$二价烷基、$NR^{47}R^{48}$或选择性地被1至5个氟取代的$(C_1-C_6)$烷基；条件是当$Y^1$是共价键或氧羰基时，则$R^{43}$不能是$NR^{47}R^{48}$；

$R^{47}$和$R^{48}$彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$烷基和$Ar^5-(C_0-C_4)$二价烷基；或者

$R^{47}$和$R^{48}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在$R^{47}$和$R^{48}$的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；在$R^{47}$和$R^{48}$的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多3个羟基、氨基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多4个羟基、氨基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被

最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

$Ar^5$彼此独立地如以上Ar和$Ar^1$所定义；

所述$Ar^5$选择性地如以上Ar和$Ar^1$中所述被取代。

61. 选自下列的化合物：

1R-(4-{1'-[2-(1R-羟基-乙基)-嘧啶-4-基]-[4,4']联哌啶-1-基}-嘧啶-2-基)-乙醇；

呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-甲酮；

(4-氯呋喃并[3,2-c]吡啶-2-基)-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-甲酮；

{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-(4-吡咯烷-1-基-呋喃并[3,2-c]吡啶-2-基)-甲酮；

{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-(4-吗啉-4-基-呋喃并[3,2c]吡啶-2-基)-甲酮；

{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-咪唑并[1,2-a]吡啶-2-基-甲酮；

呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮；

4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸吡啶-3-基酯；

4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸2-甲基-吡啶-3-基酯；

4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸5-氯-吡啶-3-基酯；

4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸6-甲基-吡啶-3-基酯；

(E)-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-3-噻吩-2-基-丙烯酮；

1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-甲氧基甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{3R,5S-二甲基-4-[2-(2-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{4-[2-(2,4-二甲基-咪唑-1-基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{4-[2-(4-异丙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{3R,5S-二甲基-4-[4-甲基-6-(4-甲基-哌嗪-1-基)-[1,3,5]三嗪-2-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4,6-二甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-乙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-异丙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]嘧啶-2-基}-乙醇;

1R-{4-[3R,5S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-

1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-羟甲基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-异丙氧基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-异丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-乙基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基)-乙醇;

1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(2,6-二甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-(4-{4-[2-(1S-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮;

1RS-(4-{4-[2-(1RS-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇;

(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮;

1R-{4-[2R,6S-二甲基-4-(2-吗啉-4-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-{4-[2R,6S-二甲基-4-(2-[1,2,4]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]嘧啶-2-基}-乙醇;

1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6R-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基]-乙醇;

1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-(4-{4-[2-(2,4-二甲基-咪唑-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇;

1R-{4-[2R,6S-二甲基-4-(4-吗啉-4-基-[1,3,5]三嗪-2-基]哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4,6-二甲氧基[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[2R,6S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3S-甲基-哌嗪-1-基]嘧啶-2-基}-乙醇;

1R-{4-[4-(2-羟甲基-嘧啶-4-基)-3S-甲基哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-3S-甲基-哌嗪-1-

基]-嘧啶-2-基}-乙醇;

1R-[4-(3S-甲基-4-噁唑并[4,5-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇;

1R-[4-(3S-甲基-4-噁唑并[4,5-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇;

1R-[4-(3S-甲基-4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇;

1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[3R,5S-二甲基-4-(4-甲基-6-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]嘧啶-2-基}-乙醇;

1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-羟甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1R-{4-[4-(4-甲氧基-6-甲氧基甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]嘧啶-2-基}-乙醇;

1R-{4-[2R,6S-二甲基-4-(4-甲基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇;

1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R*,6S*-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮;

1-(4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮;

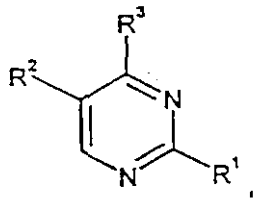
1R-{4-[4-(4-甲氧基甲基-6-苯基-[1,3,5]-三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇;

(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,5S-二甲基-哌嗪-

1-基}-嘧啶-2-基)-乙醇；和

1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。

62. 式$I^A$的化合物



$I^A$

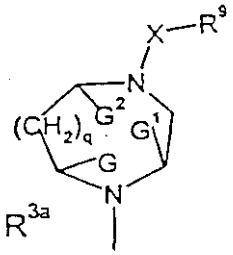
其中：

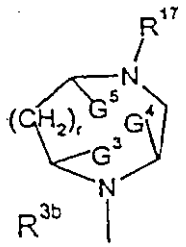
$R^1$是C-($OR^{80}$)$R^4R^5$，其中$R^{80}$彼此独立地是($C_1$-$C_4$)烷基、苄基、($C_1$-$C_6$)烷基羰基或苯基羰基，其中所述苄基和所述苯基选择性地被最多3个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、卤素或硝基所取代；

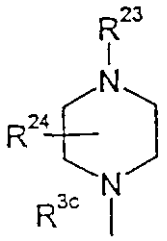
$R^4$和$R^5$彼此独立地是氢、甲基、乙基或羟基-($C_1$-$C_3$)烷基；

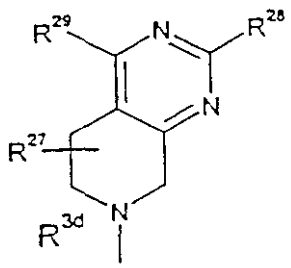
$R^2$是氢、($C_1$-$C_4$)烷基或($C_1$-$C_4$)烷氧基；

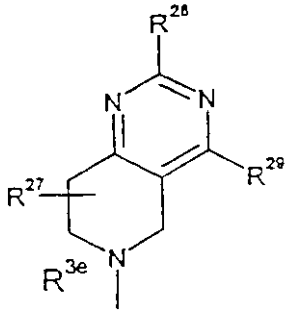
$R^3$是下式的基团

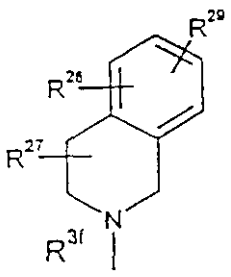


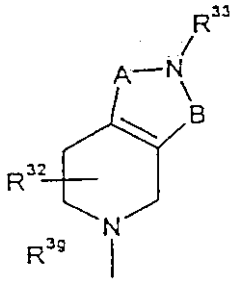


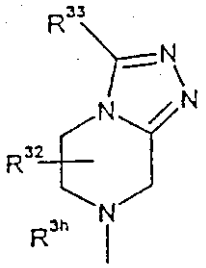


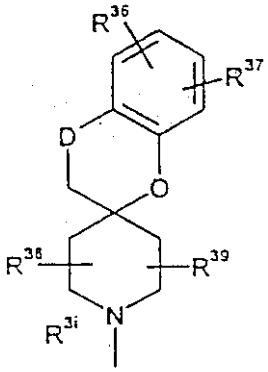


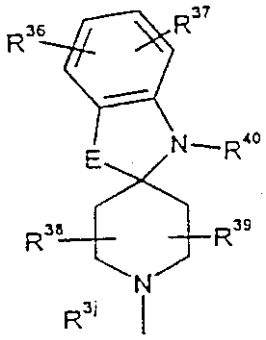


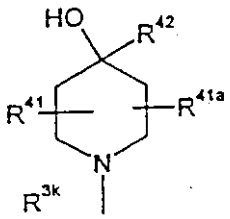


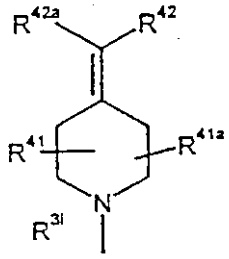


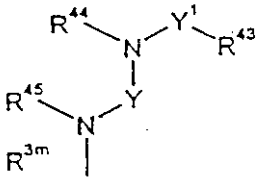


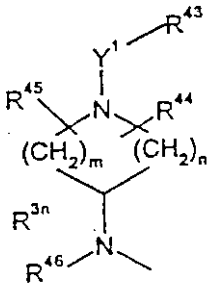


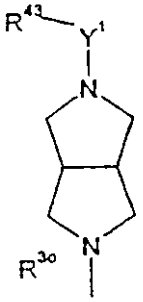




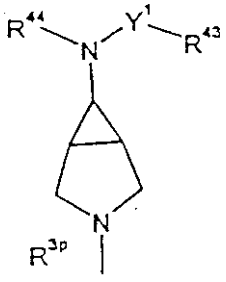


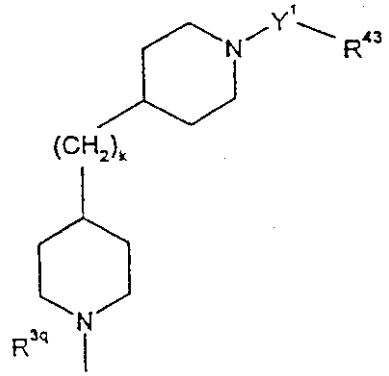






或





其中所述式$R^{3a}$的基团被$R^6$、$R^7$和$R^8$取代；

所述式$R^{3b}$的基团被$R^{18}$、$R^{19}$和$R^{20}$所取代；

G、$G^1$和$G^2$彼此独立地是氢并且$R^6$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多三个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在$R^6$的定义中的所述$(C_1-C_4)$烷基和$R^6$定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多5个氟所取代；$R^7$和$R^8$彼此独立地是氢或$(C_1-C_4)$烷基；或者

G和$G^1$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和$G^2$是氢；或者

$G^1$和$G^2$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和G是氢；

q是0或1；

X是共价键、$-(C=NR^{10})-$、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基、硫$(C_1-C_4)$二价烷基羰基、亚乙烯基磺酰基、亚磺酰基-$(C_1-C_4)$二价烷基羰基、磺酰基-$(C_1-C_4)$二价烷基羰基或羰基$(C_0-C_4)$二价烷基羰基；其中，在X的定义中的所述氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基和硫$(C_1-C_4)$二价烷基羰基选择性地并且彼此独立地被最多两个$(C_1-C_4)$烷基、苄基或Ar所取代；在X的定义中的所述亚乙烯基磺酰基和所述亚乙烯基羰基选择性地并且彼此独立地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或Ar所取代；在X的定义中的所述羰基$(C_0-C_4)$二价烷基羰基选择性地并且彼此独立地被最多三个$(C_1-C_4)$烷基、苄基或Ar所取代；

$R^{10}$是氢或$(C_1-C_4)$烷基；

$R^9$是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_3)$二价烷基或选择性地被最多5个氟取代的$(C_1-C_6)$烷基；条件是，当q=0并且X是共价键、氧羰基或$(C_1-C_4)$二价烷基羰基时，则$R^9$不是$(C_1-C_6)$烷基；

Ar和$Ar^1$彼此独立地是完全饱和的、部分饱和的或完全不饱和的5至8元环，其选择性地含有最多4个彼此独立地选自氧、硫和氮的杂原

子；或是由两个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的5至7元环组成的二环，所述的两个环分别选择性地含有最多4个彼此独立地选自氧、硫和氮的杂原子；或是由三个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的5至7元环组成的三环，所述的三个环分别选择性地含有最多4个彼此独立地选自氧、硫和氮的杂原子；所述部分饱和的、完全饱和的环或完全不饱和的单环、二环或三环选择性地带有一个或两个取代在碳上的氧代基团或一个或两个取代在硫上的氧代基团；

Ar和$Ar^1$选择性地并且彼此独立地在碳或氮上被最多共4个彼此独立地选自$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的取代基所取代，如果该部分是单环，则在一个环上被取代，如果该部分是二环，则在一个或同时在两个环上被取代，如果该部分是三环，则在一个、两个或三个环上被取代；其中$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$彼此独立地是卤素、甲酰基、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$二价烷基氧羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$C(OH)R^{15}R^{16}$、萘基、苯基、咪唑基、吡啶基、三唑基、吗啉基、$(C_0-C_4)$烷基氨磺酰基、N-$(C_0-C_4)$烷基氨基甲酰基、N,N-二-$(C_1-C_4)$烷基氨基甲酰基、N-苯基氨基甲酰基、N-$(C_1-C_4)$烷基-N-苯基氨基甲酰基、N,N-二苯基氨基甲酰基、$(C_1-C_4)$烷基羰基氨基、$(C_3-C_7)$环烷基羰基氨基、苯基羰基氨基、哌啶基、吡咯烷基、哌嗪基、氰基、苯并咪唑基、氨基、苯氨基、嘧啶基、噁唑基、异噁唑基、四唑基、噻吩基、噻唑基、苯并噻唑基、吡咯基、吡唑基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、8-$(C_1-C_4)$烷基-3,8-二氮杂[3.2.1]二环辛基、3,5-二氧代-1,2,4-三嗪基、苯氧基、噻吩氧基、$(C_1-C_4)$烷硫基、$(C_1-C_4)$烷基磺酰基、$(C_3-C_7)$环烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述萘基、苯基、吡啶基、哌啶基、苯并咪唑基、嘧啶基、噻吩基、苯并噻唑基、吡咯基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、噻吩氧基、苯氨基和苯氧基选择性地被最多3个取代基

所取代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述咪唑基、噁唑基、异噁唑基、噻唑基和吡唑基选择性地被最多2个取代基所取代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述吗啉基选择性地被最多两个彼此独立地选自$(C_1-C_4)$烷基的取代基所取代；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述吡咯烷基选择性地被最多2个取代基所取代，所述取代基彼此独立地选自羟基、羟基-$(C_1-C_3)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述哌嗪基选择性地被最多3个取代基所取代，所述取代基彼此独立地选自$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、$(C_0-C_4)$烷基氨磺酰基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述三唑基选择性地被羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述四唑基选择性地被羟基-$(C_2-C_3)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷基所取代；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的哌嗪上选择性取代的所述苯基和吡啶基选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{11}$和$R^{12}$与相邻的碳原子合在一起是$-CH_2OC(CH_3)_2OCH_2-$或$-O-(CH_2)_p-O-$，并且$R^{13}$和$R^{14}$彼此独立地是氢或$(C_1-C_4)$烷基；

p是1、2或3；

$R^{15}$和$R^{16}$彼此独立地是氢、选择性地被最多5个氟取代的$(C_1-C_4)$烷基；或者$R^{15}$是氢而$R^{16}$是$(C_3-C_6)$环烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、咪唑基、苯并噻唑基或苯并噁唑基；或者$R^{15}$和$R^{16}$合在一起是$(C_3-C_6)$亚烷基；

$G^3$、$G^4$和$G^5$分别是氢；r是0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在$R^6$的定义中的所述$(C_1-C_4)$烷基和在$R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多5个氟所取代；$R^{19}$和$R^{20}$彼此独立地是$(C_1-C_4)$烷基；或者

$G^3$、$G^4$和$G^5$分别是氢；r是1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在$R^6$的定义中的所述$(C_1-C_4)$烷基和在$R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多5个氟所取代；$R^{19}$和$R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和$G^4$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^5$是氢；或者

$G^4$和$G^5$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^3$是氢；

$R^{17}$是$SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

$R^{21}$和$R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和$Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和$R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、

氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、1,2,3,4-四氢-异喹啉基或5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在$R^{21}$和$R^{22}$的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基的取代基所取代；在$R^{21}$和$R^{22}$的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述哌嗪基选择性地被最多3个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、嘧啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷基；在$R^{21}$和$R^{22}$的定义中的所述1,2,3,4-四氢-异喹啉基和所述5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多3个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多4个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多3个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；

$Ar^2$彼此独立地如以上Ar和$Ar^1$所定义；

所述$Ar^2$选择性地如以上Ar和$Ar^1$中所述被取代；

$R^{23}$是$CONR^{25}R^{26}$或$SO_2R^{25}R^{26}$，其中$R^{25}$是氢、$(C_1-C_4)$烷基或$Ar^3-(C_0-C_4)$二价烷基，$R^{26}$是$Ar^3-(C_0-C_4)$二价烷基；条件是当$Ar^3$是苯基、萘基或联苯基时，则$R^{23}$不能是$CONR^{25}R^{26}$，其中$R^{25}$是氢或$Ar^3$，$R^{26}$是$Ar^3$；

$R^{24}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在$R^6$的定义中的所述$(C_1-C_4)$烷基和$R^6$定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多5个氟所取代；

$Ar^3$彼此独立地如以上Ar和$Ar^1$所定义；

所述$Ar^3$选择性地如以上Ar和$Ar^1$中所述被取代；

$R^{27}$是氢或$(C_1-C_4)$烷基；

$R^{28}$和$R^{29}$彼此独立地是氢、羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$或$NR^{30}R^{31}$；在$R^{28}$和$R^{29}$的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{28}$和$R^{29}$的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；

$R^{30}$和$R^{31}$彼此独立地是氢、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基或苯基，所述苯基选择性地被最多3个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{30}$和$R^{31}$与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌啶基、哌嗪基或吗啉基；在$R^{30}$和$R^{31}$的定义中的所述吡咯烷基和哌啶基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{30}$和$R^{31}$的定义中的所述二氢吲哚基和哌嗪基选择性地被最多3个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基羰基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{30}$和$R^{31}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；

A是选择性地被氢或($C_1$-$C_4$)烷基取代的N，B是羰基；或者

A是羰基而B是选择性地被氢或($C_1$-$C_4$)烷基取代的N；

$R^{32}$是氢或($C_1$-$C_4$)烷基；

$R^{33}$是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基或苯并噻吩基；在$R^{33}$的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多3个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{34}$和$R^{35}$彼此独立地是氢、($C_1$-$C_4$烷基)、苯基或苯基磺酰基；在$R^{34}$和$R^{35}$的定义中的所述苯基和苯基磺酰基选择性地被最多3个卤素、羟基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

D是CO、CHOH或$CH_2$；

E是O、NH或S；

$R^{36}$和$R^{37}$彼此独立地是氢、卤素、氰基、羟基、氨基、$(C_1-C_6)$烷基氨基、二-$(C_1-C_6)$烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、$Ar^4$、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；

$R^{38}$、$R^{39}$和$R^{40}$彼此独立地是氢或$(C_1-C_4)$-烷基；

$Ar^4$是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述$Ar^4$选择性地被最多3个羟基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、卤素、羟基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{36}$和$R^{37}$与相邻的碳原子合在一起是-O-$(CH_2)_t$-O-；

t是1、2或3；

Y是$(C_2-C_6)$亚烷基；

$R^{44}$、$R^{45}$和$R^{46}$彼此独立地是氢或$(C_1-C_4)$烷基；

m和n彼此独立地是1、2或3，条件是m和n的总和是2、3或4；

k是0、1、2、3或4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是$(C_3-C_7)$环烷基、$Ar^5$-$(C_0-C_4)$二价烷基、$NR^{47}R^{48}$或选择性地被最多5个氟取代的$(C_1-C_6)$烷基；条件是当$Y^1$是共价键或氧羰基时，则$R^{43}$不能是$NR^{47}R^{48}$；

$R^{47}$和$R^{48}$彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$烷基和$Ar^5$-$(C_0-C_4)$二价烷基；或者

$R^{47}$和$R^{48}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在$R^{47}$和$R^{48}$的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在

$R^{47}$和$R^{48}$的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{47}$和$R^{48}$的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多3个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多4个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

$Ar^5$彼此独立地如以上Ar和$Ar^1$所定义；

所述$Ar^5$选择性地如以上Ar和$Ar^1$中所述被取代；

$R^{42}$和$R^{42a}$彼此独立地是氢、($C_3$-$C_7$)环烷基、$Ar^6$-($C_0$-$C_3$)二价烷基、$Ar^6$-($C_2$-$C_4$)链烯基、$Ar^6$-羰基或选择性地被最多5个氟取代的($C_1$-$C_6$)烷基；

$Ar^6$彼此独立地如以上Ar和$Ar^1$所定义；

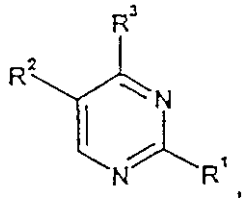
$Ar^6$选择性地如以上Ar和$Ar^1$中所述被取代；

$R^{41}$和$R^{41a}$彼此独立地是氢或($C_1$-$C_4$)烷基。

63. 权利要求 62 的化合物，选自：1R-(4-{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1R-(4-{4-[2-(1S-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1S-(4-{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-

基)-乙基丁酸酯；(E)-1R-{4-[4-(2-甲基-32-苯基-丙烯酰基)-哌嗪-1-基]-嘧啶-2-基}-乙基乙酸酯；(R)-1-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙基乙酸酯；1R-(4-{4-[2-(1RS-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1RS-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1R-[4-(3S-甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙基丁酸酯；1R-{4-[3R,5S-二甲基-4-(4-甲基-6-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-羟甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-甲氧基-6-甲氧基甲基-[1,3,5]三嗪-2-基)-R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；和 1R-{4-[2R,6S-二甲基-4-(4-甲基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯。

64. 式$I^B$的化合物，



$I^B$

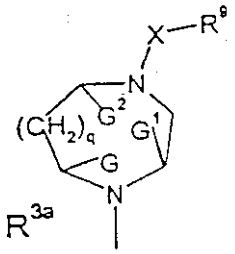
其中：

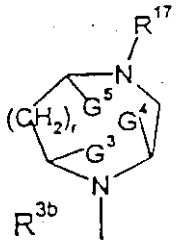
$R^1$是C-($OR^{81}$)$R^4R^5$，其中$R^{81}$是羧酸醛糖还原酶抑制剂的酰基；

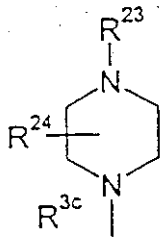
$R^4$和$R^5$彼此独立地是氢、甲基、乙基或羟基-($C_1$-$C_3$)烷基；

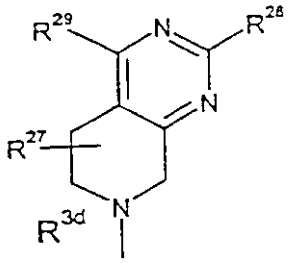
$R^2$是氢、($C_1$-$C_4$)烷基或($C_1$-$C_4$)烷氧基；

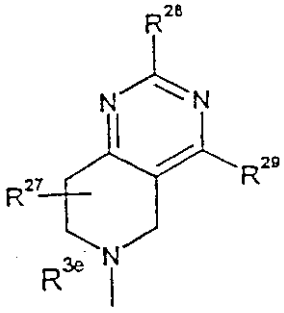
$R^3$是下式的基团

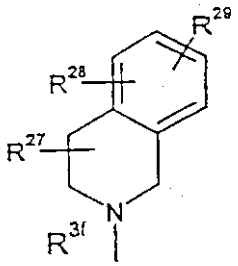


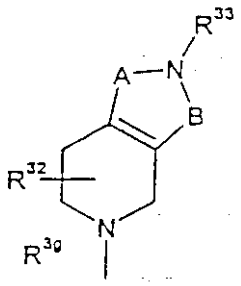


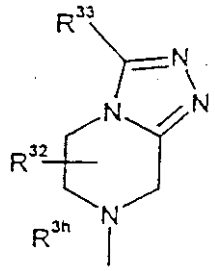


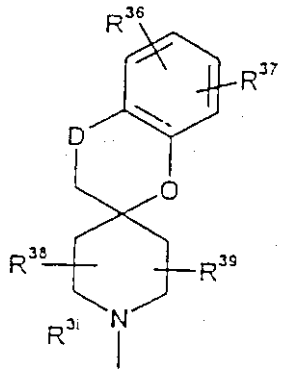


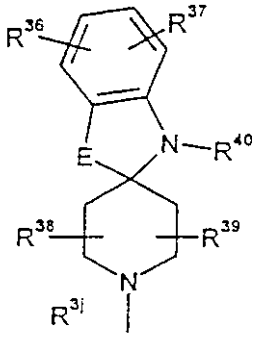


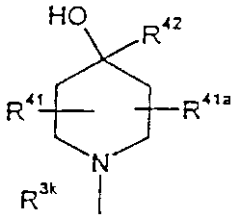


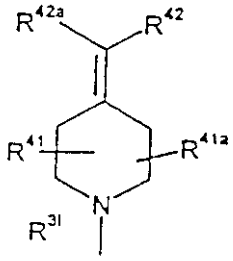


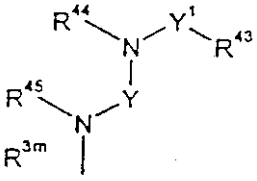


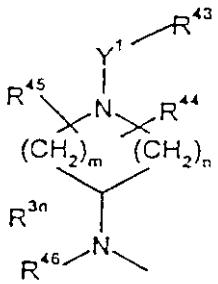


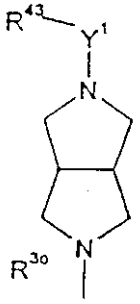




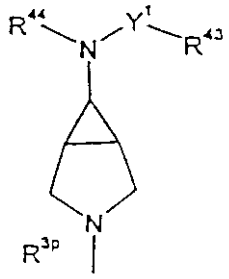


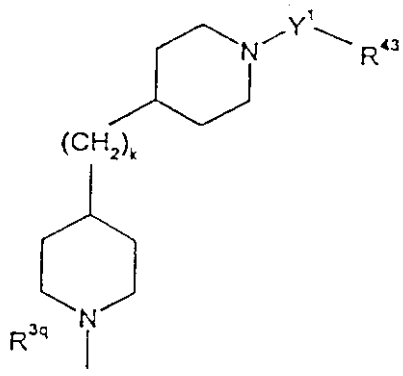






或





其中所述式$R^{3a}$的基团被$R^6$、$R^7$和$R^8$取代；

所述式$R^{3b}$的基团被$R^{18}$、$R^{19}$和$R^{20}$所取代；

G、$G^1$和$G^2$彼此独立地是氢并且$R^6$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多三个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在$R^6$的定义中的所述$(C_1-C_4)$烷基和$R^6$定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多5个氟所取代；$R^7$和$R^8$彼此独立地是氢或$(C_1-C_4)$烷基；或者

G和$G^1$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和$G^2$是氢；或者

$G^1$和$G^2$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和G是氢；

q是0或1；

X是共价键、$-(C=NR^{10})-$、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基、硫$(C_1-C_4)$二价烷基羰基、亚乙烯基磺酰基、亚磺酰基-$(C_1-C_4)$二价烷基羰基、磺酰基-$(C_1-C_4)$二价烷基羰基或羰基$(C_0-C_4)$二价烷基羰基；其中，在X的定义中的所述氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基和硫$(C_1-C_4)$二价烷基羰基选择性地并且彼此独立地被最多两个$(C_1-C_4)$烷基、苄基或Ar所取代；在X的定义中的所述亚乙烯基磺酰基和所述亚乙烯基羰基选择性地并且彼此独立地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或Ar所取代；在X的定义中的所述羰基$(C_0-C_4)$二价烷基羰基选择性地并且彼此独立地被最多三个$(C_1-C_4)$烷基、苄基或Ar所取代；

$R^{10}$是氢或$(C_1-C_4)$烷基；

$R^9$是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_3)$二价烷基或选择性地被最多5个氟取代的 $(C_1-C_6)$烷基；条件是，当q=0并且X是共价键、氧羰基或$(C_1-C_4)$二价烷基羰基时，则$R^9$不是$(C_1-C_6)$烷基；

Ar和$Ar^1$彼此独立地是完全饱和的、部分饱和的或完全不饱和的5至8元环，其选择性地含有最多4个彼此独立地选自氧、硫和氮的杂原

子；或是由两个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的5至7元环组成的二环，所述的两个环分别选择性地含有最多4个彼此独立地选自氧、硫和氮的杂原子；或是由三个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的5至7元环组成的三环，所述的三个环分别选择性地含有最多4个彼此独立地选自氧、硫和氮的杂原子；所述部分饱和的、完全饱和的环或完全不饱和的单环、二环或三环选择性地带有一个或两个取代在碳上的氧代基团或一个或两个取代在硫上的氧代基团；

Ar和$Ar^1$选择性地并且彼此独立地在碳或氮上被最多共4个彼此独立地选自$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的取代基所取代，如果该部分是单环，则在一个环上被取代，如果该部分是二环，则在一个或同时在两个环上被取代，如果该部分是三环，则在一个、两个或三个环上被取代；其中$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$彼此独立地是卤素、甲酰基、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$二价烷基氧羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$C(OH)R^{15}R^{16}$、萘基、苯基、咪唑基、吡啶基、三唑基、吗啉基、$(C_0-C_4)$烷基氨磺酰基、N-$(C_0-C_4)$烷基氨基甲酰基、N,N-二-$(C_1-C_4)$烷基氨基甲酰基、N-苯基氨基甲酰基、N-$(C_1-C_4)$烷基-N-苯基氨基甲酰基、N,N-二苯基氨基甲酰基、$(C_1-C_4)$烷基羰基氨基、$(C_3-C_7)$环烷基羰基氨基、苯基羰基氨基、哌啶基、吡咯烷基、哌嗪基、氧基、苯并咪唑基、氨基、苯氨基、嘧啶基、噁唑基、异噁唑基、四唑基、噻吩基、噻唑基、苯并噻唑基、吡咯基、吡唑基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、8-$(C_1-C_4)$烷基-3,8-二氮杂[3.2.1]二环辛基、3,5-二氧代-1,2,4-三嗪基、苯氧基、噻吩氧基、$(C_1-C_4)$烷硫基、$(C_1-C_4)$烷基磺酰基、$(C_3-C_7)$环烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述萘基、苯基、吡啶基、哌啶基、苯并咪唑基、嘧啶基、噻吩基、苯并噻唑基、吡咯基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、噻吩氧基、苯氨基和苯氧基选择性地被最多3个取代基所取代，

所述取代基彼此独立地选自羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述咪唑基、噁唑基、异噁唑基、噻唑基和吡唑基选择性地被最多2个取代基所取代，所述取代基彼此独立地选自羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述吗啉基选择性地被最多两个彼此独立地选自($C_1$-$C_4$)烷基的取代基所取代；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述吡咯烷基选择性地被最多2个取代基所取代，所述取代基彼此独立地选自羟基、羟基-($C_1$-$C_3$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述哌嗪基选择性地被最多3个取代基所取代，所述取代基彼此独立地选自($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、羟基-($C_1$-$C_3$)烷基、苯基、吡啶基、($C_0$-$C_4$)烷基氨磺酰基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述三唑基选择性地被羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的所述四唑基选择性地被羟基-($C_2$-$C_3$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷基所取代；在$R^{11}$、$R^{12}$、$R^{13}$和$R^{14}$的定义中的哌嗪上选择性取代的所述苯基和吡啶基选择性地被最多3个羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；或者

$R^{11}$和$R^{12}$与相邻的碳原子合在一起是$-CH_2OC(CH_3)_2OCH_2-$或$-O-(CH_2)_p-O-$，并且$R^{13}$和$R^{14}$彼此独立地是氢或($C_1$-$C_4$)烷基；

p是1、2或3；

$R^{15}$和$R^{16}$彼此独立地是氢、选择性地被最多5个氟取代的($C_1$-$C_4$)烷

基；或者$R^{15}$是氢而$R^{16}$是$(C_3-C_6)$环烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、咪唑基、苯并噻唑基或苯并噁唑基；或者$R^{15}$和$R^{16}$合在一起是$(C_3-C_6)$亚烷基；

$G^3$、$G^4$和$G^5$分别是氢；r是0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在$R^6$的定义中的所述$(C_1-C_4)$烷基和在$R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多5个氟所取代；$R^{19}$和$R^{20}$彼此独立地是$(C_1-C_4)$烷基；或者

$G^3$、$G^4$和$G^5$分别是氢；r是1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在$R^6$的定义中的所述$(C_1-C_4)$烷基和在$R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多5个氟所取代；$R^{19}$和$R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和$G^4$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^5$是氢；或者

$G^4$和$G^5$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^3$是氢；

$R^{17}$是$SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

$R^{21}$和$R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和$Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和$R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、1,2,3,4-四氢-异喹啉基或5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在

$R^{21}$和$R^{22}$的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基的取代基所取代；在$R^{21}$和$R^{22}$的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述哌嗪基选择性地被最多3个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、嘧啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷基；在$R^{21}$和$R^{22}$的定义中的所述1,2,3,4-四氢-异喹啉基和所述5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多3个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多4个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{21}$和$R^{22}$的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多3个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；

$Ar^2$彼此独立地如以上Ar和$Ar^1$所定义；

所述$Ar^2$选择性地如以上Ar和$Ar^1$中所述被取代；

$R^{23}$是$CONR^{25}R^{26}$或$SO_2R^{25}R^{26}$，其中$R^{25}$是氢、($C_1$-$C_4$)烷基或$Ar^3$-($C_0$-$C_4$)

二价烷基，$R^{26}$是$Ar^3$-($C_0$-$C_4$)二价烷基；条件是当$Ar^3$是苯基、萘基或联苯基时，则$R^{23}$不能是$CONR^{25}R^{26}$，其中$R^{25}$是氢或$Ar^3$，$R^{26}$是$Ar^3$；

$R^{24}$是氢、($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基羰基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、羟基-($C_1$-$C_4$)烷基或选择性地并且彼此独立地被最多3个羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷基或($C_1$-$C_4$)烷氧基取代的苯基，其中在$R^6$的定义中的所述($C_1$-$C_4$)烷基和$R^6$定义中的所述($C_1$-$C_4$)烷氧基选择性地并且彼此独立地被最多5个氟所取代；

$Ar^3$彼此独立地如以上Ar和$Ar^1$所定义；

所述$Ar^3$选择性地如以上Ar和$Ar^1$中所述被取代；

$R^{27}$是氢或($C_1$-$C_4$)烷基；

$R^{28}$和$R^{29}$彼此独立地是氢、羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$或$NR^{30}R^{31}$；在$R^{28}$和$R^{29}$的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{28}$和$R^{29}$的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多3个羟基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{30}$和$R^{31}$彼此独立地是氢、($C_1$-$C_4$)烷基、($C_3$-$C_7$)环烷基或苯基，所述苯基选择性地被最多3个羟基、卤素、羟基($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；或者

$R^{30}$和$R^{31}$与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌啶基、哌嗪基或吗啉基；在$R^{30}$和$R^{31}$的定义中的所述吡咯烷基和哌啶

基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{30}$和$R^{31}$的定义中的所述二氢吲哚基和哌嗪基选择性地被最多3个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基羰基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{30}$和$R^{31}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；

A是选择性地被氢或($C_1$-$C_4$)烷基取代的N，B是羰基；或者

A是羰基而B是选择性地被氢或($C_1$-$C_4$)烷基取代的N；

$R^{32}$是氢或($C_1$-$C_4$)烷基；

$R^{33}$是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基或苯并噻吩基；在$R^{33}$的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多3个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{34}$和$R^{35}$彼此独立地是氢、($C_1$-$C_4$烷基)、苯基或苯基磺酰基；在$R^{34}$和$R^{35}$的定义中的所述苯基和苯基磺酰基选择性地被最多3个卤素、羟基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

D是CO、CHOH或$CH_2$；

E是O、NH或S；

$R^{36}$和$R^{37}$彼此独立地是氢、卤素、氰基、羟基、氨基、($C_1$-$C_6$)烷基氨基、二-($C_1$-$C_6$)烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、

$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、$Ar^4$、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基；

$R^{38}$、$R^{39}$和$R^{40}$彼此独立地是氢或$(C_1-C_4)$-烷基；

$Ar^4$是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述$Ar^4$选择性地被最多3个羟基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、卤素、羟基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{36}$和$R^{37}$与相邻的碳原子合在一起是-O-$(CH_2)_t$-O-；

t是1、2或3；

Y是$(C_2-C_6)$亚烷基；

$R^{44}$、$R^{45}$和$R^{46}$彼此独立地是氢或$(C_1-C_4)$烷基；

m和n彼此独立地是1、2或3，条件是m和n的总和是2、3或4；

k是0、1、2、3或4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是$(C_3-C_7)$环烷基、$Ar^5$-$(C_0-C_4)$二价烷基、$NR^{47}R^{48}$或选择性地被最多5个氟取代的$(C_1-C_6)$烷基；条件是当$Y^1$是共价键或氧羰基时，则$R^{43}$不能是$NR^{47}R^{48}$；

$R^{47}$和$R^{48}$彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$烷基和$Ar^5$-$(C_0-C_4)$二价烷基；或者

$R^{47}$和$R^{48}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在$R^{47}$和$R^{48}$的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择

性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基；在$R^{47}$和$R^{48}$的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多3个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基或选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多4个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多5个氟取代的($C_1$-$C_4$)烷基和选择性地被最多5个氟取代的($C_1$-$C_4$)烷氧基所取代；

$Ar^5$彼此独立地如以上Ar和$Ar^1$所定义；

所述$Ar^5$选择性地如以上Ar和$Ar^1$中所述被取代；

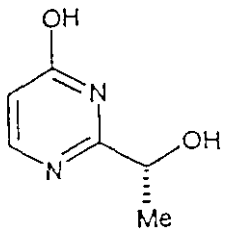
$R^{42}$和$R^{42a}$彼此独立地是氢、($C_3$-$C_7$)环烷基、$Ar^6$-($C_0$-$C_3$)二价烷基、$Ar^6$-($C_2$-$C_4$)链烯基、$Ar^6$-羰基或选择性地被最多5个氟取代的($C_1$-$C_6$)烷基；

$Ar^6$彼此独立地如以上Ar和$Ar^1$所定义；

$Ar^6$选择性地如以上Ar和$Ar^1$中所述被取代；

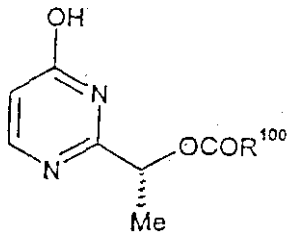
$R^{41}$和$R^{41a}$彼此独立地是氢或($C_1$-$C_4$)烷基。

65. 式Z的化合物




Z

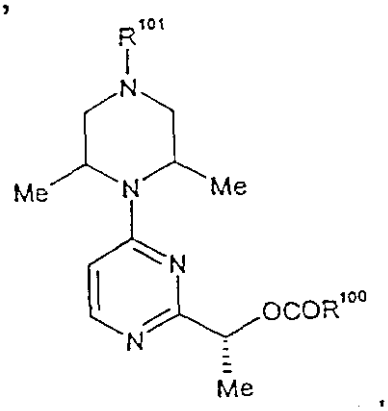
66. 式 ZZ 的化合物



ZZ

其中 $R^{100}$ 是 $(C_1-C_8)$ 烷基、苄基或苯基，其中所述的苄基和苯基选择性地被最多 3 个卤素或 $(C_1-C_4)$ 烷基所取代。

67. 式 III 化合物，



III

其中：

$R^{100}$ 是 $(C_1-C_8)$ 烷基、苄基或苯基，其中所述的苄基和苯基选择性地被最多三个卤素或 $(C_1-C_4)$ 烷基所取代；

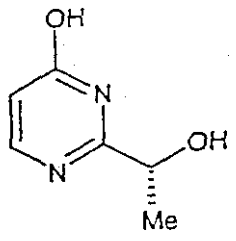
$R^{101}$ 是氢或适宜的胺保护基。

68. 权利要求 67 的化合物，其中 $R^{100}$ 是 $(C_1-C_4)$ 烷基，$R^{101}$ 是苄基或叔丁氧羰基。

69. 权利要求 68 的化合物，其中 $R^{100}$ 是正丁基或乙基，$R^{101}$ 是苄基。

70. 权利要求 68 的化合物，其中 $R^{100}$ 是正丁基或乙基，$R^{101}$ 是叔丁氧羰基。

71. 制备式 Z 化合物的方法，




Z

包括：

a) 将R-(+)-2-羟基-丙酰胺与三乙基氧鎓四氟硼酸盐在反应惰性溶剂中于0℃至室温下反应10分钟至24小时形成相应的亚胺酸酯；

b) 将所述亚胺酸酯与无水氨在反应惰性溶剂中于0℃至室温下反应2小时至24小时形成R-(+)-2-羟基-丙脒盐酸盐；和

c) 将所述R-(+)-2-羟基-丙脒盐酸盐与3-羟基-丙烯酸乙酯的钠盐和适宜的碱在反应惰性溶剂中反应形成所述式Z的化合物。

72. 一种药物组合物，其含有权利要求 1 的化合物、其前药或所述前药或所述化合物的可药用盐和糖原磷酸化酶抑制剂(GPI)、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

73. 在哺乳动物中治疗或预防糖尿病并发症的方法，该方法包括，向所述哺乳动物施用权利要求 181 的药物组合物。

74. 在哺乳动物中治疗糖尿病并发症的方法，该方法包括，向所述哺乳动物施用权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和糖原磷酸化酶抑制剂(GPI)、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

75. 在哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐和糖原磷酸化酶抑制剂(GPI)、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

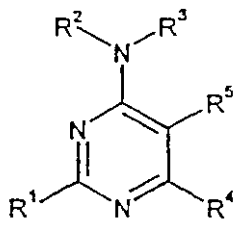
# 说　明　书

## 用作山梨醇脱氢酶抑制剂的氨基嘧啶类化合物

本发明涉及新的嘧啶衍生物以及所述衍生物和相关化合物用于在哺乳动物中抑制山梨醇脱氢酶(SDH)、降低果糖水平或治疗或预防糖尿病并发症例如糖尿病性神经病、糖尿病性视网膜病、糖尿病性肾病、糖尿病性心肌病、糖尿病性微血管病和糖尿病性大血管病的用途。本发明还涉及含有所述嘧啶衍生物和相关化合物的药物组合物。本发明还涉及含有式 I 的山梨醇脱氢酶抑制剂和醛糖还原酶抑制剂的药物组合物以及该组合物用于在哺乳动物中治疗或预防糖尿病并发症的用途。本发明还涉及含有式 I 的山梨醇脱氢酶抑制剂和 NHE-1 抑制剂的药物组合物以及该组合物用于减轻由局部缺血引起的组织损伤、特别是用于预防手术期间的心肌缺血性损伤的用途。

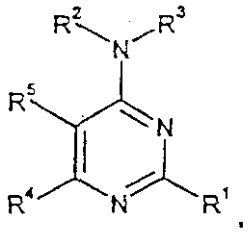
S. Ao 等, Metabolism, 40, 77-87 (1991)证实, 当用药物降低神经的果糖水平时, 在糖尿病大鼠中会出现显著的神经功能的改善(基于神经传导速度), 并且这种改善与降低神经果糖的关系比降低神经山梨醇更为密切。N. E. Cameron 和 M. A. Cotter, Diabetic Medicine, 8, Suppl. 1, 35A-36A (1991)报道了类似的结果。在以上两篇文献中, 均使用较高剂量的醛糖还原酶抑制剂来降低神经果糖, 该抑制剂可以抑制由醛糖还原酶从葡萄糖形成山梨醇(果糖的前体)。

美国专利 5,138,058 和 5,215,990(引入本文作为参考)均公开了下式的化合物



其中 $R^1$、$R^2$、$R^3$、$R^4$ 和 $R^5$ 如其文中所定义。文中公开了所述化合物具有山梨醇积聚活性，因此可以用作筛选醛糖还原酶抑制剂的工具。

共同受让的美国专利 5,728,704 和 5,866,578(引入本文作为参考)均公开了式 A 的化合物



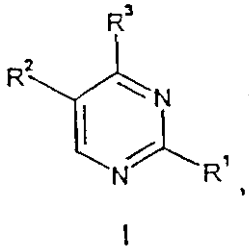
A

其中 $R^1$ 至 $R^5$ 如其文中所定义。此外，U.S. 5,728,704 还公开了山梨醇脱氢酶化合物可用于治疗糖尿病并发症。

下文中所定义的式 I 的嘧啶衍生物及其可药用盐可以降低患者糖尿病的哺乳动物组织(例如神经、肾和视网膜组织)中的果糖水平，并可用于治疗和预防上述的糖尿病并发症。这些化合物或其体内的代谢物是山梨醇脱氢酶(该酶可以催化将山梨醇氧化成果糖)的抑制剂。

## 发明概述

本发明涉及式 I 化合物



I

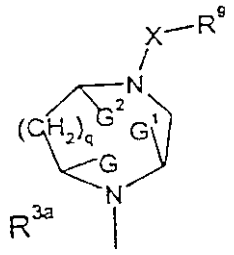
其前药或所述化合物或所述前药的可药用盐，其中：

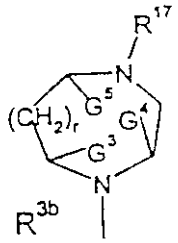
$R^1$ 是甲酰基、乙酰基、丙酰基、氨基甲酰基或-C(OH)$R^4R^5$；

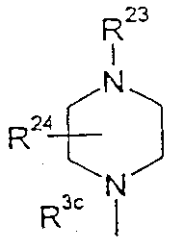
$R^4$ 和 $R^5$ 彼此独立地是氢、甲基、乙基或羟基-($C_1$-$C_3$)烷基；

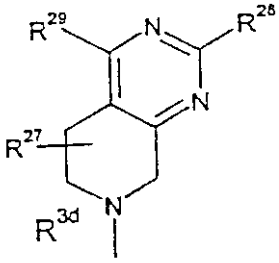
$R^2$ 是氢、($C_1$-$C_4$)烷基或($C_1$-$C_4$)烷氧基；

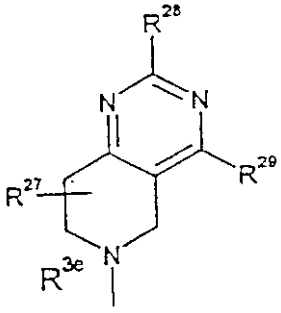
$R^3$ 是下式的基团

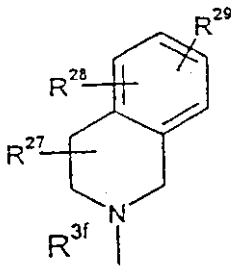


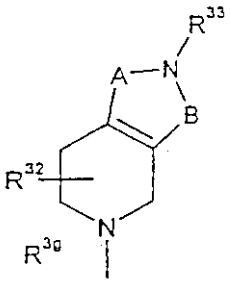


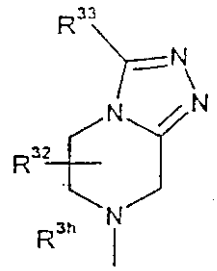


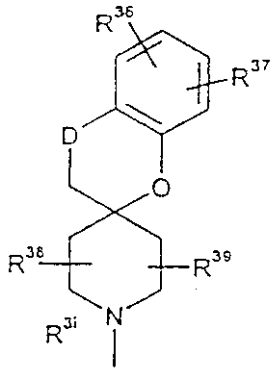


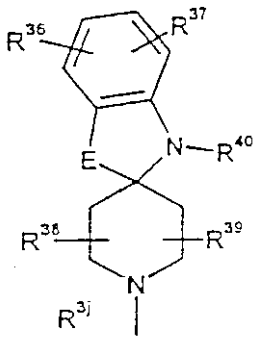


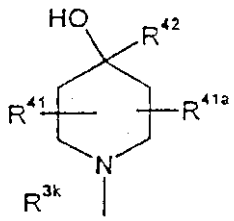


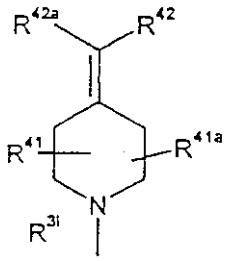


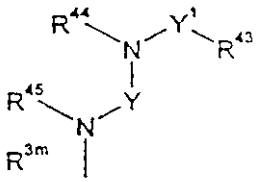


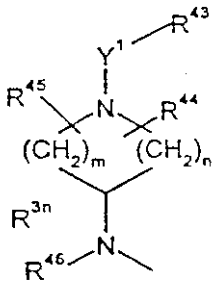


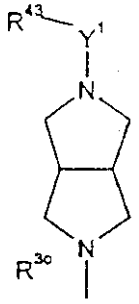




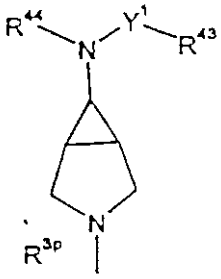


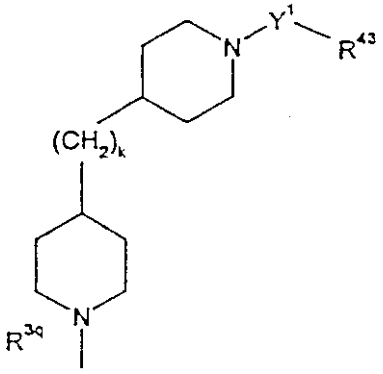






或





其中所述式 $R^{3a}$ 的基团还在环上被 $R^6$、$R^7$ 和 $R^8$ 所取代；

所述式 $R^{3b}$ 的基团还在环上被 $R^{18}$、$R^{19}$ 和 $R^{20}$ 所取代；

G、$G^1$ 和 $G^2$ 彼此独立地是氢并且 $R^6$ 是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多三个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$ 的定义中的所述$(C_1-C_4)$烷基和 $R^6$ 定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^7$ 和 $R^8$ 彼此独立地是氢或$(C_1-C_4)$烷基；或者

G 和 $G^1$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 $G^2$ 是氢；或者

$G^1$ 和 $G^2$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 G 是氢；

q 是 0 或 1；

X 是共价键、$-(C=NR^{10})-$、氧羰基、亚乙烯基(vinylenyl)羰基、氧$(C_1-C_4)$二价烷基(alkylenyl)羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基、硫$(C_1-C_4)$二价烷基羰基、亚乙烯基磺酰基、亚磺酰基-$(C_1-C_4)$二价烷基羰基、磺酰基-$(C_1-C_4)$二价烷基羰基或羰基$(C_0-C_4)$二价烷基羰基；其中，在 X 的定义中的所述氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基和硫$(C_1-C_4)$二价烷基羰基选择性地并且彼此独立地被最多两个$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述亚乙烯基磺酰基和所述亚乙烯基羰基选择性地并且彼此独立地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述羰基$(C_0-C_4)$二价烷基羰基选择性地并且彼此独立地被最多三个$(C_1-C_4)$烷基、苄基或 Ar 所取代；

$R^{10}$ 是氢或$(C_1-C_4)$烷基；

$R^9$ 是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_3)$二价烷基或选择性地被最多 5 个氟取代的 $(C_1-C_6)$烷基；条件是，当 q=0 并且 X 是共价键、氧羰基或$(C_1-C_4)$二价烷基羰基时，则 $R^9$ 不是$(C_1-C_6)$烷基；

Ar 和 $Ar^1$ 彼此独立地是完全饱和的、部分饱和的或完全不饱和的 5 至 8 元环，其选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原

子；或是由两个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的二环，所述的两个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；或是由三个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的三环，所述的三个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；所述部分饱和的、完全饱和的环或完全不饱和的单环、二环或三环选择性地带有一个或两个取代在碳上的氧代基团或一个或两个取代在硫上的氧代基团；

Ar 和 $Ar^1$ 选择性地并且彼此独立地在碳或氮上被最多共 4 个彼此独立地选自 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的取代基所取代，如果该部分是单环，则在一个环上被取代，如果该部分是二环，则在一个或同时在两个环上被取代，如果该部分是三环，则在一个、两个或三个环上被取代；其中 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 彼此独立地是卤素、甲酰基、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$二价烷基氧羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$C(OH)R^{15}R^{16}$、萘基、苯基、咪唑基、吡啶基、三唑基、吗啉基、$(C_0-C_4)$烷基氨磺酰基、N-$(C_0-C_4)$烷基氨基甲酰基、N,N-二-$(C_1-C_4)$烷基氨基甲酰基、N-苯基氨基甲酰基、N-$(C_1-C_4)$烷基-N-苯基氨基甲酰基、N,N-二苯基氨基甲酰基、$(C_1-C_4)$烷基羰基氨基、$(C_3-C_7)$环烷基羰基氨基、苯基羰基氨基、哌啶基、吡咯烷基、哌嗪基、氧基、苯并咪唑基、氨基、苯氨基、嘧啶基、噁唑基、异噁唑基、四唑基、噻吩基、噻唑基、苯并噻唑基、吡咯基、吡唑基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、8-$(C_1-C_4)$烷基-3,8-二氮杂[3.2.1]二环辛基、3,5-二氧代-1,2,4-三嗪基、苯氧基、噻吩氧基、$(C_1-C_4)$烷硫基、$(C_1-C_4)$烷基磺酰基、$(C_3-C_7)$环烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述萘基、苯基、吡啶基、哌啶基、苯并咪唑基、嘧啶基、噻吩基、苯并噻唑基、吡咯基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、噻吩氧基、苯氨基和苯氧基选择性地被最多 3 个取代基所取

代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述咪唑基、噁唑基、异噁唑基、噻唑基和吡唑基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述吗啉基选择性地被最多两个彼此独立地选自$(C_1-C_4)$烷基的取代基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述吡咯烷基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、羟基-$(C_1-C_3)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、$(C_0-C_4)$烷基氨磺酰基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述三唑基选择性地被羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述四唑基选择性地被羟基-$(C_2-C_3)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的哌嗪上选择性取代的所述苯基和吡啶基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

或者 $R^{11}$ 和 $R^{12}$ 与相邻的碳原子合在一起是$-CH_2OC(CH_3)_2OCH_2-$或$-O-(CH_2)_p-O-$，并且 $R^{13}$和 $R^{14}$彼此独立地是氢或$(C_1-C_4)$烷基；

p 是 1、2 或 3；

$R^{15}$和$R^{16}$彼此独立地是氢、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基；或者 $R^{15}$是氢而 $R^{16}$是$(C_3-C_6)$环烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、咪唑基、苯并噻唑基或苯并噁唑基；或者$R^{15}$和$R^{16}$合在一起是$(C_3-C_6)$亚烷基；

$G^3$、$G^4$和$G^5$分别是氢；r 是 0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和$R^{20}$彼此独立地是$(C_1-C_4)$烷基；或者

$G^3$、$G^4$和$G^5$分别是氢；r 是 1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和$R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和$G^4$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和$G^5$是氢；或者

$G^4$和$G^5$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和$G^3$是氢；

$R^{17}$是 $SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

$R^{21}$和$R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和 $Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和 $R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、

氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、1,2,3,4-四氢-异喹啉基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基的取代基所取代；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、嘧啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 1,2,3,4-四氢-异喹啉基和所述 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多 3 个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

$Ar^2$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

所述 $Ar^2$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{23}$ 是 $CONR^{25}R^{26}$ 或 $SO_2R^{25}R^{26}$，其中 $R^{25}$ 是氢、$(C_1-C_4)$烷基或 $Ar^3-(C_0-C_4)$二价烷基，$R^{26}$ 是 $Ar^3-(C_0-C_4)$二价烷基；条件是当 $Ar^3$ 是苯基、萘基或联苯基时，则 $R^{23}$ 不能是 $CONR^{25}R^{26}$，其中 $R^{25}$ 是氢或 $Ar^3$，$R^{26}$ 是 $Ar^3$；

$R^{24}$ 是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$ 的定义中的所述$(C_1-C_4)$烷基和 $R^6$ 定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；

$Ar^3$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

所述 $Ar^3$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{27}$ 是氢或$(C_1-C_4)$烷基；

$R^{28}$ 和 $R^{29}$ 彼此独立地是氢、羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$ 或 $NR^{30}R^{31}$；在 $R^{28}$ 和 $R^{29}$ 的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{28}$ 和 $R^{29}$ 的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

$R^{30}$ 和 $R^{31}$ 彼此独立地是氢、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基或苯基，所述苯基选择性地被最多 3 个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{30}$ 和 $R^{31}$ 与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌

啶基、哌嗪基或吗啉基；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述吡咯烷基和哌啶基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述二氢吲哚基和哌嗪基选择性地被最多 3 个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基羰基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

A 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N，B 是羰基；或者

A 是羰基而 B 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N；

$R^{32}$ 是氢或($C_1$-$C_4$)烷基；

$R^{33}$ 是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基或苯并噻吩基；在 $R^{33}$ 的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多 3 个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{34}$ 和 $R^{35}$ 彼此独立地是氢、($C_1$-$C_4$ 烷基)、苯基或苯基磺酰基；在 $R^{34}$ 和 $R^{35}$ 的定义中的所述苯基和苯基磺酰基选择性地被最多 3 个卤素、羟基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

D 是 CO、CHOH 或 $CH_2$；

E 是 O、NH 或 S；

$R^{36}$ 和 $R^{37}$ 彼此独立地是氢、卤素、氰基、羟基、氨基、($C_1$-$C_6$)烷基氨基、二-($C_1$-$C_6$)烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、($C_1$-

$C_4$)烷氧基-($C_1$-$C_4$)烷基、羟基-($C_1$-$C_4$)烷基、$Ar^4$、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

$R^{38}$、$R^{39}$和 $R^{40}$彼此独立地是氢或($C_1$-$C_4$)-烷基；

$Ar^4$是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述 $Ar^4$选择性地被最多 3 个羟基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、卤素、羟基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；或者

$R^{36}$和 $R^{37}$与相邻的碳原子合在一起是-O-$(CH_2)_t$-O-；

t 是 1、2 或 3；

Y 是($C_2$-$C_6$)亚烷基；

$R^{44}$、$R^{45}$和 $R^{46}$彼此独立地是氢或($C_1$-$C_4$)烷基；

m 和 n 彼此独立地是 1、2 或 3，条件是 m 和 n 的总和是 2、3 或 4；

k 是 0、1、2、3 或 4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是($C_3$-$C_7$)环烷基、$Ar^5$-($C_0$-$C_4$)二价烷基、$NR^{47}R^{48}$或选择性地被最多 5 个氟取代的($C_1$-$C_6$)烷基；条件是当 $Y^1$是共价键或氧羰基时，则 $R^{43}$不能是$NR^{47}R^{48}$；

$R^{47}$和 $R^{48}$彼此独立地选自氢、$Ar^5$、($C_1$-$C_6$)烷基和 $Ar^5$-($C_0$-$C_4$)二价烷基；或者

$R^{47}$和 $R^{48}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{47}$和 $R^{48}$的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$和 $R^{48}$的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$和 $R^{48}$的定义中的所述吗啉基选

择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在$R^{47}$和$R^{48}$的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个羟基、氨基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在$R^{47}$和$R^{48}$的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个羟基、氨基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

$Ar^5$彼此独立地如以上 Ar 和$Ar^1$所定义；

所述$Ar^5$选择性地如以上 Ar 和$Ar^1$中所述被取代；

$R^{42}$和$R^{42a}$彼此独立地是氢、$(C_3-C_7)$环烷基、$Ar^6$-$(C_0-C_3)$二价烷基、$Ar^6$-$(C_2-C_4)$链烯基、$Ar^6$-羰基或选择性地被最多 5 个氟取代的$(C_1-C_6)$烷基；

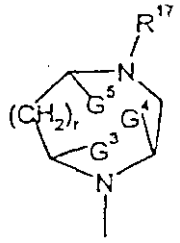
$Ar^6$彼此独立地如以上 Ar 和$Ar^1$所定义；

$Ar^6$选择性地如以上 Ar 和$Ar^1$中所述被取代；

$R^{41}$和$R^{41a}$彼此独立地是氢或$(C_1-C_4)$烷基。

一组优选的式 I 化合物(称为 A 组)是如下式 I 化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^3$是




；

其被$R^{18}$、$R^{19}$或$R^{20}$所取代；

$G^3$、$G^4$和$G^5$分别是氢；r是0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基取代的苯基；$R^{19}$和$R^{20}$彼此独立地是$(C_1-C_4)$烷基；

$G^3$、$G^4$和$G^5$分别是氢；r是1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基或选择性地被最多3个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基或选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基取代的苯基；$R^{19}$和$R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和$G^4$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^5$是氢；或者

$G^4$和$G^5$合在一起是$(C_1-C_3)$亚烷基；r是0或1；$R^{18}$、$R^{19}$、$R^{20}$和$G^3$是氢；

$R^{17}$是$SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

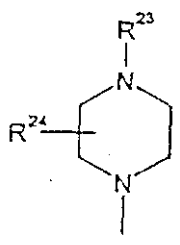
$R^{21}$和$R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和$Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和$R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、1,2,3,4-四氢-异喹啉基或5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在$R^{21}$和$R^{22}$的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多5个氟取代的$(C_1-C_4)$烷基和选择性地被最多5个氟取代的$(C_1-C_4)$烷氧基的取代基所取代；在$R^{21}$和$R^{22}$的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷

基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、嘧啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 1,2,3,4-四氢-异喹啉基和所述 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多 3 个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基。

另一组优选的式I化合物(称为B组)是如下式I化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^3$ 是

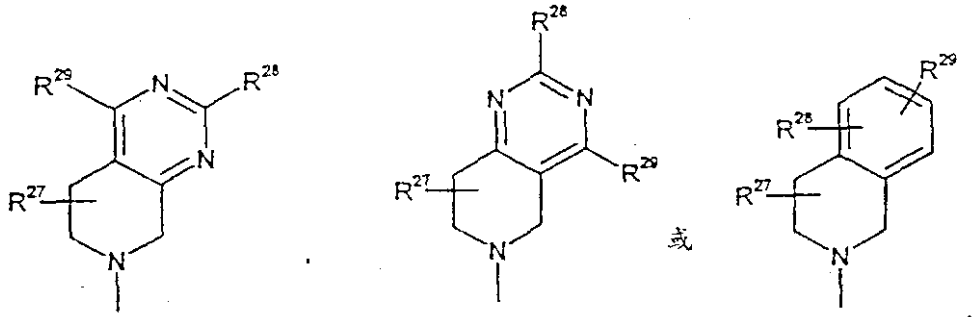


$R^{23}$是 $CONR^{25}R^{26}$、$SO_2R^{25}R^{26}$，其中 $R^{25}$是氢、$(C_1-C_4)$烷基或 $Ar^3-(C_0-C_4)$二价烷基，$R^{26}$是 $Ar^3-(C_0-C_4)$二价烷基；条件是当 $Ar^3$是苯基、萘基或联苯基时，则 $R^{23}$不能是 $CONR^{25}R^{26}$，其中 $R^{25}$是氢或 $Ar^3$，$R^{26}$是 $Ar^3$；

$R^{24}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基或选择性地被最多 3 个选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基、羟基、卤素或羟基-$(C_1-C_3)$烷基取代的苯基。

另一组优选的式I化合物(称为C组)是如下式I化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^3$是



或

$R^{27}$是氢或$(C_1-C_4)$烷基；

$R^{28}$和 $R^{29}$彼此独立地是氢、羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$或 $NR^{30}R^{31}$；在 $R^{28}$和 $R^{29}$的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{28}$和 $R^{29}$的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

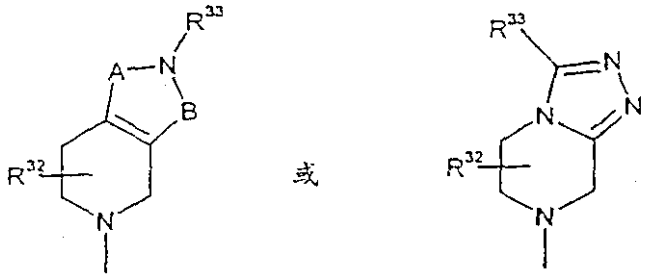
$R^{30}$和 $R^{31}$彼此独立地是氢、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基或苯基，所述

苯基选择性地被最多 3 个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基$-(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{30}$和 $R^{31}$与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌啶基、哌嗪基或吗啉基；在 $R^{30}$和 $R^{31}$的定义中的所述吡咯烷基和哌啶基选择性地被最多两个羟基、氨基、羟基$-(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基$-(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{30}$和 $R^{31}$的定义中的所述二氢吲哚基和哌嗪基选择性地被最多 3 个羟基、氨基、羟基$-(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基$-(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{30}$和 $R^{31}$的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基$-(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基$-(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基。

另一组优选的式I化合物(称为D组)是如下式I化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^3$是




A 是选择性地被氢或$(C_1-C_4)$烷基取代的 N，B 是羰基；或者

A 是羰基而 B 是选择性地被氢或$(C_1-C_4)$烷基取代的 N；

$R^{32}$是氢或$(C_1-C_4)$烷基；

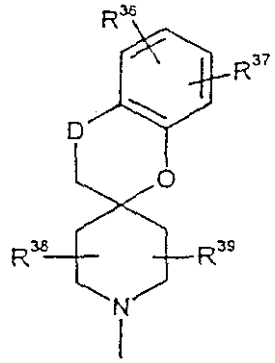
$R^{33}$是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃

基或苯并噻吩基；在 $R^{33}$ 的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多 3 个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

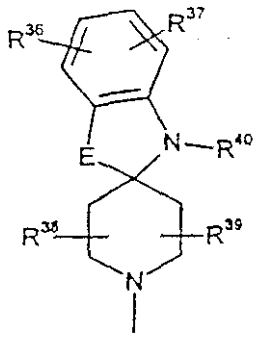
$R^{34}$ 和 $R^{35}$ 彼此独立地是氢、$(C_1-C_4$ 烷基)、苯基或苯基磺酰基；在 $R^{34}$ 和 $R^{35}$ 的定义中的所述苯基和苯基磺酰基选择性地被最多 3 个卤素、羟基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代。

另一组优选的式I化合物(称为E组)是如下式I化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^3$ 是



或



D 是 CO、CHOH 或 $CH_2$；

E 是 O、NH 或 S；

$R^{36}$ 和 $R^{37}$ 彼此独立地是氢、卤素、氰基、羟基、氨基、$(C_1-C_6)$烷基氨基、二-$(C_1-C_6)$烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、$Ar^4$、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；

$R^{38}$、$R^{39}$ 和 $R^{40}$ 彼此独立地是氢或$(C_1-C_4)$-烷基；

$Ar^4$ 是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述 $Ar^4$ 选择性地被最多 3 个羟基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、卤素、羟基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或

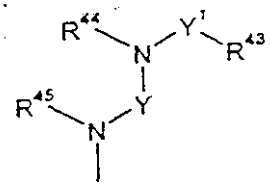
选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

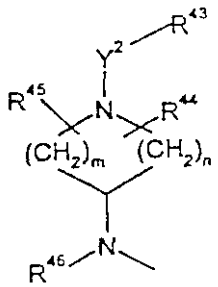
$R^{36}$和$R^{37}$与相邻的碳原子合在一起是$-O-(CH_2)_t-O-$；

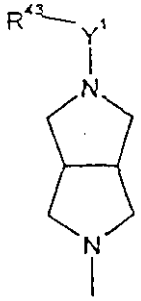
t 是 1、2 或 3。

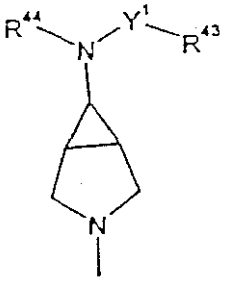
另一组优选的式I化合物(称为F组)是如下式I化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^3$是

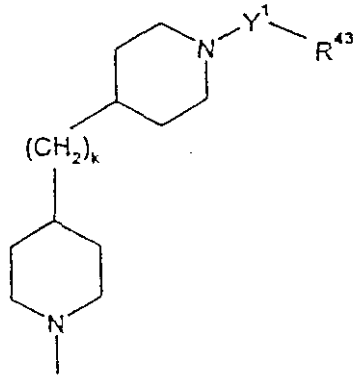








或



；

Y 是$(C_2-C_6)$亚烷基；

$R^{44}$、$R^{45}$和$R^{46}$彼此独立地是氢或$(C_1-C_4)$烷基；

m 和 n 彼此独立地是 1、2 或 3，条件是 m 和 n 的总和是 2、3 或 4；

k 是 0 至 4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是$(C_3-C_7)$环烷基、$Ar^5-(C_0-C_4)$二价烷基、$NR^{47}R^{48}$或选择性地被最多 5 个氟取代的$(C_1-C_6)$烷基；条件是当 $Y^1$是共价键或氧羰基时，则 $R^{43}$不能是$NR^{47}R^{48}$；

$R^{47}$和 $R^{48}$彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$烷基和 $Ar^5-(C_0-C_4)$二价烷基；或者

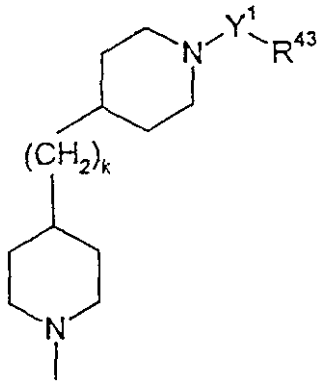
$R^{47}$ 和 $R^{48}$ 与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代。

F组中的一组优选的化合物(称为FA组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^2$是氢；

$R^3$是



k是0;

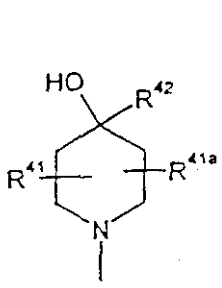
$Y^1$是共价键;

$R^{43}$是在2位被1-羟甲基取代的4-嘧啶基。

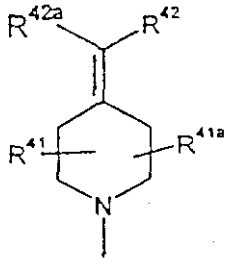
FA 组中的一组优选的化合物(称为 FB 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，所述化合物是 1R-(4-{1'-[2-(1R-羟基-乙基)-嘧啶-4-基]-[4,4']联哌啶-1-基}-嘧啶-2-基)-乙醇。

另一组优选的式I化合物(称为G组)是如下式I化合物、其前药和所述化合物或所述前药的可药用盐，其中:

$R^3$是



或



$R^{42}$和 $R^{42a}$彼此独立地是氢、$(C_3-C_7)$环烷基、$Ar^6-(C_0-C_3)$二价烷基、$Ar^6-(C_2-C_4)$链烯基、$Ar^6$-羰基或选择性地被最多 5 个氟取代的$(C_1-C_6)$烷基;

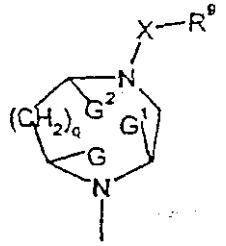
$R^{41}$和 $R^{41a}$彼此独立地是氢或$(C_1-C_4)$烷基。

另一组优选的式I化合物(称为H组)是如下式I化合物、其前药和所述化合物或所述前药的可药用盐，其中:

$R^1$是$C(OH)R^4R^5$，其中$R^4$和$R^5$彼此独立地是氢或甲基；

$R^2$是氢；

$R^3$是



其中所述的$R^3$被$R^6$、$R^7$或$R^8$取代；

G、$G^1$和$G^2$彼此独立地是氢并且$R^6$是氢或$(C_1-C_4)$烷基；$R^7$和$R^8$彼此独立地是氢或$(C_1-C_4)$烷基；或者

G和$G^1$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和$G^2$是氢；或者

$G^1$和$G^2$合在一起是$(C_1-C_3)$亚烷基并且$R^6$、$R^7$、$R^8$和G是氢；

q是0或1；

X是共价键、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、硫$(C_1-C_4)$二价烷基羰基或亚乙烯基磺酰基；在X的定义中的所述亚乙烯基羰基和所述亚乙烯基磺酰基选择性地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或Ar所取代；在X的定义中的所述氧$(C_1-C_4)$二价烷基羰基和所述硫$(C_1-C_4)$二价烷基羰基选择性地被最多两个$(C_1-C_4)$烷基、苄基或Ar所取代；

$R^9$是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_4)$二价烷基或选择性地被最多5个氟取代的$(C_1-C_6)$烷基；

$Ar^1$是苯基、萘基、吡啶基、嘧啶基、吡嗪基、哒嗪基、三嗪基、喹啉基、异喹啉基、喹唑啉基、喹喔啉基、酞嗪基、噌啉基、萘啶基、蝶啶基、吡嗪并吡嗪基、吡嗪并哒嗪基、嘧啶并哒嗪基、嘧啶并嘧啶基、吡啶并嘧啶基、吡啶并吡嗪基、吡啶并哒嗪基、吡咯基、呋喃基、噻吩基、咪唑基、噁唑基、噻唑基、吡唑基、异噁唑基、异噻唑基、三唑基、噁二唑基、噻二唑基、四唑基、吲哚基、苯并呋喃基、

苯并噻吩基、苯并咪唑基、苯并噁唑基、苯并噻唑基、吲唑基、苯并异噁唑基、苯并异噻唑基、吡咯并吡啶基、呋喃并吡啶基、噻吩并吡啶基、咪唑并吡啶基、噁唑并吡啶基、噻唑并吡啶基、吡唑并吡啶基、异噁唑并吡啶基、异噻唑并吡啶基、吡咯并嘧啶基、呋喃并嘧啶基、噻吩并嘧啶基、咪唑并嘧啶基、噁唑并嘧啶基、噻唑并嘧啶基、吡唑并嘧啶基、异噁唑并嘧啶基、异噻唑并嘧啶基、吡咯并吡嗪基、呋喃并吡嗪基、噻吩并吡嗪基、咪唑并吡嗪基、噁唑并吡嗪基、噻唑并吡嗪基、吡唑并吡嗪基、异噁唑并吡嗪基、异噻唑并吡嗪基、吡咯并哒嗪基、呋喃并哒嗪基、噻吩并哒嗪基、咪唑并哒嗪基、噁唑并哒嗪基、噻唑并哒嗪基、吡唑并哒嗪基、异噁唑并哒嗪基或异噻唑并哒嗪基；

所述 $Ar^1$ 选择性地按照以上描述被取代。

H组中的一组优选的化合物(称为HA组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

X 是共价键、氧羰基或选择性地在一个或两个亚乙烯基碳原子上被 $(C_1-C_4)$ 烷基、苄基或 Ar 取代的亚乙烯基羰基；

$R^9$ 是 $Ar^1-(C_0-C_4)$ 二价烷基；

$Ar^1$ 是苯基、萘基、吡啶基、嘧啶基、吡嗪基、三嗪基、喹啉基、异喹啉基、喹唑啉基、喹喔啉基、呋喃基、噻吩基、吲哚基、苯并呋喃基、苯并噻吩基、苯并噁唑基、苯并噻唑基、呋喃并吡啶基、噁唑并吡啶基、噻唑并吡啶基、噻吩并吡啶基、呋喃并嘧啶基、噻吩并嘧啶基、噁唑并嘧啶基或噻唑并嘧啶基；

所述 $Ar^1$ 选择性地按照权利要求 1 所述被取代。

HA组中的一组优选的化合物(称为HB组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^2$ 是氢；

$R^4$ 是氢或甲基；

$R^5$ 是甲基；

G、$G^1$ 和 $G^2$ 是氢；

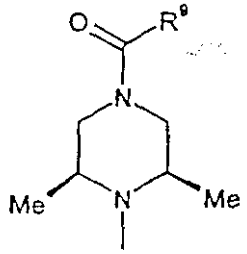
$R^6$和$R^7$彼此独立地是氢或甲基；

$R^8$是氢。

HB组中的一组优选的化合物(称为HC组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




HC 组中的优选化合物是其中 $R^9$是 2-呋喃并[3,2-c]吡啶基的化合物、其前药或所述化合物或所述前药的可药用盐。

HC 组中的另一个优选的化合物是其中 $R^9$是 2-(4-氯-呋喃并[3,2-c]吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

HC 组中的另一个优选的化合物是其中 $R^9$是 2-(4-吡咯烷-1-基-呋喃并[3,2-c]吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

HC 组中的另一个优选的化合物是其中 $R^9$是 2-(4-吗啉-4-基-呋喃并[3,2-c]吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

HC 组中的另一个优选的化合物是其中 $R^9$是 2-咪唑并[1,2-a]吡啶基的化合物、其前药或所述化合物或所述前药的可药用盐。

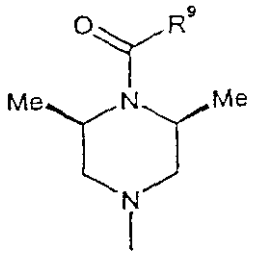
HC 组中的优选的化合物是呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-甲酮；(4-氯-呋喃并[3,2-c]吡啶-2-基)-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-甲酮；{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-(4-吡咯烷-1-基-呋喃并[3,2-c]吡

啶-2-基)-甲酮；{4-[2-(1R-羟基乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-(4-吗啉-4-基-呋喃并[3,2-c]吡啶-2-基)-甲酮；和{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-呋喃并[1,2-a]吡啶-2-基-甲酮。

HB 组中的另一组优选的化合物(称为 HD 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是



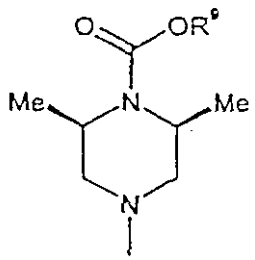

HD 组中的优选的化合物是其中 $R^9$是 2-呋喃并[3,2-c]吡啶基的化合物、其前药或所述化合物或所述前药的可药用盐。

HD 组中特别优选的化合物是呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮。

HB 组中的另一组优选的化合物(称为 HE 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




HE 组中的优选化合物是其中 $R^9$是 3-吡啶基的化合物、其前药或

所述化合物或所述前药的可药用盐。

HE 组中的另一个优选的化合物是其中 $R^9$ 是 3-(2-甲基吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

HE 组中的另一个优选的化合物是其中 $R^9$ 是 3-(5-氯吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

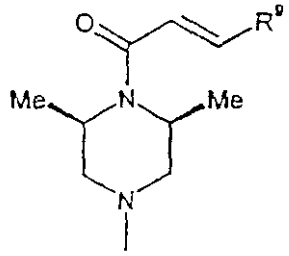
HE 组中的另一个优选的化合物是其中 $R^9$ 是 3-(6-甲基吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

HE 组中的优选化合物是 4-[2-(1R-羟基-乙基)-嘧啶 4-基]-2R,6S-二甲基-哌嗪-1-甲酸吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 2-甲基-吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 5-氯-吡啶-3-基酯；和 4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 6-甲基-吡啶-3-基酯。

HB 组中的另一组优选的化合物(称为 HF 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$ 是(R)-1-羟基-乙基；

$R^3$ 是



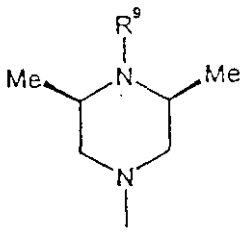

HF 组中的优选的化合物是其中 $R^9$ 是 2-噻吩基的化合物、其前药或所述化合物或所述前药的可药用盐。

HF 组中特别优选的化合物是(E)-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-3-噻吩-2-基-丙烯酮。

HB 组中的另一组优选的化合物(称为 HG 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




；和

$R^9$是嘧啶基或三嗪基；所述嘧啶基或三嗪基选择性地被最多两个羟基、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基、$(C_1-C_4)$烷氧基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$二价烷基、苯基、被$(C_1-C_4)$烷基选择性取代的哌嗪基或被最多两个$(C_1-C_4)$烷基选择性取代的咪唑基所取代。

HG 组中的一组优选的化合物(称为 HH 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多两个$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基取代的嘧啶-2-基。

HH 组中的优选化合物是其中 $R^9$是 4,6-二甲基嘧啶-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HH 组中的另一个优选的化合物是其中 $R^9$是 4-甲氧基-6-甲基嘧啶-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HH 组中的另一个优选的化合物是其中 $R^9$是 4-羟甲基-6-甲基嘧啶-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HH 组中的优选化合物是 1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；和 1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。

HG 组中的另一组优选的化合物(称为 HI 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多

两个($C_1$-$C_4$)烷基哌嗪-1-基或咪唑基取代的嘧啶-4-基；所述咪唑基选择性地被最多两个($C_1$-$C_4$)烷基取代。

HI 组中的优选化合物是其中 $R^9$ 是 2-(4-甲基哌嗪-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HI 组中的另一个优选的化合物是其中 $R^9$ 是 2-(4-乙基哌嗪-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HI 组中的另一个优选的化合物是其中 $R^9$ 是 2-(4-甲基咪唑-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HI 组中的另一个优选的化合物是其中 $R^9$ 是 2-(2-甲基咪唑-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HI 组中的另一个优选的化合物是其中 $R^9$ 是 2-(2,4-二甲基咪唑-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HI 组中的另一个优选的化合物是其中 $R^9$ 是 2-(4-异丙基哌嗪-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HI 组中的优选化合物是 1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(2-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(2,4-二甲基咪唑-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；和 1R-(4-{4-[2-(4-异丙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。

HG 组中的另一组优选的化合物(称为 HJ 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：$R^9$ 是选择性地被最多两个羟基、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基、$(C_1-C_4)$烷氧基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基哌嗪-1-基或苯基取代的[1,3,5]-三嗪-2-基。

HJ 组中的优选的化合物是其中 $R^9$ 是 4-甲基-6-(4-甲基哌嗪-1-基)-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-甲氧基-6-甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4,6-二甲氧基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-乙氧基-6-甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-异丙氧基-6-甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-苯基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-羟甲基-6-甲氧基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-异丙氧基-6-甲氧基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-异丙基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-乙基-6-甲氧基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-环丙基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4,6-二甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

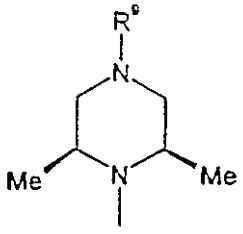
HJ 组中的另一个优选的化合物是其中 $R^9$ 是 4-甲基-6-苯基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HJ 组中的优选化合物是 1R-(4-{3R,5S-二甲基-4-[4-甲基-6-(4-甲基-哌嗪-1-基-[1,3,5]三嗪-2-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-乙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-异丙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[3R,5S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基-嘧啶-2-基}-乙醇；1R-{4-[4-(4-异丙氧基-6-甲氧基[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-异丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[3R,5S-二甲基-4-(4-甲基-6-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；和 1R-{4-[4-(4-乙基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。

HB 组中的另一组优选的化合物(称为 HK 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是



；和

$R^9$是嘧啶基或三嗪基，所述嘧啶基和三嗪基选择性地被最多两个羟基、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基、$(C_1-C_4)$烷氧基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、三唑基、乙酰基、吗啉基、$(C_1-C_4)$烷基哌嗪基、苯基或选择性地被最多两个$(C_1-C_4)$烷基取代的咪唑基所取代。

HK 组中的一组优选的化合物(称为 HL 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：$R^9$是选择性地被最多两个$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或三唑基取代的嘧啶-2-基。

HL 组中的优选的化合物是其中 $R^9$是 4,6-二甲基-嘧啶-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HL 组中的另一个优选的化合物是其中 $R^9$是 4-羟甲基-6-甲基嘧啶-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HL 组中的另一个优选的化合物是其中 $R^9$是 4-[1,2,4]-三唑-1-基-嘧啶-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HL 组中的优选的化合物是 1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；和 1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇。

HK 组中的另一组优选的化合物(称为 HM 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：$R^9$ 是选择性地被最多两个($C_1$-$C_4$)烷基、羟基-($C_1$-$C_4$)烷基、乙酰基、吗啉基、($C_1$-$C_4$)烷基哌嗪基、三唑基或选择性地被最多两个($C_1$-$C_4$)烷基取代的咪唑基取代的嘧啶-4-基。

HM 组中的优选的化合物是其中 $R^9$ 是 2,6-二甲基-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-羟甲基-6-甲基-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-乙酰基-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-吗啉-4-基-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-(4-甲基哌嗪-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-[1,2,4]-三唑-1-基-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-(1S-羟基乙基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-(1R-羟基乙基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-(4-乙基哌嗪-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

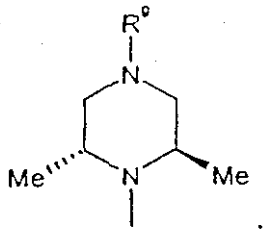
HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-(4-甲基咪唑-1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HM 组中的另一个优选的化合物是其中 $R^9$ 是 2-(2,4-二甲基咪唑-

1-基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HB 组中的优选的化合物是 1R-{4-[4-(2,6-二甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇; 1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-(4-{4-[2-(1S-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇; (4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮; 1R-{4-[2R,6S-二甲基-4-(2 吗啉-4-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇; 1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇; 1R-{4-[2R,6S-二甲基-4-(2-[1,2,4]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]嘧啶-2-基}-乙醇; 1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6R-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇; 1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇; 1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇;和 1R-(4-{4-[2-(2,4-二甲基-咪唑-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。

HB 组中的另一个优选的化合物是其中 $R^1$ 是(R)-1-羟基乙基; $R^3$ 是




; 和

$R^9$ 是 2-(1R-羟基乙基-嘧啶-4-基)的化合物、其前药或所述化合物或所述前药的可药用盐。

HK 组中的一组优选的化合物(称为 HN 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐, 其中: $R^9$ 是选择性地被最多两

个羟基、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基、吗啉基或苯基取代的[1,3,5]-三嗪-2-基。

HN 组的一种优选的化合物是其中 $R^9$ 是 4-吗啉-4-基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4-甲氧基-6-甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4,6-二甲氧基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4-苯基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4-环丙基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4,6-二甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4-羟甲基-6-苯基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4-甲氧基-6-甲氧基甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4-甲基-[1,3,5]-三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HN 组中的另一个优选的化合物是其中 $R^9$ 是 4-甲氧基甲基-6-苯基-[1,3,5]三嗪-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

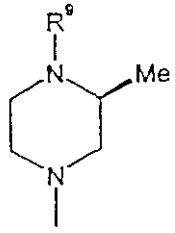
HN 组中的优选的化合物是 1R-{4-[2R,6S-二甲基-4-(4-吗啉-4-基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-

(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基)乙醇；1R-{4-[4-(4,6-二甲氧基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基-6-甲氧基甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]嘧啶-2-基}-乙醇；1R-{4-[2R,6S-二甲基-4-(4-甲基-[1,3,5]三嗪-2-基)哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；和 1R-{4-[2R,6S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇。

HB组中的另一组优选的化合物(称为HO)组是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是




；和

$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基或羟基-($C_1$-$C_4$)烷基取代的嘧啶基、喹喔啉基或噁唑并吡啶基。

HO组中的一个优选的化合物是其中$R^9$是4-羟甲基-6-甲基-嘧啶-2-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HO组中的另一个优选的化合物是其中$R^9$是2-羟甲基-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HO组中的另一个优选的化合物是其中$R^9$是2-羟甲基-6-甲基-嘧

啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HO 组中的另一个优选的化合物是其中 $R^9$ 是 2-(噁唑并[5,4-b]吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

HO 组中的另一个优选的化合物是其中 $R^9$ 是 2-(噁唑并[4,5-b]吡啶基)的化合物、其前药或所述化合物或所述前药的可药用盐。

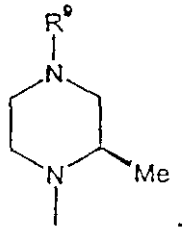
HO 组中的另一个优选的化合物是其中 $R^9$ 是 2-喹喔啉基的化合物、其前药或所述化合物或所述前药的可药用盐。

HO 组中的优选的化合物是 1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(2-羟甲基-嘧啶-4-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-[4-(3S-甲基-4-噁唑并[5,4b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇；1R-[4-(3S-甲基-4-噁唑并[4,5b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇；和 1R-[4-(3S-甲基-4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇。

HB 组中的另一组优选的化合物(称为 HP 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$ 是(R)-1-羟基-乙基；

$R^3$ 是




；和

$R^9$ 是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

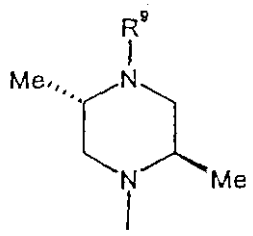
HP 组中的优选的化合物是其中 $R^9$ 是 2-(1R-羟基乙基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HP 组中的优选的化合物是 1R-(4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R-甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。

HB 组中的另一组优选的化合物(称为 HQ 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(R)-1-羟基-乙基；

$R^3$是



；和

$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

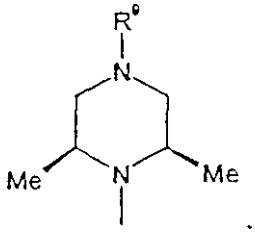
HQ 组中的优选的化合物是其中 $R^9$是 2-(1R-羟基乙基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HQ 组中特别优选的化合物是(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。

HB 组中的另一组优选的化合物(称为 HR 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是(S)-1-羟基-乙基；

$R^3$是



；和

$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基或羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

HR 组中的一个优选的化合物是其中 $R^9$是 2-(1R-羟基-乙基)-嘧

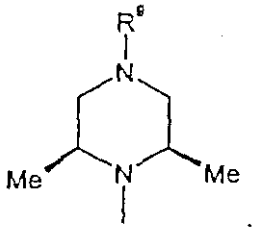
啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HR 组中特别优选的化合物是 1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。

HB 组中的又一组优选的化合物(称为 HS 组)是如下化合物、其前药和所述化合物或所述前药的可药用盐，其中：

$R^1$是乙酰基；

$R^3$是




；和

$R^9$是选择性地被最多两个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、乙酰基或羟基-($C_1$-$C_4$)烷基取代的嘧啶基。

HS 组中的一个优选的化合物是其中 $R^9$是 2-乙酰基-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HS 组中的一个优选的化合物是其中 $R^9$是 2-(1R-羟基乙基)-嘧啶-4-基的化合物、其前药或所述化合物或所述前药的可药用盐。

HS 组中特别优选的化合物是 1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R*,6S*-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮或 1-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮。

一种药物组合物，称为组合物 A，其含有式 I 化合物、其前药或所述化合物或所述前药的可药用盐以及可药用载体或稀释剂。

在需要抑制山梨醇脱氢酶的哺乳动物中抑制山梨醇脱氢酶的方法，该方法包括，向所述哺乳动物施用山梨醇脱氢酶抑制量的式 I 化合物、其前药或所述化合物或所述前药的可药用盐。

在患有糖尿病的哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用有效量的式 I 化合物、其前药或所述化合物或所述

前药的可药用盐。

在哺乳动物中治疗或预防糖尿病并发症的方法，称为方法 A，该方法包括，向所述哺乳动物施用有效量的式 I 化合物、其前药或所述化合物或所述前药的可药用盐。

方法 A 的方法，其中所述哺乳动物患有糖尿病。

方法 A 的方法，其中所述的糖尿病并发症是糖尿病神经病。

方法 A 的方法，其中所述的糖尿病并发症是糖尿病性肾病。

方法 A 的方法，其中所述的糖尿病并发症是糖尿病性视网膜病.

方法 A 的方法，其中所述的糖尿病并发症是脚溃疡。

方法 A 的方法，其中所述的糖尿病并发症是心血管疾病。

一种药物组合物，称为组合物 B，其含有式 I 化合物、其前药或所述化合物或所述前药的可药用盐，和醛糖还原酶抑制剂、其前药或所述醛糖还原酶抑制剂或所述前药的可药用盐。

组合物 B 的组合物，还含有可药用载体或稀释剂。

在患有糖尿病的哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用有效量的式 I 化合物、其前药或所述化合物或所述前药的可药用盐和醛糖还原酶抑制剂、其前药或所述醛糖还原酶抑制剂或所述前药的可药用盐。

在哺乳动物中治疗或预防糖尿病并发症的方法，称为方法 B，该方法包括，向所述哺乳动物施用有效量的式 I 化合物、其前药或所述化合物或所述前药的可药用盐和醛糖还原酶抑制剂、其前药或所述醛糖还原酶抑制剂或所述前药的可药用盐。

方法 B 的方法，其中所述哺乳动物患有糖尿病。

方法 B 的方法，其中所述的糖尿病并发症是糖尿病神经病。

方法 B 的方法，其中所述的糖尿病并发症是糖尿病性肾病。

方法 B 的方法，其中所述的糖尿病并发症是糖尿病性视网膜病.

方法 B 的方法，其中所述的糖尿病并发症是脚溃疡。

方法 B 的方法，其中所述的糖尿病并发症是心血管疾病。

药物组合物，称为组合物 C，其含有式 I 化合物、其前药或所述化合物或所述前药的可药用盐，和钠氢离子交换(NHE-1)抑制剂、所

述 NHE-1 抑制剂的前药或所述 NHE-1 抑制剂或所述前药的可药用盐。

在患有局部缺血的哺乳动物中治疗局部缺血的方法，称为方法 C，该方法包括，向所述哺乳动物施用有效量的权利要求 1 的化合物、其前药或所述化合物或所述前药的可药用盐，和钠氢离子交换(NHE-1)抑制剂、所述 NHE-1 抑制剂的前药或所述 NHE-1 抑制剂或所述前药的可药用盐。

方法 C 的方法，其中所述的局部缺血是手术期间的心肌缺血。

在哺乳动物中治疗或预防糖尿病并发症的方法，称为方法 D，该方法包括，向所述哺乳动物施用有效量的式 I 化合物、其前药或所述化合物或所述前药的可药用盐和钠氢离子交换(NHE-1)抑制剂、所述 NHE-1 抑制剂的前药或所述 NHE-1 抑制剂或所述前药的可药用盐。

方法 D 的方法，其中所述哺乳动物患有糖尿病。

方法 D 的方法，其中所述的糖尿病并发症是糖尿病神经病。

方法 D 的方法，其中所述的糖尿病并发症是糖尿病性肾病。

方法 D 的方法，其中所述的糖尿病并发症是糖尿病性视网膜病.

方法 D 的方法，其中所述的糖尿病并发症是脚溃疡。

方法 D 的方法，其中所述的糖尿病并发症是心血管疾病。

在患有糖尿病的哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用有效量的式 I 化合物、其前药或所述化合物或所述前药的可药用盐，和钠氢离子交换(NHE-1)抑制剂、所述 NHE-1 抑制剂的前药或所述 NHE-1 抑制剂或所述前药的可药用盐。

一种药盒，其含有：

a. 在第一单位剂量形式中的式 I 化合物、其前药或所述化合物或所述前药的可药用盐；

b. 在第二单位剂量形式中的醛糖还原酶抑制剂、其前药或所述前药或所述醛糖还原酶抑制剂的可药用盐；和

c. 容器。

一种药盒，其含有：

a. 在第一单位剂量形式中的式 I 化合物、其前药或所述化合物或所述前药的可药用盐；

b. 在第二单位剂量形式中的钠氢离子交换(NHE-1)抑制剂、其前药或所述前药或所述 NHE-1 抑制剂的可药用盐；和

c. 容器。

在需要抑制山梨醇脱氢酶的哺乳动物中抑制山梨醇脱氢酶的方法，称为方法 E，该方法包括，向所述哺乳动物施用组合物 A。

方法 E 的方法，其中所述的局部缺血是手术期间的心肌缺血。

在患有局部缺血的哺乳动物中治疗局部缺血的方法，该方法包括，向所述哺乳动物施用组合物 C。

在哺乳动物中治疗或预防糖尿病并发症的方法，称为方法 F，该方法包括，向所述哺乳动物施用组合物 A。

方法 F 的方法，其中所述的哺乳动物患有糖尿病。

在哺乳动物中治疗或预防糖尿病并发症的方法，称为方法 G，该方法包括，向所述哺乳动物施用组合物 B。

方法 G 的方法，其中所述的哺乳动物患有糖尿病。

在哺乳动物中治疗或预防糖尿病并发症的方法，称为方法 H，该方法包括，向所述哺乳动物施用组合物 C。

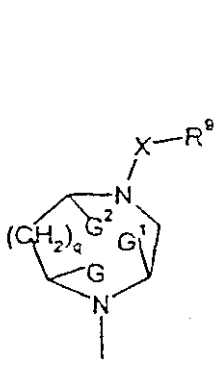
方法 H 的方法，其中所述的哺乳动物患有糖尿病。

式 I 化合物、其前药或所述化合物或所述前药的可药用盐，其中：

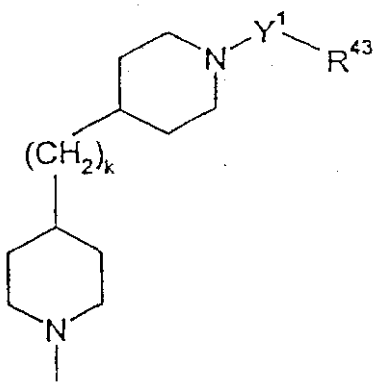
$R^1$是-C(OH)$R^4R^5$，其中 $R^4$和 $R^5$彼此独立地是氢或甲基；

$R^2$是氢；

$R^3$是




或




；

其中所述的哌嗪基 $R^3$被 $R^6$、$R^7$或 $R^8$取代；

G、$G^1$和 $G^2$彼此独立地是氢并且 $R^6$是氢或$(C_1-C_4)$烷基；$R^7$和 $R^8$彼此独立地是氢或$(C_1-C_4)$烷基；或者

G 和 $G^1$合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$和 $G^2$是氢；或者

$G^1$和 $G^2$合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$和 G 是氢；

q 是 0 或 1；

X 是共价键、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、硫$(C_1-C_4)$二价烷基羰基或亚乙烯基磺酰基；在 X 的定义中的所述亚乙烯基羰基和所述亚乙烯基磺酰基选择性地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述氧$(C_1-C_4)$二价烷基羰基和所述硫$(C_1-C_4)$二价烷基羰基选择性地被最多两个$(C_1-C_4)$烷基、苄基或 Ar 所取代；

$R^9$是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_4)$二价烷基或选择性地被最多 5 个氟取代的 $(C_1-C_6)$烷基；

$Ar^1$是苯基、萘基、吡啶基、嘧啶基、吡嗪基、哒嗪基、三嗪基、喹啉基、异喹啉基、喹唑啉基、喹喔啉基、酞嗪基、噌啉基、萘啶基、蝶啶基、吡嗪并吡嗪基、吡嗪并哒嗪基、嘧啶并哒嗪基、嘧啶并嘧啶基、吡啶并嘧啶基、吡啶并吡嗪基、吡啶并哒嗪基、吡咯基、呋喃基、噻吩基、咪唑基、噁唑基、噻唑基、吡唑基、异噁唑基、异噻唑基、三唑基、噁二唑基、噻二唑基、四唑基、吲哚基、苯并呋喃基、苯并噻吩基、苯并咪唑基、苯并噁唑基、苯并噻唑基、吲唑基、苯并异噁唑基、苯并异噻唑基、吡咯并吡啶基、呋喃并吡啶基、噻吩并吡啶基、咪唑并吡啶基、噁唑并吡啶基、噻唑并吡啶基、吡唑并吡啶基、异噁唑并吡啶基、异噻唑并吡啶基、吡咯并嘧啶基、呋喃并嘧啶基、噻吩并嘧啶基、咪唑并嘧啶基、噁唑并嘧啶基、噻唑并嘧啶基、吡唑并嘧啶基、异噁唑并嘧啶基、异噻唑并嘧啶基、吡咯并吡嗪基、呋喃并吡嗪基、噻吩并吡嗪基、咪唑并吡嗪基、噁唑并吡嗪基、噻唑并吡嗪基、吡唑并吡嗪基、异噁唑并吡嗪基、异噻唑并吡嗪基、吡咯并哒嗪基、呋喃并哒嗪基、噻吩并哒嗪基、咪唑并哒嗪基、噁唑并哒嗪基、噻唑并哒嗪基、吡唑并哒嗪基、异噁唑并哒嗪基或异噻唑并哒

嗪基；

所述 $Ar^1$ 选择性地按照以上描述被取代；

k 是 0、1、2、3 或 4；

$Y^1$ 是共价键、羰基、磺酰基或氧羰基；

$R^{43}$ 是 $(C_3-C_7)$ 环烷基、$Ar^5-(C_0-C_4)$ 二价烷基、$NR^{47}R^{48}$ 或选择性地被 1 至 5 个氟取代的 $(C_1-C_6)$ 烷基；条件是当 $Y^1$ 是共价键或氧羰基时，则 $R^{43}$ 不能是 $NR^{47}R^{48}$；

$R^{47}$ 和 $R^{48}$ 彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$ 烷基和 $Ar^5-(C_0-C_4)$ 二价烷基；或者

$R^{47}$ 和 $R^{48}$ 与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-$(C_1-C_4)$ 烷基、$(C_1-C_4)$ 烷氧基-$(C_1-C_4)$ 烷基、选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷基或选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-$(C_1-C_4)$ 烷基、$(C_1-C_4)$ 烷氧基-$(C_1-C_4)$ 烷基、选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷基或选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-$(C_1-C_4)$ 烷基、$(C_1-C_4)$ 烷氧基$(C_1-C_4)$ 烷基、选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷基和选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷氧基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个羟基、氨基、卤素、羟基-$(C_1-C_4)$ 烷基、$(C_1-C_4)$ 烷氧基-$(C_1-C_4)$ 烷基、选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷基或选择性地被最多 5 个氟取代的 $(C_1-C_4)$ 烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个羟基、氨基、卤素、羟基-

$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

$Ar^5$彼此独立地如以上 Ar 和 $Ar^1$所定义；

所述 $Ar^5$选择性地如以上 Ar 和 $Ar^1$中所述被取代。

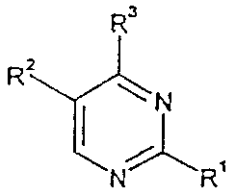
化合物下列的化合物：1R-(4-{1'-[2-(1R-羟基-乙基)-嘧啶-4-基]-[4,4']联哌啶-1-基}-嘧啶-2-基)-乙醇；呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-甲酮；(4-氯呋喃并[3,2-c]吡啶-2-基)-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-甲酮；{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-(4-吡咯烷-1-基-呋喃并[3,2-c]吡啶-2-基)-甲酮；{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-(4-吗啉-4-基-呋喃并[3,2c]吡啶-2-基)-甲酮；{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-咪唑并[1,2-a]吡啶-2-基-甲酮；呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 2-甲基-吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 5-氯-吡啶-3-基酯；4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸 6-甲基-吡啶-3-基酯；(E)-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-3-噻吩-2-基-丙烯酮；1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-咪唑-

1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{3R,5S-二甲基-4-[2-(2-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(2,4-二甲基-咪唑-1-基)-嘧啶-4-基]-3R,5S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{4-[2-(4-异丙基-哌嗪-1-基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-(4-{3R,5S-二甲基-4-[4-甲基-6-(4-甲基-哌嗪-1-基)-[1,3,5]三嗪-2-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-乙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-异丙氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]嘧啶-2-基}-乙醇；1R-{4-[3R,5S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-异丙氧基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-异丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-乙基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基)-乙醇；1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(2,6-二甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇；1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-(4-{4-[2-(1S-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-

基)-乙醇； 1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇； 1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮； 1RS-(4-{4-[2-(1RS-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇； (4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮； 1R-{4-[2R,6S-二甲基-4-(2-吗啉-4-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇； 1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇； 1R-{4-[2R,6S-二甲基-4-(2-[1,2,4]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]嘧啶-2-基}-乙醇； 1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6R-二甲基哌嗪-1-基}-嘧啶-2-基)-乙醇； 1R-(4-{4-[2-(4-乙基-哌嗪-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基]-乙醇； 1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-咪唑-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇； 1R-(4-{4-[2-(2,4-二甲基-咪唑-1-基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇； 1R-{4-[2R,6S-二甲基-4-(4-吗啉-4-基-[1,3,5]三嗪-2-基]哌嗪-1-基]-嘧啶-2-基}-乙醇； 1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇； 1R-{4-[4-(4,6-二甲氧基[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇； 1R-{4-[2R,6S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇； 1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3S-甲基-哌嗪-1-基]嘧啶-2-基}-乙醇； 1R-{4-[4-(2-羟甲基-嘧啶-4-基)-3S-甲基哌嗪-1-基]-嘧啶-2-基}-乙醇； 1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇； 1R-[4-(3S-甲基-4-噁唑并[4,5-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇； 1R-[4-(3S-甲基-4-噁唑并[4,5-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇； 1R-[4-(3S-甲基-4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇； (4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇； 1R-

{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[3R,5S-二甲基-4-(4-甲基-6-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]嘧啶-2-基}-乙醇；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-羟甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；1R-{4-[4-(4-甲氧基-6-甲氧基甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]嘧啶-2-基}-乙醇；1R-{4-[2R,6S-二甲基-4-(4-甲基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇；1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R*,6S*-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮；1-(4-{4-[2-(1R-羟基-乙基)嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮；1R-{4-[4-(4-甲氧基甲基-6-苯基-[1,3,5]-三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇；和 1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。

式 $I^A$ 的化合物



$I^A$

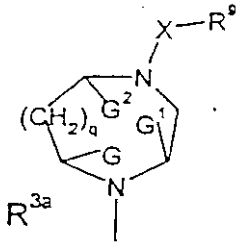
其中：

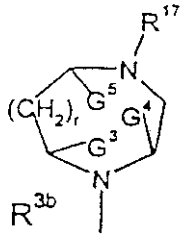
$R^1$ 是 C-($OR^{80}$)$R^4R^5$，其中 $R^{80}$ 彼此独立地是($C_1$-$C_4$)烷基、苄基、($C_1$-$C_6$)烷基羰基或苯基羰基，其中所述苄基和所述苯基选择性地被最多 3 个($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基、卤素或硝基所取代；

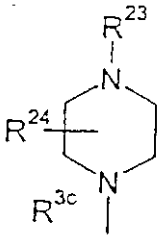
$R^4$ 和 $R^5$ 彼此独立地是氢、甲基、乙基或羟基-($C_1$-$C_3$)烷基；

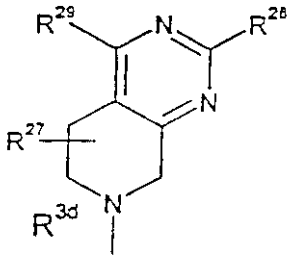
$R^2$是氢、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基；

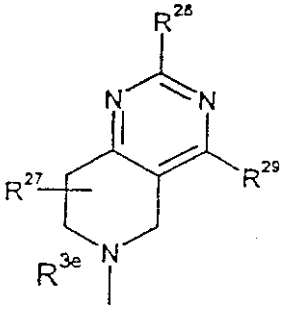
$R^3$是下式的基团

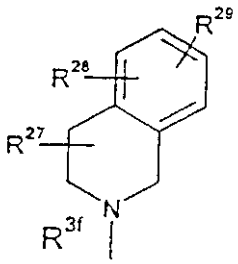


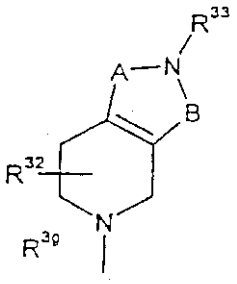


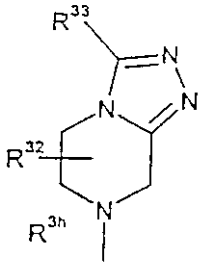


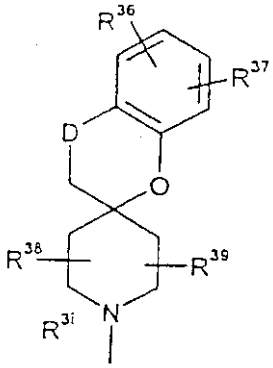


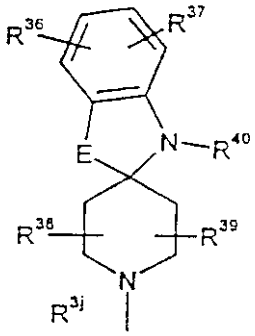


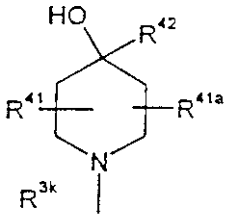


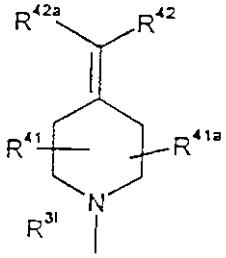


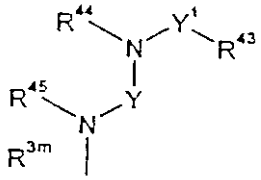


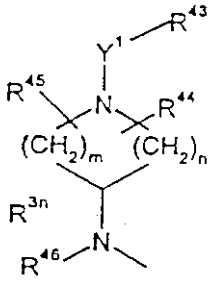


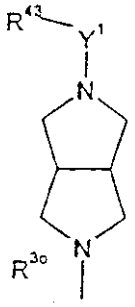


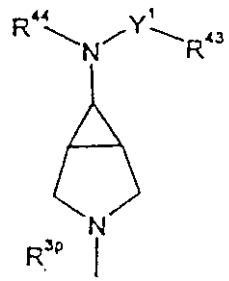




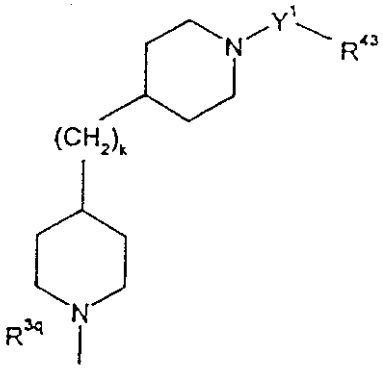








或



其中所述式 $R^{3a}$ 的基团被 $R^6$、$R^7$ 和 $R^8$ 取代；

所述式 $R^{3b}$ 的基团被 $R^{18}$、$R^{19}$ 和 $R^{20}$ 所取代；

G、$G^1$ 和 $G^2$ 彼此独立地是氢并且 $R^6$ 是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多三个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$ 的定义中的所述$(C_1-C_4)$烷基和 $R^6$ 定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^7$ 和 $R^8$ 彼此独立地是氢或$(C_1-C_4)$烷基；或者

G 和 $G^1$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 $G^2$ 是氢；或者

$G^1$ 和 $G^2$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 G 是氢；

q 是 0 或 1；

X 是共价键、$-(C=NR^{10})-$、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基、硫$(C_1-C_4)$二价烷基羰基、亚乙烯基磺酰基、亚磺酰基-$(C_1-C_4)$二价烷基羰基、磺酰基-$(C_1-C_4)$二价烷基羰基或羰基$(C_0-C_4)$二价烷基羰基；其中，在 X 的定义中的所述氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基和硫$(C_1-C_4)$二价烷基羰基选择性地并且彼此独立地被最多两个$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述亚乙烯基磺酰基和所述亚乙烯基羰基选择性地并且彼此独立地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述羰基$(C_0-C_4)$二价烷基羰基选择性地并且彼此独立地被最多三个$(C_1-C_4)$烷基、苄基或 Ar 所取代；

$R^{10}$ 是氢或$(C_1-C_4)$烷基；

$R^9$ 是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_3)$二价烷基或选择性地被最多 5 个氟取代的 $(C_1-C_6)$烷基；条件是，当 q=0 并且 X 是共价键、氧羰基或$(C_1-C_4)$二价烷基羰基时，则 $R^9$ 不是$(C_1-C_6)$烷基；

Ar 和 $Ar^1$ 彼此独立地是完全饱和的、部分饱和的或完全不饱和的 5 至 8 元环，其选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原

子；或是由两个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的二环，所述的两个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；或是由三个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的三环，所述的三个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；所述部分饱和的、完全饱和的环或完全不饱和的单环、二环或三环选择性地带有一个或两个取代在碳上的氧代基团或一个或两个取代在硫上的氧代基团；

Ar 和 $Ar^1$ 选择性地并且彼此独立地在碳或氮上被最多共 4 个彼此独立地选自 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的取代基所取代，如果该部分是单环，则在一个环上被取代，如果该部分是二环，则在一个或同时在两个环上被取代，如果该部分是三环，则在一个、两个或三个环上被取代；其中 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 彼此独立地是卤素、甲酰基、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$二价烷基氧羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$C(OH)R^{15}R^{16}$、萘基、苯基、咪唑基、吡啶基、三唑基、吗啉基、$(C_0-C_4)$烷基氨磺酰基、N-$(C_0-C_4)$烷基氨基甲酰基、N,N-二-$(C_1-C_4)$烷基氨基甲酰基、N-苯基氨基甲酰基、N-$(C_1-C_4)$烷基-N-苯基氨基甲酰基、N,N-二苯基氨基甲酰基、$(C_1-C_4)$烷基羰基氨基、$(C_3-C_7)$环烷基羰基氨基、苯基羰基氨基、哌啶基、吡咯烷基、哌嗪基、氰基、苯并咪唑基、氨基、苯氨基、嘧啶基、噁唑基、异噁唑基、四唑基、噻吩基、噻唑基、苯并噻唑基、吡咯基、吡唑基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、8-$(C_1-C_4)$烷基-3,8-二氮杂[3.2.1]二环辛基、3,5-二氧代-1,2,4-三嗪基、苯氧基、噻吩氧基、$(C_1-C_4)$烷硫基、$(C_1-C_4)$烷基磺酰基、$(C_3-C_7)$环烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述萘基、苯基、吡啶基、哌啶基、苯并咪唑基、嘧啶基、噻吩基、苯并噻唑基、吡咯基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、噻吩氧基、苯氨基和苯氧基选择性地被最多 3 个取代基所取

代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述咪唑基、噁唑基、异噁唑基、噻唑基和吡唑基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述吗啉基选择性地被最多两个彼此独立地选自$(C_1-C_4)$烷基的取代基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述吡咯烷基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、羟基-$(C_1-C_3)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、$(C_0-C_4)$烷基氨磺酰基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述三唑基选择性地被羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述四唑基选择性地被羟基-$(C_2-C_3)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的哌嗪上选择性取代的所述苯基和吡啶基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{11}$和 $R^{12}$与相邻的碳原子合在一起是$-CH_2OC(CH_3)_2OCH_2-$或$-O-(CH_2)_p-O-$，并且 $R^{13}$和 $R^{14}$彼此独立地是氢或$(C_1-C_4)$烷基；

p 是 1、2 或 3；

$R^{15}$和 $R^{16}$彼此独立地是氢、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基；或者 $R^{15}$是氢而 $R^{16}$是$(C_3-C_6)$环烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、咪唑基、苯并噻唑基或苯并噁唑基；或者 $R^{15}$和 $R^{16}$合在一起是$(C_3-C_6)$亚烷基；

$G^3$、$G^4$和 $G^5$分别是氢；r 是 0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和 $R^{20}$彼此独立地是$(C_1-C_4)$烷基；或者

$G^3$、$G^4$和 $G^5$分别是氢；r 是 1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和 $R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和 $G^4$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和 $G^5$是氢；或者

$G^4$和 $G^5$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和 $G^3$是氢；

$R^{17}$是 $SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

$R^{21}$和 $R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和 $Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和 $R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、

氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、1,2,3,4-四氢-异喹啉基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基的取代基所取代；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、嘧啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 1,2,3,4-四氢-异喹啉基和所述 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多 3 个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

$Ar^2$彼此独立地如以上 Ar 和 $Ar^1$所定义；

所述 $Ar^2$选择性地如以上 Ar 和 $Ar^1$中所述被取代；

$R^{23}$是 $CONR^{25}R^{26}$或 $SO_2R^{25}R^{26}$，其中 $R^{25}$是氢、$(C_1-C_4)$烷基或 $Ar^3-(C_0-C_4)$二价烷基，$R^{26}$是 $Ar^3-(C_0-C_4)$二价烷基；条件是当 $Ar^3$是苯基、萘基或联苯基时，则 $R^{23}$不能是 $CONR^{25}R^{26}$，其中 $R^{25}$是氢或 $Ar^3$，$R^{26}$是 $Ar^3$；

$R^{24}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$的定义中的所述$(C_1-C_4)$烷基和 $R^6$定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；

$Ar^3$彼此独立地如以上 Ar 和 $Ar^1$所定义；

所述 $Ar^3$选择性地如以上 Ar 和 $Ar^1$中所述被取代；

$R^{27}$是氢或$(C_1-C_4)$烷基；

$R^{28}$和 $R^{29}$彼此独立地是氢、羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$或 $NR^{30}R^{31}$；在 $R^{28}$和 $R^{29}$的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{28}$和 $R^{29}$的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

$R^{30}$和 $R^{31}$彼此独立地是氢、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基或苯基，所述苯基选择性地被最多 3 个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性

地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；或者

$R^{30}$ 和 $R^{31}$ 与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌啶基、哌嗪基或吗啉基；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述吡咯烷基和哌啶基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述二氢吲哚基和哌嗪基选择性地被最多 3 个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基羰基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

A 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N，B 是羰基；或者

A 是羰基而 B 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N；

$R^{32}$ 是氢或($C_1$-$C_4$)烷基；

$R^{33}$ 是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基或苯并噻吩基；在 $R^{33}$ 的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多 3 个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{34}$ 和 $R^{35}$ 彼此独立地是氢、($C_1$-$C_4$ 烷基)、苯基或苯基磺酰基；在 $R^{34}$ 和 $R^{35}$ 的定义中的所述苯基和苯基磺酰基选择性地被最多 3 个卤素、羟基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

D 是 CO、CHOH 或 $CH_2$；

E 是 O、NH 或 S；

$R^{36}$ 和 $R^{37}$ 彼此独立地是氢、卤素、氰基、羟基、氨基、$(C_1-C_6)$烷基氨基、二-$(C_1-C_6)$烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、$Ar^4$、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；

$R^{38}$、$R^{39}$ 和 $R^{40}$ 彼此独立地是氢或$(C_1-C_4)$-烷基；

$Ar^4$ 是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述 $Ar^4$ 选择性地被最多 3 个羟基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、卤素、羟基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{36}$ 和 $R^{37}$ 与相邻的碳原子合在一起是-O-$(CH_2)_t$-O-；

t 是 1、2 或 3；

Y 是$(C_2-C_6)$亚烷基；

$R^{44}$、$R^{45}$ 和 $R^{46}$ 彼此独立地是氢或$(C_1-C_4)$烷基；

m 和 n 彼此独立地是 1、2 或 3，条件是 m 和 n 的总和是 2、3 或 4；

k 是 0、1、2、3 或 4；

$Y^1$ 是共价键、羰基、磺酰基或氧羰基；

$R^{43}$ 是$(C_3-C_7)$环烷基、$Ar^5$-$(C_0-C_4)$二价烷基、$NR^{47}R^{48}$ 或选择性地被最多 5 个氟取代的$(C_1-C_6)$烷基；条件是当 $Y^1$ 是共价键或氧羰基时，则 $R^{43}$ 不能是 $NR^{47}R^{48}$；

$R^{47}$ 和 $R^{48}$ 彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$烷基和 $Ar^5$-$(C_0-C_4)$二价烷基；或者

$R^{47}$ 和 $R^{48}$ 与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

$Ar^5$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

所述 $Ar^5$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{42}$ 和 $R^{42a}$ 彼此独立地是氢、($C_3$-$C_7$)环烷基、$Ar^6$-($C_0$-$C_3$)二价烷基、$Ar^6$-($C_2$-$C_4$)链烯基、$Ar^6$-羰基或选择性地被最多 5 个氟取代的($C_1$-$C_6$)烷基；

$Ar^6$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

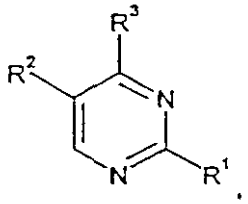
$Ar^6$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{41}$ 和 $R^{41a}$ 彼此独立地是氢或($C_1$-$C_4$)烷基。

选自下列的式 $I^A$ 化合物：1R-(4-{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1R-(4-{4-[2-(1S-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1S-(4-{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；(E)-1R-{4-[4-(2-甲基-32-苯基-丙烯酰基)-哌嗪-1-基]-嘧啶-2-

基}-乙基乙酸酯；(R)-1-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙基乙酸酯；1R-(4-{4-[2-(1RS-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1RS-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙基丁酸酯；1R-[4-(3S-甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙基丁酸酯；1R-{4-[3R,5S-二甲基-4-(4-甲基-6-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-环丙基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-羟甲基-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；1R-{4-[4-(4-甲氧基-6-甲氧基甲基-[1,3,5]三嗪-2-基)-R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯；和 1R-{4-[2R,6S-二甲基-4-(4-甲基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙基丁酸酯。

本发明还涉及式 $I^B$ 的交互(mutual)前药，



$I^B$

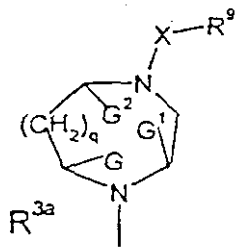
其中：

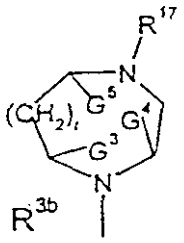
$R^1$ 是 $C-(OR^{81})R^4R^5$，其中 $R^{81}$ 彼此独立地是羧酸醛糖还原酶抑制剂的酰基；

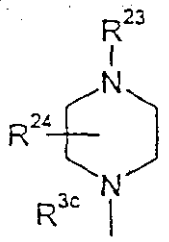
$R^4$ 和 $R^5$ 彼此独立地是氢、甲基、乙基或羟基-$(C_1-C_3)$烷基；

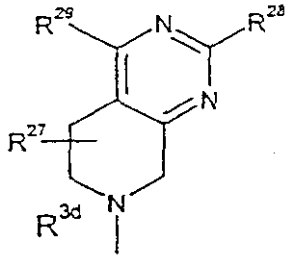
$R^2$ 是氢、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基；

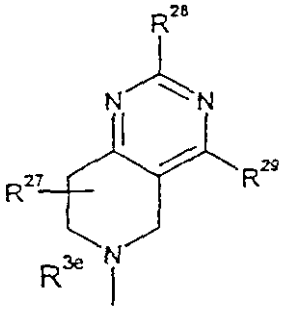
$R^3$ 是下式的基团

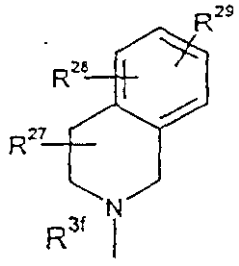


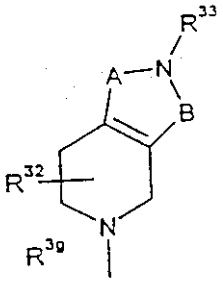


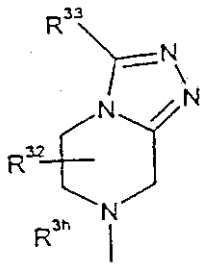


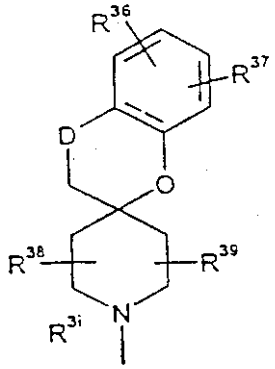


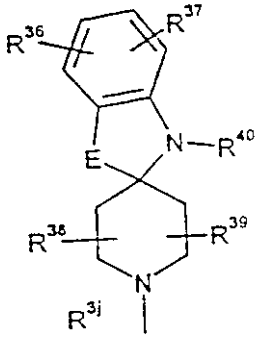


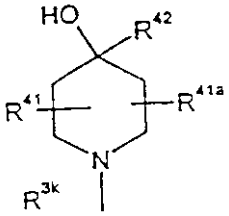


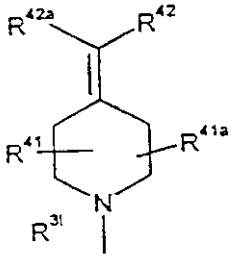


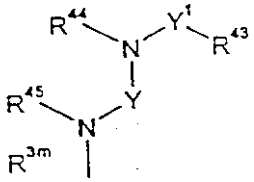


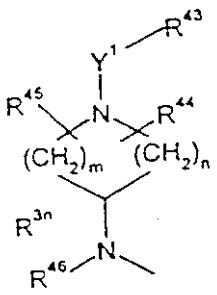


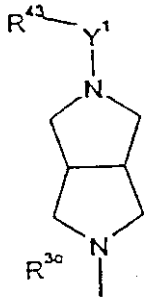


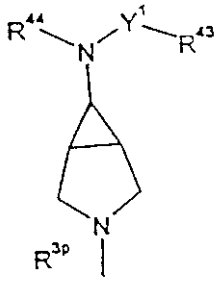




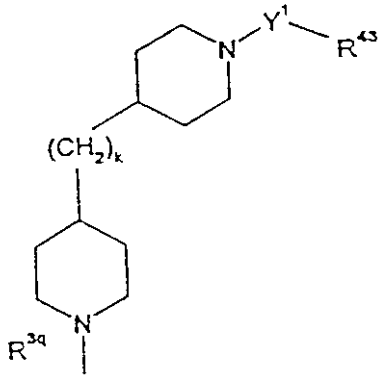








或



其中所述式 $R^{3a}$ 的基团被 $R^6$、$R^7$ 和 $R^8$ 取代；

所述式 $R^{3b}$ 的基团被 $R^{18}$、$R^{19}$ 和 $R^{20}$ 所取代；

G、$G^1$ 和 $G^2$ 彼此独立地是氢并且 $R^6$ 是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多三个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$ 的定义中的所述$(C_1-C_4)$烷基和 $R^6$ 定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^7$ 和 $R^8$ 彼此独立地是氢或$(C_1-C_4)$烷基；或者

G 和 $G^1$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 $G^2$ 是氢；或者

$G^1$ 和 $G^2$ 合在一起是$(C_1-C_3)$亚烷基并且 $R^6$、$R^7$、$R^8$ 和 G 是氢；

q 是 0 或 1；

X 是共价键、$-(C=NR^{10})-$、氧羰基、亚乙烯基羰基、氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基、硫$(C_1-C_4)$二价烷基羰基、亚乙烯基磺酰基、亚磺酰基-$(C_1-C_4)$二价烷基羰基、磺酰基-$(C_1-C_4)$二价烷基羰基或羰基$(C_0-C_4)$二价烷基羰基；其中，在 X 的定义中的所述氧$(C_1-C_4)$二价烷基羰基、$(C_1-C_4)$二价烷基羰基、$(C_3-C_4)$链烯基羰基和硫$(C_1-C_4)$二价烷基羰基选择性地并且彼此独立地被最多两个$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述亚乙烯基磺酰基和所述亚乙烯基羰基选择性地并且彼此独立地在一个或两个亚乙烯基碳原子上被$(C_1-C_4)$烷基、苄基或 Ar 所取代；在 X 的定义中的所述羰基$(C_0-C_4)$二价烷基羰基选择性地并且彼此独立地被最多三个$(C_1-C_4)$烷基、苄基或 Ar 所取代；

$R^{10}$ 是氢或$(C_1-C_4)$烷基；

$R^9$ 是$(C_3-C_7)$环烷基、$Ar^1-(C_0-C_3)$二价烷基或选择性地被最多 5 个氟取代的 $(C_1-C_6)$烷基；条件是，当 q=0 并且 X 是共价键、氧羰基或$(C_1-C_4)$二价烷基羰基时，则 $R^9$ 不是$(C_1-C_6)$烷基；

Ar 和 $Ar^1$ 彼此独立地是完全饱和的、部分饱和的或完全不饱和的 5 至 8 元环，其选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原

子；或是由两个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的二环，所述的两个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；或是由三个稠合的、彼此独立地是部分饱和的、完全饱和的或完全不饱和的 5 至 7 元环组成的三环，所述的三个环分别选择性地含有最多 4 个彼此独立地选自氧、硫和氮的杂原子；所述部分饱和的、完全饱和的环或完全不饱和的单环、二环或三环选择性地带有一个或两个取代在碳上的氧代基团或一个或两个取代在硫上的氧代基团；

Ar 和 $Ar^1$ 选择性地并且彼此独立地在碳或氮上被最多共 4 个彼此独立地选自 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的取代基所取代，如果该部分是单环，则在一个环上被取代，如果该部分是二环，则在一个或同时在两个环上被取代，如果该部分是三环，则在一个、两个或三个环上被取代；其中 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 彼此独立地是卤素、甲酰基、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$二价烷基氧羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$C(OH)R^{15}R^{16}$、萘基、苯基、咪唑基、吡啶基、三唑基、吗啉基、$(C_0-C_4)$烷基氨磺酰基、N-$(C_0-C_4)$烷基氨基甲酰基、N,N-二-$(C_1-C_4)$烷基氨基甲酰基、N-苯基氨基甲酰基、N-$(C_1-C_4)$烷基-N-苯基氨基甲酰基、N,N-二苯基氨基甲酰基、$(C_1-C_4)$烷基羰基氨基、$(C_3-C_7)$环烷基羰基氨基、苯基羰基氨基、哌啶基、吡咯烷基、哌嗪基、氧基、苯并咪唑基、氨基、苯氨基、嘧啶基、噁唑基、异噁唑基、四唑基、噻吩基、噻唑基、苯并噻唑基、吡咯基、吡唑基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、8-$(C_1-C_4)$烷基-3,8-二氮杂[3.2.1]二环辛基、3,5-二氧代-1,2,4-三嗪基、苯氧基、噻吩氧基、$(C_1-C_4)$烷硫基、$(C_1-C_4)$烷基磺酰基、$(C_3-C_7)$环烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$ 和 $R^{14}$ 的定义中的所述萘基、苯基、吡啶基、哌啶基、苯并咪唑基、嘧啶基、噻吩基、苯并噻唑基、吡咯基、四氢喹啉基、四氢异喹啉基、苯并噁唑基、哒嗪基、吡啶氧基、吡啶硫基、呋喃基、噻吩氧基、苯氨基和苯氧基选择性地被最多 3 个取代基所取

代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述咪唑基、噁唑基、异噁唑基、噻唑基和吡唑基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述吗啉基选择性地被最多两个彼此独立地选自$(C_1-C_4)$烷基的取代基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述吡咯烷基选择性地被最多 2 个取代基所取代，所述取代基彼此独立地选自羟基、羟基-$(C_1-C_3)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、$(C_0-C_4)$烷基氨磺酰基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述三唑基选择性地被羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的所述四唑基选择性地被羟基-$(C_2-C_3)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基所取代；在 $R^{11}$、$R^{12}$、$R^{13}$和 $R^{14}$的定义中的哌嗪上选择性取代的所述苯基和吡啶基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基和选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{11}$和 $R^{12}$与相邻的碳原子合在一起是$-CH_2OC(CH_3)_2OCH_2-$或$-O-(CH_2)_p-O-$，并且 $R^{13}$和 $R^{14}$彼此独立地是氢或$(C_1-C_4)$烷基；

p 是 1、2 或 3；

$R^{15}$和 $R^{16}$彼此独立地是氢、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基；或者 $R^{15}$是氢而 $R^{16}$是$(C_3-C_6)$环烷基、羟基-$(C_1-C_3)$烷基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、咪唑基、苯并噻唑基或苯并噁唑基；或者 $R^{15}$和 $R^{16}$合在一起是$(C_3-C_6)$亚烷基；

$G^3$、$G^4$和 $G^5$分别是氢；r 是 0；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和 $R^{20}$彼此独立地是$(C_1-C_4)$烷基；或者

$G^3$、$G^4$和 $G^5$分别是氢；r 是 1；$R^{18}$是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中，在 $R^6$的定义中的所述$(C_1-C_4)$烷基和在 $R^6$的定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；$R^{19}$和 $R^{20}$彼此独立地是氢或$(C_1-C_4)$烷基；或者

$G^3$和 $G^4$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和 $G^5$是氢；或者

$G^4$和 $G^5$合在一起是$(C_1-C_3)$亚烷基；r 是 0 或 1；$R^{18}$、$R^{19}$、$R^{20}$和 $G^3$是氢；

$R^{17}$是 $SO_2NR^{21}R^{22}$、$CONR^{21}R^{22}$、$(C_1-C_6)$烷氧基羰基、$(C_1-C_6)$烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$烷基磺酰基、$(C_1-C_6)$烷基亚磺酰基、$Ar^2$-磺酰基、$Ar^2$-亚磺酰基和$(C_1-C_6)$烷基；

$R^{21}$和 $R^{22}$彼此独立地选自氢、$(C_1-C_6)$烷基、$(C_3-C_7)$环烷基和 $Ar^2$-$(C_0-C_4)$二价烷基；或者

$R^{21}$和 $R^{22}$与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、6,7-二氢-5H-二苯并[c,e]吖庚因基、

1,2,3,4-四氢-异喹啉基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述氮杂环丁基选择性地被一个选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基的取代基所取代；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吡咯烷基、哌啶基、吖庚因基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自苯基、吡啶基、嘧啶基、($C_1$-$C_4$)烷氧基羰基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 1,2,3,4-四氢-异喹啉基和所述 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个取代基所取代，所述取代基彼此独立地选自羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个取代基所取代，所述取代基彼此独立地羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{21}$ 和 $R^{22}$ 的定义中的所述哌嗪上选择性取代的所述嘧啶基、吡啶基和苯基选择性地被最多 3 个取代基所取代，所述取代基选自羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

$Ar^2$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

所述 $Ar^2$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{23}$ 是 $CONR^{25}R^{26}$ 或 $SO_2R^{25}R^{26}$，其中 $R^{25}$ 是氢、$(C_1-C_4)$烷基或 $Ar^3-(C_0-C_4)$二价烷基，$R^{26}$ 是 $Ar^3-(C_0-C_4)$二价烷基；条件是当 $Ar^3$ 是苯基、萘基或联苯基时，则 $R^{23}$ 不能是 $CONR^{25}R^{26}$，其中 $R^{25}$ 是氢或 $Ar^3$，$R^{26}$ 是 $Ar^3$；

$R^{24}$ 是氢、$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基羰基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基或选择性地并且彼此独立地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基或$(C_1-C_4)$烷氧基取代的苯基，其中在 $R^6$ 的定义中的所述$(C_1-C_4)$烷基和 $R^6$ 定义中的所述$(C_1-C_4)$烷氧基选择性地并且彼此独立地被最多 5 个氟所取代；

$Ar^3$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

所述 $Ar^3$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{27}$ 是氢或$(C_1-C_4)$烷基；

$R^{28}$ 和 $R^{29}$ 彼此独立地是氢、羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基、苯基、吡啶基、嘧啶基、噻吩基、呋喃基、噻唑基、噁唑基、苯氧基、噻吩氧基、$SO_2NR^{30}R^{31}$、$CONR^{30}R^{31}$ 或 $NR^{30}R^{31}$；在 $R^{28}$ 和 $R^{29}$ 的定义中的所述噻吩基、嘧啶基、呋喃基、噻唑基和噁唑基选择性地被最多两个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{28}$ 和 $R^{29}$ 的定义中的所述苯基、吡啶基、苯氧基和噻吩氧基选择性地被最多 3 个羟基、卤素、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；

$R^{30}$ 和 $R^{31}$ 彼此独立地是氢、$(C_1-C_4)$烷基、$(C_3-C_7)$环烷基或苯基，所述苯基选择性地被最多 3 个羟基、卤素、羟基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{30}$ 和 $R^{31}$ 与它们所连接的氮合在一起形成二氢吲哚基、吡咯烷基、哌啶基、哌嗪基或吗啉基；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述吡咯烷基和哌啶基选择性地被最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述二氢吲哚基和哌嗪基选择性地被最多 3 个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基羰基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{30}$ 和 $R^{31}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；

A 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N，B 是羰基；或者

A 是羰基而 B 是选择性地被氢或($C_1$-$C_4$)烷基取代的 N；

$R^{32}$ 是氢或($C_1$-$C_4$)烷基；

$R^{33}$ 是苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基或苯并噻吩基；在 $R^{33}$ 的定义中的所述苯基、吡啶基、嘧啶基、噻唑基、噁唑基、苄基、喹啉基、异喹啉基、酞嗪基、quinoxanlyl、苯并噻唑基、苯并噁唑基、苯并呋喃基和苯并噻吩基选择性地被最多 3 个苯基、苯氧基、$NR^{34}R^{35}$、卤素、羟基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

$R^{34}$ 和 $R^{35}$ 彼此独立地是氢、($C_1$-$C_4$ 烷基)、苯基或苯基磺酰基；在 $R^{34}$ 和 $R^{35}$ 的定义中的所述苯基和苯基磺酰基选择性地被最多 3 个卤素、羟基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

D 是 CO、CHOH 或 $CH_2$；

E 是 O、NH 或 S；

$R^{36}$ 和 $R^{37}$ 彼此独立地是氢、卤素、氰基、羟基、氨基、$(C_1-C_6)$烷基氨基、二-$(C_1-C_6)$烷基氨基、1-吡咯烷基、1-哌啶基、4-吗啉基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、羟基-$(C_1-C_4)$烷基、$Ar^4$、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基；

$R^{38}$、$R^{39}$和 $R^{40}$彼此独立地是氢或$(C_1-C_4)$-烷基；

$Ar^4$是苯基、呋喃基、噻吩基、吡啶基、嘧啶基、吡嗪基或哒嗪基；所述 $Ar^4$ 选择性地被最多 3 个羟基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、卤素、羟基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；或者

$R^{36}$和 $R^{37}$与相邻的碳原子合在一起是-O-$(CH_2)_t$-O-；

t 是 1、2 或 3；

Y 是$(C_2-C_6)$亚烷基；

$R^{44}$、$R^{45}$和 $R^{46}$彼此独立地是氢或$(C_1-C_4)$烷基；

m 和 n 彼此独立地是 1、2 或 3，条件是 m 和 n 的总和是 2、3 或 4；

k 是 0、1、2、3 或 4；

$Y^1$是共价键、羰基、磺酰基或氧羰基；

$R^{43}$是$(C_3-C_7)$环烷基、$Ar^5$-$(C_0-C_4)$二价烷基、$NR^{47}R^{48}$或选择性地被最多 5 个氟取代的$(C_1-C_6)$烷基；条件是当 $Y^1$ 是共价键或氧羰基时，则 $R^{43}$ 不能是 $NR^{47}R^{48}$；

$R^{47}$ 和 $R^{48}$ 彼此独立地选自氢、$Ar^5$、$(C_1-C_6)$烷基和 $Ar^5$-$(C_0-C_4)$二价烷基；或者

$R^{47}$ 和 $R^{48}$ 与它们所连接的氮原子合在一起形成氮杂环丁基、吡咯烷基、哌啶基、哌嗪基、吗啉基、吖庚因基、氮杂二环[3.2.2]壬基、氮杂二环[2.2.1]庚基、1,2,3,4-四氢异喹啉基、6,7-二氢-5H-二苯并[c,e]吖庚因基或 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述氮杂环丁基选择性地被一个羟基、氨基、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基-$(C_1-C_4)$烷基、选择性地被最多 5 个氟取代的$(C_1-C_4)$烷基或选择性地被最多 5 个氟取代的$(C_1-C_4)$烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吡咯烷基、哌啶基和吖庚因基选择性地被

最多两个羟基、氨基、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述吗啉基选择性地被最多两个取代基所取代，所述取代基彼此独立地选自羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述哌嗪基、1,2,3,4-四氢-异喹啉基和 5,6,7,8-四氢吡啶并[4,3-d]嘧啶基选择性地被最多 3 个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基或选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；在 $R^{47}$ 和 $R^{48}$ 的定义中的所述 6,7-二氢-5H-二苯并[c,e]吖庚因基选择性地被最多 4 个羟基、氨基、卤素、羟基-($C_1$-$C_4$)烷基、($C_1$-$C_4$)烷氧基-($C_1$-$C_4$)烷基、选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷基和选择性地被最多 5 个氟取代的($C_1$-$C_4$)烷氧基所取代；

$Ar^5$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

所述 $Ar^5$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

$R^{42}$ 和 $R^{42a}$ 彼此独立地是氢、($C_3$-$C_7$)环烷基、$Ar^6$-($C_0$-$C_3$)二价烷基、$Ar^6$-($C_2$-$C_4$)链烯基、$Ar^6$-羰基或选择性地被最多 5 个氟取代的($C_1$-$C_6$)烷基；

$Ar^6$ 彼此独立地如以上 Ar 和 $Ar^1$ 所定义；

$Ar^6$ 选择性地如以上 Ar 和 $Ar^1$ 中所述被取代；

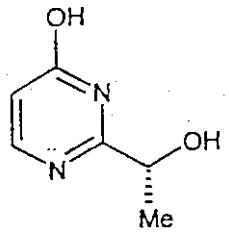
$R^{41}$ 和 $R^{41a}$ 彼此独立地是氢或($C_1$-$C_4$)烷基。

式 $I^B$ 化合物中的一组优选的化合物是如下化合物，其中 $R^{81}$ 是泊那司他、托瑞司他、折那司他、唑泊司他、依帕司他、ZD5522 或索比尼尔的酰基。

特别优选的本发明的交互前药选自(E)-[4-氧代-3-(5-三氟甲基-苯并噻唑-2-基甲基)-3,4-二氢-酞嗪-1-基]-乙酸 1R-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯和(E)-[4-氧代-3-(5-三氟甲基-苯并噻唑-2-基甲基)-3,4-二氢-酞嗪-1-基]-乙酸 1R-{4-[4-(3-噻

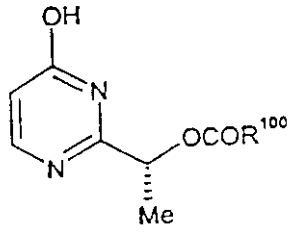
吩-2-基-丙烯酰基)-哌嗪-1-基]-嘧啶-2-基}-乙酯。

本发明还涉及式 Z 的中间体化合物



Z

本发明还涉及式 ZZ 的中间体化合物，称为 AA 组，



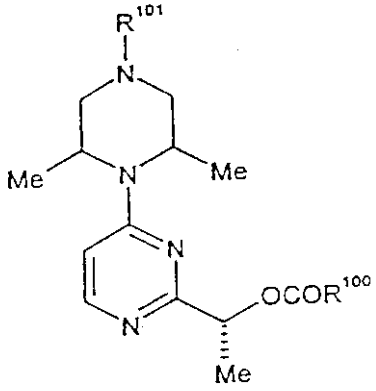
ZZ

其中 $R^{100}$ 是($C_1$-$C_8$)烷基、苄基或苯基，其中所述苄基和苯基选择性地被最多 3 个卤素或($C_1$-$C_4$)烷基所取代。

AA 组中的一组优选的化合物(称为 AB 组)是其中 $R^{100}$ 是($C_1$-$C_4$)烷基的化合物。

AB 组中更优选的化合物是其中 $R^{100}$ 是正丁基或乙基的化合物。

本发明还涉及式 ZZZ 的化合物，



ZZZ

其中：

$R^{100}$ 是 $(C_1-C_8)$ 烷基、苄基或苯基，其中所述的苄基和苯基选择性地被最多三个卤素或 $(C_1-C_4)$ 烷基所取代；

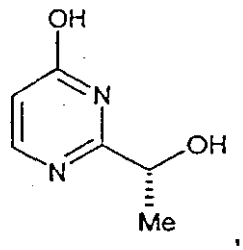
$R^{101}$ 是氢或适宜的胺保护基。

一组优选的式 ZZZ 化合物（称为 AC 组）是其中 $R^{100}$ 是 $(C_1-C_4)$ 烷基并且 $R^{101}$ 是苄基或叔丁氧基羰基的化合物。

AC 组中的一组优选的化合物是其中 $R^{100}$ 是正丁基或乙基并且 $R^{101}$ 是苄基的化合物。

AC 组中的另一组优选的化合物是其中 $R^{100}$ 是正丁基或乙基并且 $R^{101}$ 是叔丁氧羰基的化合物。

本发明还涉及制备式 Z 化合物的方法，




Z

包括：

a）将 R-(+)-2-羟基-丙酰胺与三乙基氧鎓四氟硼酸盐在反应惰性溶剂中于 0℃ 至室温下反应 10 分钟至 24 小时形成相应的亚胺酸酯；

b）将所述亚胺酸酯与无水氨在反应惰性溶剂中于 0℃ 至室温下反应 2 小时至 24 小时形成 R-(+)-2-羟基-丙脒盐酸盐；和

c）将所述 R-(+)-2-羟基-丙脒盐酸盐与 3-羟基-丙烯酸乙酯的钠盐和适宜的碱在反应惰性溶剂中反应形成所述式 Z 的化合物。

本发明还涉及药物组合物，称为组合物 AA，该组合物含有权利要求 1 的化合物、其前药或所述前药或所述化合物的可药用盐和糖原磷酸化酶抑制剂（GPI）、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

本发明还涉及一种药盒，其含有：

a. 在第一单位剂量形式中的权利要求 1 的化合物、其前药或所述前药或所述化合物的可药用盐;

b. 在第二单位剂量形式中的糖原磷酸化酶抑制剂(GPI)、其前药或所述前药或所述 GPI 的可药用盐; 和

c. 容器。

本发明还涉及在哺乳动物中治疗或预防糖尿病并发症的方法，该方法包括，向所述哺乳动物施用组合物 AA 的药物组合物。

本发明还涉及在哺乳动物中治疗高血糖的方法，该方法包括，向所述哺乳动物施用组合物 AA 的药物组合物。

本发明还涉及在患有局部缺血的哺乳动物中治疗局部缺血的方法，该方法包括，向所述哺乳动物施用组合物 AA 的药物组合物。

本发明还涉及在哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用组合物 AA 的药物组合物。

本发明还涉及在哺乳动物中治疗糖尿病并发症的方法，该方法包括，向所述哺乳动物施用式 I 化合物、其前药或所述化合物或所述前药的可药用盐和糖原磷酸化酶抑制剂(GPI)、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

本发明还涉及在哺乳动物中治疗高血糖的方法，该方法包括，向所述哺乳动物施用式 I 化合物、其前药或所述化合物或所述前药的可药用盐和糖原磷酸化酶抑制剂(GPI)、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

本发明还涉及在哺乳动物中治疗局部缺血的方法，该方法包括，向所述哺乳动物施用式 I 化合物、其前药或所述化合物或所述前药的可药用盐和糖原磷酸化酶抑制剂(GPI)、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

本发明还涉及在哺乳动物中治疗糖尿病的方法，该方法包括，向所述哺乳动物施用式 I 化合物、其前药或所述化合物或所述前药的可药用盐和糖原磷酸化酶抑制剂(GPI)、所述 GPI 的前药或所述 GPI 或所述前药的可药用盐。

本发明还包括同位素标记的化合物，这些化合物与式I所述的化合物相同，但有一个或多个原子被原子质量或原子数不同于自然界中常见的原子质量或原子数的原子所代替。可以掺入到本发明化合物中的同位素的例子包括氢、碳、氮、氧、磷、硫、氟和氯的同位素，例如$^{2}H$、$^{3}H$、$^{13}C$、$^{14}C$、$^{15}N$、$^{18}O$、$^{17}O$、$^{31}P$、$^{32}P$、$^{35}S$、$^{18}F$和$^{36}Cl$。含有上述同位素和/或其它原子的其它同位素的本发明化合物、其前药以及所述化合物或所述前药的可药用盐均包括在本发明的范围内。某些同位素标记的本发明化合物，例如掺入了放射性同位素$^{3}H$和$^{14}C$的化合物，可用于药物和/或底物组织分布试验。特别优选氚(即$^{3}H$)和碳-14(即$^{14}C$)同位素，因其易于制备和检测。此外，用较重的同位素例如氘(即$^{2}H$)取代可以因代谢稳定性较大而产生某些治疗上的优点，例如体内半衰期增加或所需剂量减少，因此在某些情况下是优选的。同位素标记的本发明式I化合物及其前药可以按照以下反应方案和/或实施例中描述的方法，通过用易得的同位素标记的试剂代替非同位素标记的试剂进行制备。

术语“减轻”包括部分预防或大于由于不服用化合物或由于服用安慰剂所产生所效果但小于100%的预防以及基本上完全的预防。

文中所用的术语“由于局部缺血引起的损伤”是指与流向组织的血液减少直接相关的病症，它是由于例如血块或向组织供血的血管梗阻所引起的，并且会导致向所述组织运氧量的降低、使组织的性能受到损伤、引起组织机能障碍和/或坏死。或者，当血流或者器管灌注可能在量上是足够的，但血液或器管灌注液的载氧能力有可能下降，例如，在低氧环境中，从而向组织的氧气供给下降，于是出现组织的性能受损、组织机能障碍和/或组织坏死。

文中所用的术语“治疗”包括预防性和减轻性的治疗。

“可药用的”是指载体、稀释剂、赋形剂和/或盐必需与制剂中的其它成分是相容性的，并且对其接受者无害。

术语“前药”是药物的前体，其在给药后可以通过某些化学或生理学的过程在体内释放出药物(例如，前药在生理 pH 环境中或通过酶

的作用转化成所需的药物形式)。

本发明还涉及醛糖还原酶抑制剂和山梨醇脱氢酶抑制剂的交互前药。交互前药是指含有两种活性成分的化合物，在该情况下，两种活性成分是醛糖还原酶抑制剂和山梨醇脱氢酶抑制剂，其在给药后可以裂解释放出两种单独的活性成分。所述醛糖还原酶抑制剂和山梨醇脱氢酶抑制剂的交互前药是在本领域技术人员熟知的常规成酯条件下形成的。

亚烷基是指从末端的碳上各去除了一个氢原子的饱和烃(直链或支链的)。所述基团的例子(假定指明的长度包括了特定的例子)是亚甲基、亚乙基、亚丙基、亚丁基、亚戊基、亚己基、亚庚基。

卤素是指氯、溴、碘或氟。

烷基是指直链的饱和烃或支链的饱和烃。所述烷基的例子(假定指明的长度包括了特定的例子)是甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基、戊基、异戊基、新戊基、叔戊基、1-甲基丁基、2-甲基丁基、3-甲基丁基、己基、异己基、庚基和辛基。

烷氧基是指通过氧连接的直链饱和烷基或支链饱和烷基。所述烷氧基的例子(假定指明的长度包括了特定的例子)是甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基、异丁氧基、叔丁氧基、戊氧基、异戊氧基、新戊氧基、叔戊氧基、己氧基、异己氧基、庚氧基和辛氧基。

应当理解，如果碳环或杂环部分可以与指定的底物通过不同的环原子结合或连接而没有指明具体的连接点时，则所有可能的点均可以连接，无论是碳原子还是例如三价的氮原子。例如，术语“吡啶基”是指 2-、3-或 4-吡啶基，术语“噻吩基”是指 2-或 3-噻吩基，等等。

术语“可药用盐”是指含有阴离子的无毒阴离子盐，例如(但不仅限于)氯化物、溴化物、碘化物、硫酸盐、硫酸氢盐、磷酸盐、乙酸盐、马来酸盐、富马酸盐、草酸盐、乳酸盐、酒石酸盐、葡萄糖酸盐、甲磺酸盐和 4-甲苯磺酸盐。当存在一个以上的碱性部分时，该术语还包括多盐(例如二盐)。该术语还指无毒的阳离子盐例如(但不仅限

于)钠盐、钾盐、钙盐、镁盐、铵盐或质子化的苯乍生(N,N'-二苄基乙二胺)、胆碱、乙醇胺、二乙醇胺、乙二胺、葡甲胺(N-甲基-葡糖胺)、苄乙胺(N-苄基苯乙胺)、哌嗪或氨丁三醇(2-氨基-2-羟甲基-1,3-丙二醇)的盐。

文中所用术语“反应惰性的溶剂”和“惰性溶剂”是指不会与原料、试剂、中间体或产物以会对所需产物的收率产生不利影响的方式相互作用的溶剂或溶剂的混合物。

普通的化学工作者可以理解，本发明的某些式 I 化合物含有一个或多个具有特定的立体化学或几何构型的原子，从而形成了立体异构体和构型异构体。所有这些异构体及其混合物均包括在本发明的范围内。式 I 化合物可以是手性的。在该情况下，优选其中的 $R^1$ 具有 R 构型的异构体。本发明还包括本发明式 I 化合物的水合物。

本领域的普通化学工作者可以理解，本发明的某些式 I 化合物可以以互变异构体的形式存在，也就是说，在彼此之间处于快速平衡的两种异构体之间存在着平衡。互变异构的一个常见的例子是酮-烯醇互变异构，即

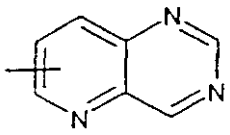



可以以互变异构体形式存在的化合物的例子包括羟基吡啶、羟基嘧啶和羟基喹啉化合物。其它例子是本领域技术人员可以确定的。所有互变异构体及其混合物均包括在本发明的范围内。

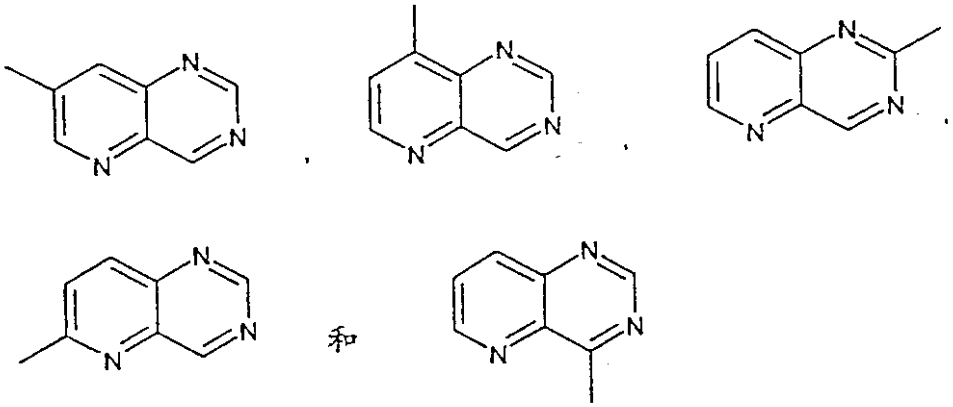
DMF 是指 N,N-二甲基甲酰胺。DMSO 是指二甲亚砜。THF 是指四氢呋喃。

当所示的环状基团的结构带有从环外划到环内的键时，本领域技术人员应当理解，该键可以连接在具有结合位点的环的任何原子上。如果环状基团是二环或三环基团，则该键可以连接在具有结合位点的

任何环的任何原子上。例如，



表示下列基团之一或全部：

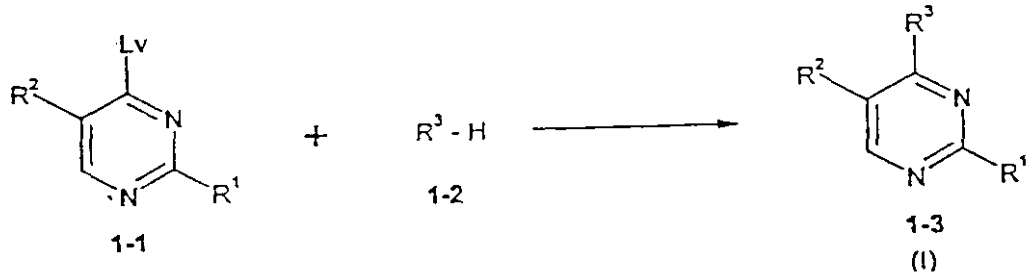


从本发明的说明书和权利要求书可以清楚地看出其它特点和优点。

## 发明详述

本发明的式 I 化合物可以按照本文中的描述，通过包括化学领域中的已知方法在内的方法来制备。某些生产本发明式 I 化合物的方法构成了本发明的另一些特征，并在如下反应方案中进行了说明。其它方法在实验部分进行了描述。

反应方案 1




式 1-3 (即，式 I)化合物按照反应方案 1 中的描述制备，具体描述如下。

式 1-3 的化合物通过式 1-1 的嘧啶的置换反应来制备，其中 $R^1$ 和 $R^2$ 如文中所定义。 Lv 是离去基，优选选自氟、氯、溴、碘、甲硫基、甲砜或 $OSO_2J$，其中 J 是($C_1$-$C_6$)-低级烷基、三氟甲基、五氟乙基、选择性地被最多 3 个($C_1$-$C_4$)烷基、硝基或卤素取代的苯基。离去基 Lv 被式 1-2 的胺置换，其中 $R^3$ 如上所定义。反应在无水碱的存在下进行，优选有机胺或无机碱。优选的有机胺包括三乙胺、吡啶、二甲氨基吡啶和 N,N'-二异丙基乙基胺(Hunig's 碱)。优选的无机碱包括碱金属碳酸盐和碳酸氢盐，例如碳酸钠或碳酸钾和碳酸氢钠或碳酸氢钾。特别优选的无机碱是碳酸钾。特别优选的有机胺是三乙胺。或者，可以使用过量的反应物胺 1-2 作为该反应的碱。反应可以在不含溶剂的条件下进行，或在反应惰性溶剂中进行。本文中所用的“反应惰性溶剂”是指不会与原料、试剂、中间体或产物以会对所需产物的收率产生不利影响的方式相互作用的溶剂。优选的反应惰性溶剂包括含水溶媒、吡啶、($C_1$-$C_4$)醇、($C_2$-$C_6$)二醇、卤化碳、脂肪族/芳香族烃、醚类溶剂、极性非质子溶剂、酮类溶剂或其混合物。反应时间为 15 分钟至 3 天，反应温度为 0℃至 180℃。通常，反应可以在所用溶剂的回流温度下进行。反应优选在常压下进行。本文中所用的术语常压是指进行反应的室内的压力。本文中所用的术语室温是指进行反应的室内的温度。

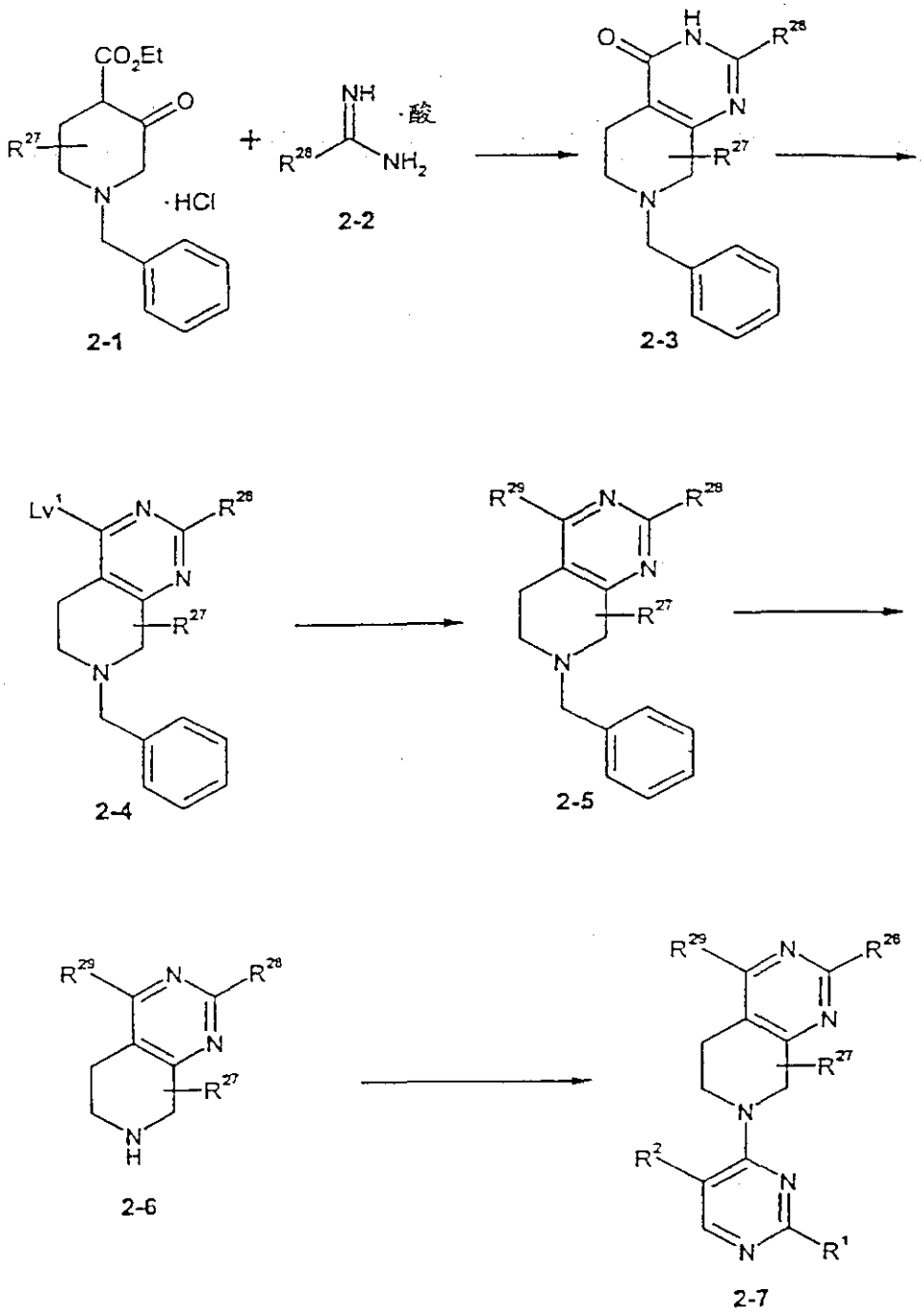
当 $R^1$ 含有羟基时，该羟基可以是保护或未保护的。当羟基是保护的时，保护基可以是任何适宜的羟基保护基。用于除去式 1-3 化合物中的 $R^1$ 所含的选择性的羟基保护基的条件如下。当保护基是酯时，所述酯保护基的脱除用无机氢氧化物或碳酸盐在碱性条件下进行，优选氢氧化锂、氢氧化钠、氢氧化钾或碳酸钾。反应在反应惰性溶剂中进行，优选醇类溶剂。特别优选的是甲醇或甲醇与共溶剂例如水、四氢呋喃或二氧六环的混合物。反应时间为 15 分钟至 24 小时，反应温度为 0℃至 100℃或所用溶剂的回流温度。或者，酯裂解可以在酸性条件下完成。优选采用含水的盐酸，通常为 2N 至浓盐酸，可以含或不含共溶剂。当使用共溶剂时，二氧六环或甲醇是优选的。反应时间为 4 小

时至 3 天，反应温度为 0℃至 60℃。

当保护基是烷基醚时，所述烷基醚保护基的脱除用熟知的脱烷基化条件来完成。例如，烷基醚可以通过与三溴化硼或二乙基溴化硼在反应惰性溶剂、优选卤化碳溶剂中反应来裂解。本领域技术人员可以理解，可以用缓冲剂例如三乙胺来完成反应。反应时间为 15 分钟至 24 小时，反应温度为 0℃至 60℃。另外，苄醚保护基可以通过常规的或转移氢解用钯催化剂例如钯碳来除去。氢解反应在常压至 50 psi 的氢气氛下于反应惰性溶剂、优选甲醇中进行。氢源可以是氢气、甲酸铵或三烷基甲酸铵或环己烯。反应温度为室温至所用溶剂的回流温度。反应时间为 15 分钟至 24 小时。

当采用硅烷基醚保护基时，所述硅烷基醚保护基的脱除在酸性条件下进行，优选使用盐酸水溶液例如 1N 至 6N 的盐酸。脱保护可以在共溶剂例如甲醇或四氢呋喃的存在下进行。反应时间为 2 小时至 48 小时，反应温度为 0℃至 100℃。或者，硅烷基醚保护基可以通过氟化物介导的脱保护反应来脱除。在该情况下，脱保护用四丁基氟化铵或各种可以产生氢氟酸的物质之一在反应惰性溶剂中进行。优选使用醚类溶剂例如乙醚、二氧六环或四氢呋喃，特别优选四氢呋喃。反应时间为 2 小时至 48 小时，反应温度为 0℃至所用溶剂的回流温度。脱除上述保护基的其它方法是本领域技术人员熟知的，并且可以参见 Greene, T. W.; Wuts, P. G. M., Protective Groups in Organic Synthesis, 第 2 版; John Wiley & Sons Inc.: New York, 1991。在其中还可以看到其它适宜的羟基保护基及其脱除方法。当 $R^3$ 是 $R^{3k、l、m、n、o、p和q}$ 时，反应方案 I 的方法是优选的。因此，将式 1-2 的化合物与式 1-1 的化合物反应。其中 $R^3$ 是 $R^{3k、l、m、n、o、p或q}$ 的式 1-2 化合物可以购买到，或者可以通过本领域技术人员熟知的方法制备。

反应方案 2




式 2-7 化合物按照反应方案 2 的描述制备，具体描述如下。

当 $R^{27}$ 是 H 时，将 1-苄基-3-氧代-4-哌啶-甲酸乙酯盐酸盐(式 2-1 化合物，可以购买到)与式 2-2 化合物缩合得到式 2-3 的化合物。其

中 $R^{27}$ 不是 H 的式 2-1 化合物可以按照本领域技术人员熟知的方法制备。反应在过量碱的存在下进行，所述的碱包括非水碱、有机胺和无机碱。优选的有机胺包括三乙胺和吡啶。优选的非水碱包括碱金属($C_1$-$C_4$)醇盐。优选的无机碱包括碳酸钾。反应在反应惰性溶剂中进行。优选的该类溶剂包括($C_1$-$C_4$)醇、芳香族或脂肪族烃、极性非质子溶剂、卤化碳和醚类溶剂。($C_1$-$C_4$)醇是特别优选的。反应时间为 2 小时至 3 天。反应温度为室温至所用溶剂的回流温度。反应优选在常压下进行，但也可以在最高 250 psi 的压力下进行。

式 2-4 化合物从式 2-3 化合物通过将式 2-3 化合物转化成活泼的式 2-4 化合物来制备，其中 $Lv^1$ 选自氟、氯、溴、碘、三氟甲磺酸酯、($C_1$-$C_6$)烷基磺酸酯或苯磺酸酯，其中所述的苯基选择性地被最多 3 个($C_1$-$C_4$)烷基、卤素或硝基取代。该反应通过将式 2-3 化合物与氯化试剂例如三氯氧磷和/或五氯化磷反应来完成，生成其中 $Lv^1$ 是氯的式 2-4 化合物。该反应在常压下、在不含溶剂或在反应惰性溶剂、优选卤化碳溶剂中、在室温至 180℃的温度下进行。将所形成的氯化合物用所需的无机酸处理得到其中 $Lv^1$ 是溴或碘的式 2-4 化合物。式 2-4 的磺酸酯通过将式 2-3 化合物与磺酰氯或磺酸酐在有机胺碱、优选三乙胺或吡啶的存在下反应进行制备。在一些情况下可能需要向反应中加入催化剂，这本领域技术人员可以理解的。在这些情况下，优选的催化剂是 4-二甲氨基吡啶。该反应在常压下在反应惰性溶剂中进行，所述溶剂优选吡啶、卤化碳例如氯仿、二氯甲烷或四氯化碳、芳香族或脂肪族烃、醚类溶剂或其混合物。反应温度为-20℃至 100℃，反应时间为 15 分钟至 1 天。

其中的 $R^{29}$ 如上所定义的式 2-5 化合物从式 2-4 化合物通过还原反应或通过将 $Lv^1$ 用亲核试剂置换来制备。还原反应用还原剂在反应惰性溶剂中进行，所述还原剂优选甲酸铵或氢气。还原反应在钯催化剂的存在下在常压或在最高 50 psi 的氢气压力下进行。优选的溶剂包括($C_1$-$C_4$)醇例如甲醇和乙醇、醚类溶剂例如乙醚、二氧六环和四氢呋喃。亲核置换反应可以通过直接加入亲核试剂或者预先从亲核试剂的

前体另外或就地形成亲核试剂来进行。优选的亲核试剂包括有机铝、有机硼、有机铜、有机锡、有机锌或格氏试剂；$R^{29}$-H；或者，当 $R^{29}$ 含有羟基或巯基时，$R^{29}$ 的阴离子。术语有机铝、有机硼、有机铜、有机锡和有机锌中的术语“有机”是指选自 $R^{29}$ 的有机基团。本领域技术人员可以理解，可能需要过渡金属催化剂来完成某些置换反应。当需要时，所述过渡金属催化剂可以包括钯(0)、钯(II)、镍(0)和镍(II)配合物。二(二苯基膦基丁烷)二氯化钯(II)是优选的这种类型的催化剂。另外，在置换反应中可能还需要含水或非水的碱。优选的碱包括碳酸钠、氢化钠、三乙胺和叔丁醇钠。反应在常压下在反应惰性溶剂例如卤化碳、芳香族或脂肪族烃、醚或极性非质子溶剂或其混合物中进行。在某些情况下，优选使用($C_1$-$C_4$)醇作为溶剂或共溶剂。反应温度为-20℃至所用溶剂的回流温度。反应时间为 1 小时至 3 天。

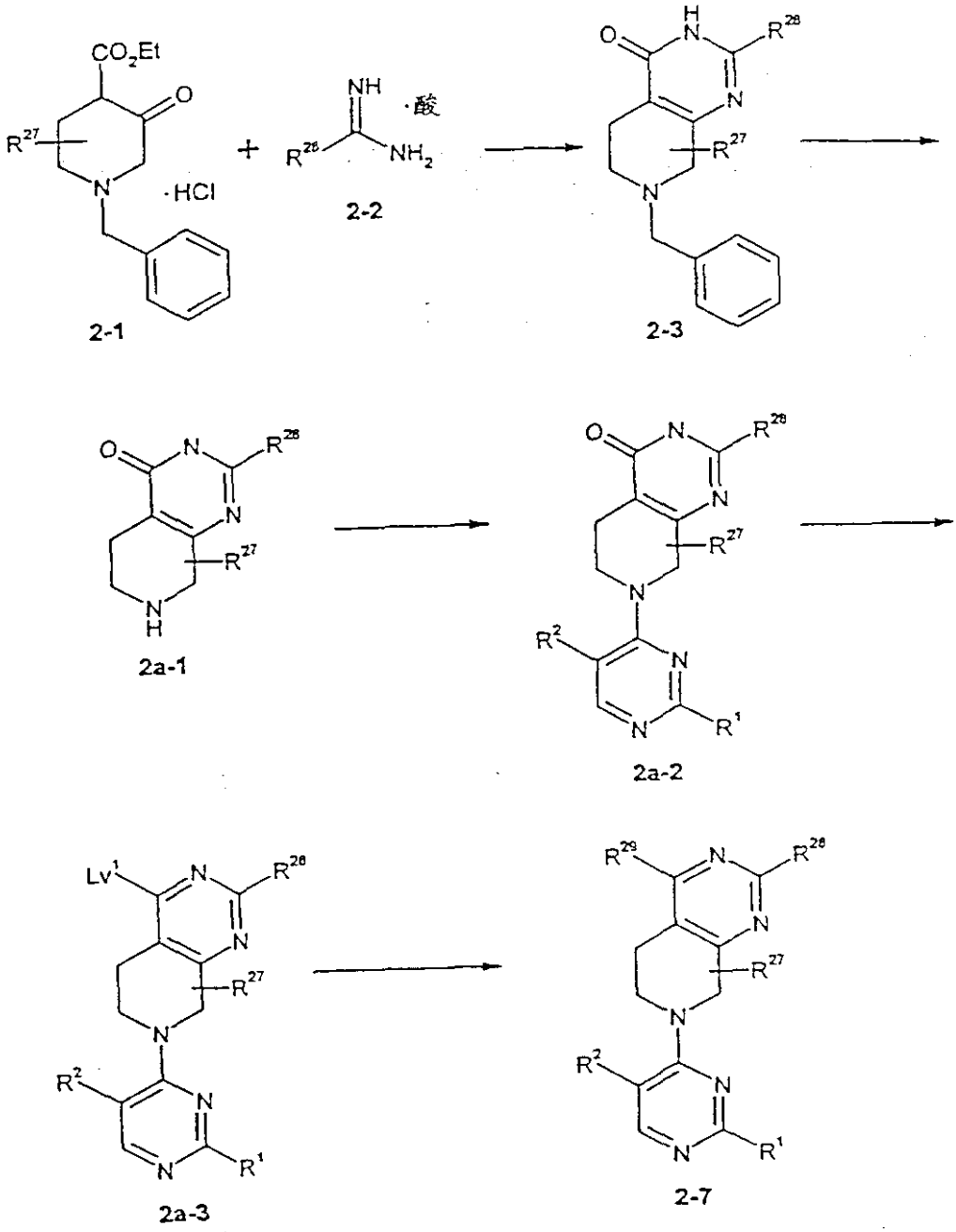
式 2-6 化合物通过从式 2-3 或 2-5 化合物脱除苄基保护基来制备。该转化用游离碱或者优选用预先形成的盐酸盐或类似的盐在常规或转移氢解条件下完成。可用于氢解反应的催化剂包括但不仅限于，钯碳、氢氧化钯/碳和氧化铂(IV)。反应在反应惰性溶剂、优选甲醇或乙醇中进行，反应温度为室温至所用溶剂的回流温度。氢源是氢气、甲酸铵、三烷基甲酸铵或环己烯。反应时间为 15 分钟至 3 天。通常，反应在常压下进行，但也可以采用最高 50 psi 的氢气压力。或者，如需要，可将苄基保护基通过氯甲酸酯引发的酰化脱烷基化反应分两步脱除。该方法包括，与氯甲酸酯衍生物反应生成氨基甲酸酯，然后将氨基甲酸酯裂解。尽管该反应优选用氯甲酸 1-氯乙酯在碘化钠的催化下进行，但本领域技术人员可以理解，在某些情况下可以不用催化。反应在室温下在反应惰性溶剂例如卤化碳、芳香族或脂肪族烃、酮、醚或极性非质子溶剂中进行。反应温度为-78℃至所用溶剂的回流温度，反应时间为 15 分钟至 1 天。通过与氯甲酸 1-氯乙酯反应形成的氨基甲酸酯的裂解可以通过与甲醇或乙醇在在常压下接触来完成，生成盐酸盐形式的式 2-6 化合物。反应在室温至所用溶剂的回流温度下进行，反应时间为 15 分钟至 1 天。其它氨基甲酸酯的脱保护条

件可以参见 Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 第 2 版; John Wiley & Sons Inc.: New York, 1991, 315-348 页。

式 2-7 化合物通过胺 2-6 的置换反应按照反应方案 1 的描述制备，其中胺 2-6 相当于 $R^3$-NH。

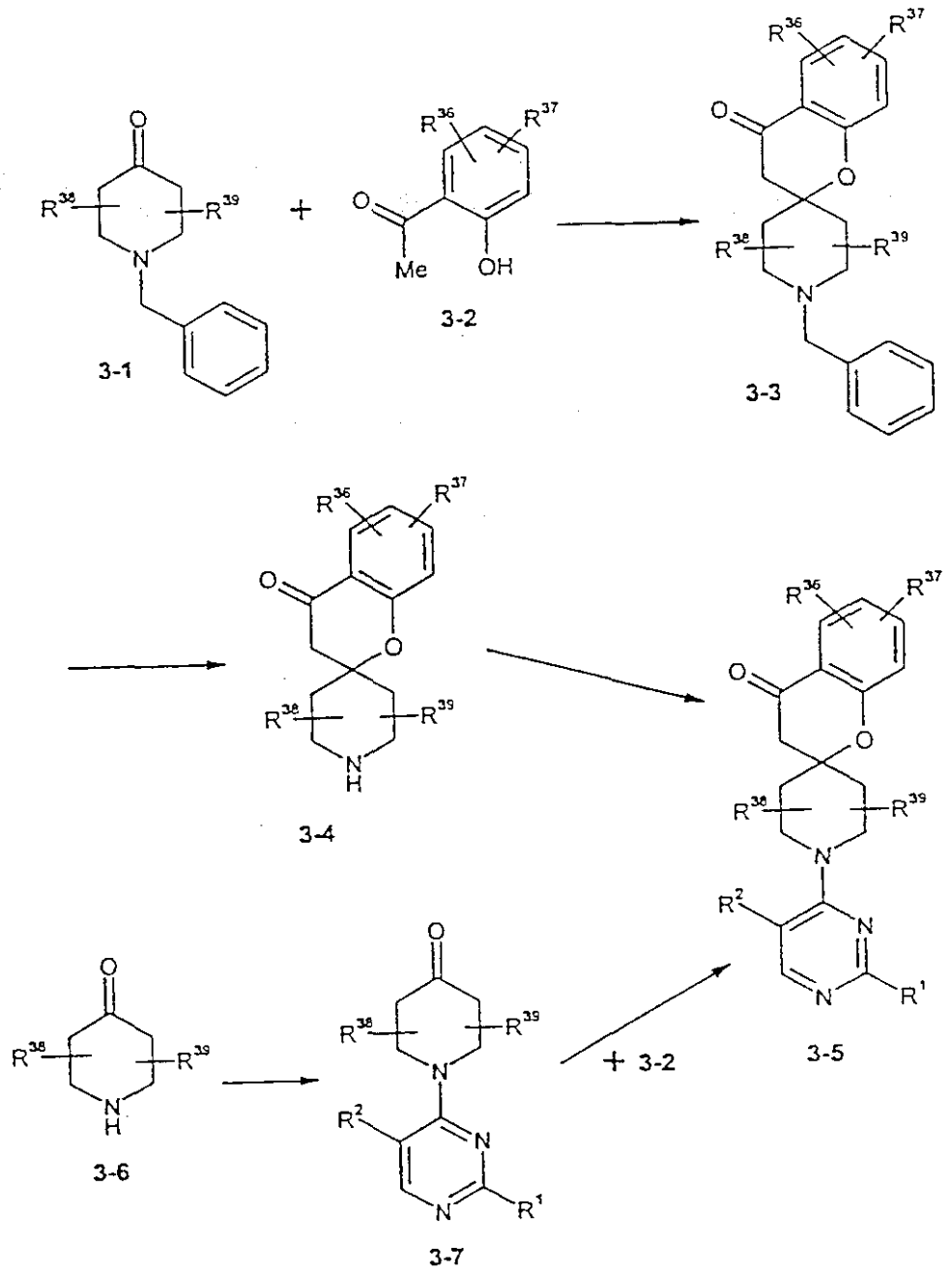
或者，其中的 $R^{29}$ 如上所定义的式 2-7 化合物可以从其中 $R^{29}$ 是 OH 的式 2-3 化合物按照如下反应方案 2a 中所述的顺序制备，其中的条件如反应方案 2 中所述。

反应方案 2a




以上反应方案 2 和 2a 中所用的式 2-2 化合物可以购买到，或者可以按照本领域技术人员熟知的方法制备，例如 March, J. Advanced Organic Chemistry, 第 3 版; John Wiley & Sons.: New York, 1985, p 359, 374 中描述的方法。

反应方案 3




式 3-5 化合物按照以上反应方案 3 的描述制备，具体描述如下。

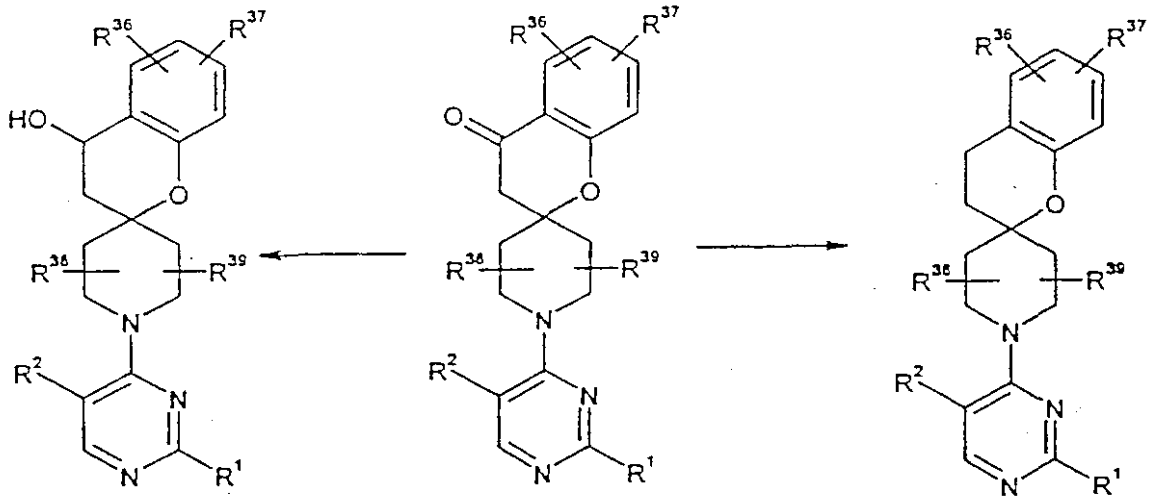
式 3-3 化合物通过将式 3-1 化合物与式 3-2 化合物缩合进行制备。当 $R^{38}$ 和 $R^{39}$ 均是 H 时，式 3-1 化合物是 1-苄基-4-哌啶酮，该化合物可从 Aldrich 购买到。式 3-2 化合物可以购买到，或者可以按照本领域技术人员熟知的方法制备，特别是按照 March, J. Advanced Organic Chemistry, 第 3 版; John Wiley & Sons Inc.: New York, 1985, 499-500 页中描述的方法制备。反应在常压下、在仲胺

的存在下进行。通常使用过量的仲胺，优选吡咯烷、哌啶、吗啉或二乙胺。特别优选的仲胺是吡咯烷。反应在反应惰性溶剂、优选($C_1$-$C_4$)醇、芳香族或脂肪族烃、极性非质子溶剂、卤化碳或醚中进行。特别优选的溶剂是乙醇。反应时间为 2 小时至 3 天，反应温度为室温至所用溶剂的回流温度。

式 3-4 化合物通过从式 3-3 化合物上脱除苄基保护基进行制备。该转化通过与以上制备式 2-6 化合物所述相似的方式进行。

式 3-5 化合物通过胺 3-4 的置换反应按照反应方案 1 的描述制备，其中胺 3-4 相当于 $R^3$-NH。

反应方案 3a

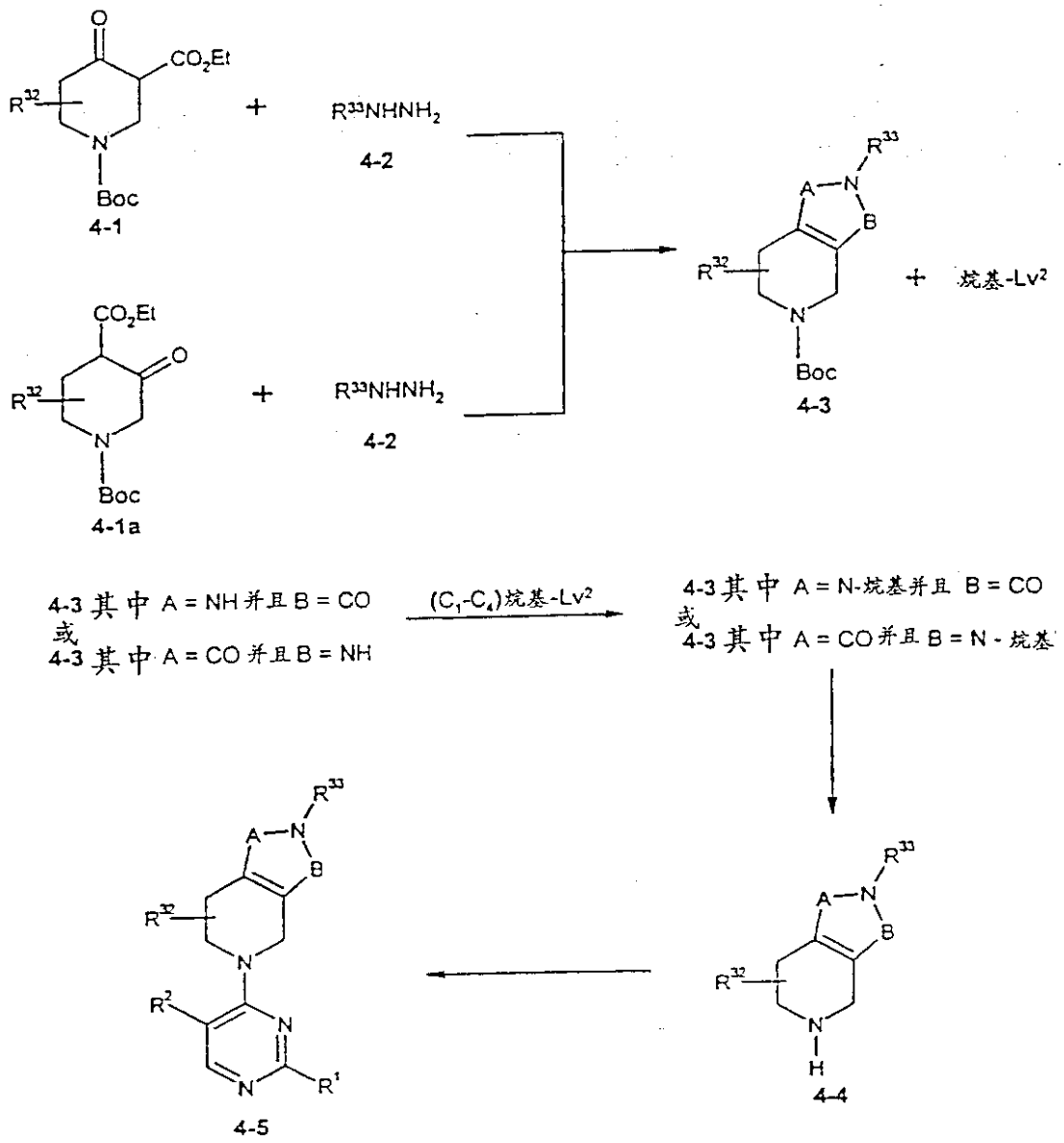



式 3a-1 和 3a-2 的化合物按照反应方案 3a 所示从式 3-5 化合物制备。因此，为了制备化合物 3a-1，将式 3-5 化合物用常用的还原剂例如硼氢化钠、氢化锂铝或二异丁基氢化铝还原。可将酮还原成醇的其它还原剂是本领域技术人员熟知的（例如 Larock, R. D. Comprehensive Organic Transformations, VCH Publishers, Inc.: New York, 1989, pp 527-547）。类似的，式 3a-2 化合物从式 3-5 化合物通过用能够将酮彻底还原成亚甲基的还原剂还原来制备。优选的该类型的还原剂是三氯化铝/硼烷-叔丁基胺复合物。该类

型的其它还原剂是本领域技术人员熟知的(例如 J. Org. Chem. 1989, 54, 4350; Larock, R. D. Comprehensive Organic Transformations, VCH Publishers, Inc.: New York, 1989, pp 35-37)。本领域技术人员可以理解，3-5 向 3a-1 或 3a-2 的转化可以在反应方案 3 中的不同位置来进行，这取决于特定系统的动力学。

或者，其中的 $R^{38}$ 和 $R^{39}$ 是氢的式 3-5 化合物可以从 4-哌啶酮一水合物一氯化物按照与反应方案 1 中所述的方法类似的方式制备，其中的胺 3-6 相当于 $R^3$-NH，反应生成式 3-7 化合物。将式 3-7 化合物与式 3-2 化合物按照与合成式 3-3 化合物所述所述的方法类似的方式反应生成式 3-5 化合物。

反应方案 4




式 4-5 化合物按照反应方案 4 制备，具体描述如下。

式 4-3 化合物通过将式 4-2 化合物与式 4-1 或 4-1a 化合物反应制备。式 4-1 和 4-1a 的化合物按照本领域技术人员熟知的方法制备。当 $R^{32}$ 是氢时，将 4-氧代-哌啶-1,3-二甲酸 1-叔丁酯 3-乙酯与式 4-2 化合物缩合生成式 4-3 化合物。所述式 4-2 化合物很容易从公知的销售商处获得，或者可以在本领域技术人员熟知的常规条件下合成。从其中 A 是 CO 并且 B 是 NH 的式 4-1 化合物或从其中 A 是 NH 而 B 是 CO 的式 4-1a 化合物制备式 4-3 化合物的优选条件可以参见

March, J. Advanced Organic Chemistry, 第 3 版; John Wiley & Sons Inc.: New York, 1985, 1163 页。反应在常压下在反应惰性溶剂中进行。优选的该类型溶剂包括含水溶媒、($C_1$-$C_4$)醇、冰乙酸、芳香族或脂肪族烃、极性非质子溶剂、卤化碳和醚或其混合物。反应时间为 2 小时至 3 天，反应温度为室温至所用溶剂的回流温度。在某些情况下，可以采用使用含水或非水碱的选择性的第二步骤，这是本领域技术人员可以理解的。该第二步骤在常压下在反应惰性溶剂中进行。优选的该类型溶剂包括含水溶媒、($C_1$-$C_4$)醇、冰乙酸、芳香族或脂肪族烃、极性非质子溶剂、卤化碳和醚或其混合物。反应时间为 2 小时至 3 天，反应温度为室温至所用溶剂的回流温度。

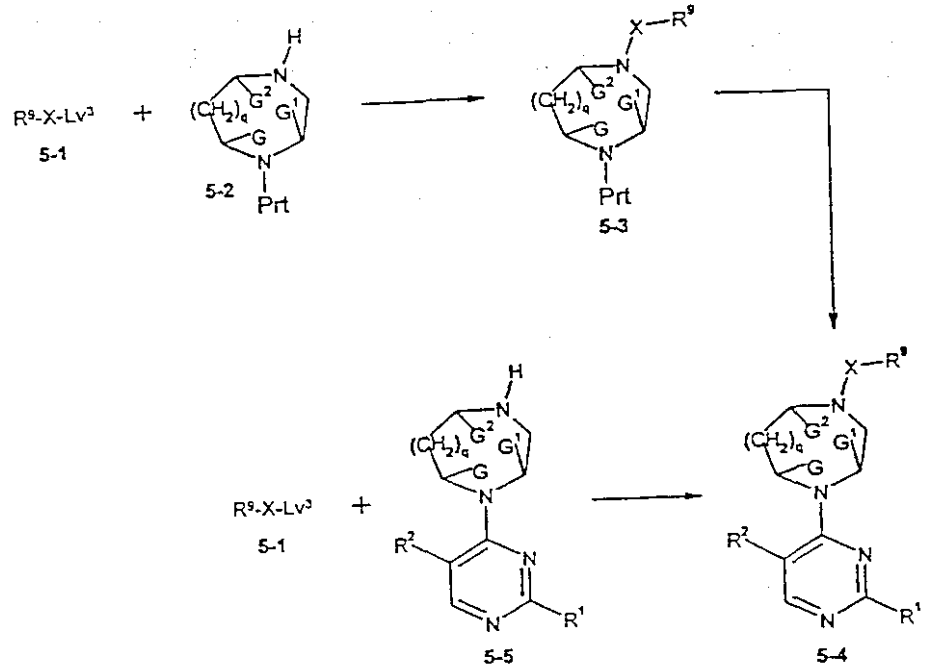
其中 B 是 CO 并且 A 是 N-烷基或者其中 B 是 N-烷基而 A 是 CO 的式 4-3 化合物通过将其中 B 是 CO 并且 A 是 NH 或者其中 B 是 NH 而 A 是 CO 的式 4-3 化合物烷基化制得。这些式 4-3 化合物的阴离子通过与适宜的碱反应生成。优选的该类型的碱包括氢化钠和六甲基乙硅氮烷基钠，但在条件许可时也可以使用其它的碱，这可由本领域技术人员确定。反应在反应惰性溶剂、优选醚例如四氢呋喃、乙醚、二氧六环或二甘醇二甲醚或极性非质子溶剂例如二甲基甲酰胺中进行 。反应在常压和-100℃至室温的温度下进行。反应时间为 10 分钟至 2 小时。($C_1$-$C_4$)烷基卤化物或($C_1$-$C_4$)烷基磺酸酯例如甲磺酸酯、甲苯磺酸酯或 nosylate 对 4-3 的阴离子的加成反应在常压和-20℃至 50℃的温度下进行。反应时间为 10 分钟至 1 天。

式 4-4 化合物可从其中 A 是 N-烷基并且 B 是 CO 或者其中 A 是 CO 而 B 是 N-烷基的式 4-3 化合物通过酸催化的 Boc 氨基甲酸酯脱保护在常规条件下制备，例如用盐酸或三氟乙酸在反应惰性溶剂中或在不含溶剂的条件下制备。所述条件是本领域技术人员熟知的。示范性的条件公开于 Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 第 2 版; John Wiley & Sons Inc.: New York, 1991, pp 327-330.

式 4-5 化合物通过胺 4-4 的置换反应按照反应方案 1 的描述制

备，其中胺 4-4 相当于 $R^3$-H。

反应方案 5




其中 X 是共价键并且 G、$G^1$、$G^2$、q、$R^1$、$R^2$、$R^6$、$R^7$和 $R^8$如上所定义的式 5-4 化合物按照以上反应方案 5 制备，具体描述如下。

式 5-3 化合物通过将式 5-1 化合物与式 5-2 化合物反应进行制备，其中 Prt 是选自苄基和 $CO_2R^{90}$的选择性的胺保护基，其中 $R^{90}$选自 $(C_1-C_4)$烷基、$(C_1-C_4)$烯丙基、三氯乙基和被最多两个$(C_1-C_4)$烷氧基取代的苄基。其中 $R^9$是 $Ar^1$，$Lv^3$是卤素、$(C_1-C_4)$烷基硫化物、$(C_1-C_4)$烷基砜、三氟甲磺酸酯、$(C_1-C_6)$烷基磺酸酯或苯磺酸酯并且其中的所述苯基选择性地被最多 3 个卤素、硝基或$(C_1-C_4)$烷基取代的式 5-1 化合物可以购买到或者可以按照本领域技术人员熟知的方法制备。例如，为了制备其中 $Lv^3$是氯的式 5-1 化合物，可将式 $Ar^1$-OH 的化合物或其 $Ar^1$-(=O)互变异构体与氯化试剂例如三氯氧磷和/或五氯化磷反应。该氯化反应在常压下，在不含溶剂的条件下或在反应惰性溶剂、优选卤化碳溶剂中、在室温至 180℃的温度下进行。将氯代化合物用所需的无机酸处理得到其中 $Lv^3$是溴或碘的式 5-1 化合物。其中 $Lv^3$是三氟甲磺酸酯、$(C_1-C_6)$烷基磺酸酯或苯磺酸酯的式 5-1 化合物从式

$Ar^1$-OH 的化合物或其 $Ar^1$-(=O)互变异构体通过与磺酰氯或磺酸酐在碱、优选有机胺例如三乙胺、N,N'-二异丙基乙胺、二甲氨基吡啶或吡啶的存在下反应进行制备。本领域技术人员可以理解，在某些情况下可能需要催化剂来完成反应。在这些情况下，优选的催化剂是 4-二甲氨基吡啶。该反应在常压下在反应惰性溶剂例如吡啶、卤化碳、芳香族或脂肪族烃、醚或其混合物中进行。反应温度为-20℃至 100℃，反应时间为 15 分钟至 1 天。其中 $Lv^3$是甲硫基的式 5-1 化合物通过将式 $Ar^1$-SH 的化合物或其 $Ar^1$-(=S)互变异构体与碘甲烷或硫酸二甲酯在无机碱、优选碳酸钾的存在下反应进行制备。该反应在常压下、在反应惰性溶剂、优选醚或极性非质子溶剂中进行。特别优选的极性非质子溶剂是温度在 0℃至 100℃之间的二甲基甲酰胺。其中 $Lv^3$是甲基砜的式 5-1 化合物从其中 $Lv^3$是甲硫基的式 5-1 化合物通过将其按照本领域技术人员熟知的方法氧化进行制备，具体描述参见 March, J. Advanced Organic Chemistry, 第 3 版; John Wiley & Sons.: New York, 1985, 1089-1090 页。

可以购买到的或者可以按照与文献中的方法类似的方法制备的一组代表性的式 5-1 化合物包括 4-氯吡啶(Aldrich, P. O. Box 355, Milwaukee, Wisconsin 53201, USA)、3-氯-6-甲基-哒嗪(Maybridge, c/o Ryan Scientific, 443 Long Point Road, Suite D, Mount Pleasant, South Carolina 29464, USA)、2-氯-吡嗪(Aldrich)、2,6-二氯-吡嗪(Aldrich)、3-氯-2,5-二甲基吡嗪(Aldrich)、2,4-二氯-嘧啶(Aldrich)、4,6-二氯-嘧啶(Aldrich)、4-氯-2-甲基嘧啶(Chem. Ber. 1904, 37, 3641)、4-氯-6-甲基-嘧啶(Chem. Ber. 1899, 32, 2931)、4-氯-2,6-二甲基-嘧啶(J. Am. Chem. Soc. 1946,、68, 1299)、4-氯-2,6-二(三氟甲基)-嘧啶(J. Org. Chem. 1961, 26, 4504)、4-氯-2-甲硫基-嘧啶(Aldrich)、4-氯-2-甲氧基甲基-嘧啶(美国专利 5215990)、1-氯-异喹啉(J. Am. Chem. Soc. 1946,、68,、1299)、2-氯-喹啉(Aldrich)、4-氯-喹唑啉(J. Am. Chem. Soc. 1909, 31, 509)、

2-氯-喹喔啉(美国专利 2537870)、2-氯-3-甲基-喹喔啉(Aldrich)、2,6,7-三氯-喹喔啉(J. Chem. Soc., Chem. Commun. 1956, 4731)、4-氯-蝶啶(J. Chem. Soc., Chem. Commun. 1954, 3832)、7-氯-蝶啶(J. Chem. Soc., Chem. Commun. 1954, 3832)和 6-氯-9H-嘌呤(Aldrich)。其它式 5-1 化合物可以用本领域技术人员熟知的方法或通过与上述参考文献中所述的方法类似的方法制备。

式 5-3 化合物通过式 5-1 化合物与式 5-2 的胺的置换反应进行制备。反应在非水碱的存在下进行，所述非水碱优选有机胺例如吡啶、4-二甲氨基吡啶、三乙胺或 N,N'-二异丙基乙胺；无机碱例如钾或钠的碳酸盐或碳酸氢盐；或碱金属醇盐例如叔丁醇钾。或者，可以使用过量的反应物胺 5-2 代替加入的碱。当离去基 $Lv^3$ 是未活化的时，或者在本领域技术人员可以确定的特殊情况下，可能需要使用过渡金属催化剂例如钯(0)、钯(II)、镍(0)或镍(II)以及含膦的配体例如 2,2'-二(二苯基膦基)-1,1'-二萘基(BINAP)来完成反应。关于该反应的更详细描述可以参见如下参考文献：J. Org. Chem. 1997, 62, 1264; J. Org. Chem. 1997, 62, 1568; SynLett 1997, 329。反应可以在不含溶剂的条件下或在反应惰性溶剂中进行。优选的反应惰性溶剂包括含水溶媒、($C_1$-$C_4$)醇、($C_2$-$C_6$)二醇、卤化碳、脂肪族或芳香族烃、醚、极性非质子溶剂、酮或其混合物。反应时间为 15 分钟至 3 天，反应温度为 0℃至 180℃或所用溶剂的回流温度。反应是优选在常压下进行。

在本领域技术人员可以确定的一些情况下，可能需要将化合物 5-3 的 $Ar^1$ 中存在功能基进行转化以生成式 5-4 化合物。这涉及例如 5-3 中的 $R^9$ 含有芳香族或杂芳族卤化物、($C_1$-$C_4$)烷基磺酸酯或三氟甲磺酸酯的情况。其中 $Ar^1$ 含有最多两个选自卤化物、($C_1$-$C_4$)烷基磺酸酯或三氟甲磺酸酯的取代基的所述式 5-3 化合物可以转化为式 $Ar^1$ 化合物，其中通过还原反应或通过所述卤化物、($C_1$-$C_4$)烷基磺酸酯或三氟甲磺酸酯与亲核试剂的置换反应所述的卤化物、($C_1$-$C_4$)烷基磺酸酯或三氟甲磺酸酯转化成了其它功能基。还原反应用还原剂(优选甲酸铵或

氢气)在反应惰性溶剂中进行。还原在钯催化剂的存在下在常压或最高50psi 的氢气压力下仅。优选的溶剂包括($C_1$-$C_4$)醇例如甲醇和乙醇，以及醚溶剂例如乙醚、二氧六环和四氢呋喃。亲核置换反应可以通过直接加入亲核试剂或者预先从亲核试剂的前体另外或就地形成亲核试剂来进行。优选的亲核试剂包括有机铝、有机硼、有机铜、有机锡、有机锌或格氏试剂；$R^{11}$-氧化物或 $R^{11}$-thioxide；或苯氧基，其中的苯氧基在 $R^{11}$ 的范围内。本领域技术人员可以理解，在某些置换反应中可能需要过渡金属催化剂来完成反应。当需要时，所述过渡金属催化剂可以包括钯(0)、钯(II)、镍(0)和镍(II)配合物。二(二苯基膦基丁烷)二氯化钯(II)是优选的这种类型的催化剂。另外，在置换反应中可能还需要含水或非水的碱。优选的碱包括碳酸钠、氢化钠、三乙胺和叔丁醇钠。反应在常压下在反应惰性溶剂例如卤化碳、芳香族或脂肪族烃、醚或极性非质子溶剂或其混合物中进行。在某些情况下，优选使用($C_1$-$C_4$)醇作为溶剂或共溶剂。反应温度为-20℃至所用溶剂的回流温度。反应时间为 1 小时至 3 天。

可能存在于式 5-3 化合物中的选择性的保护基可以按照以上描述进行脱除，或按照本领域技术人员熟知的方法进行脱除，具体描述参见：Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 第 2 版; John Wiley & Sons Inc.: New York, 1991。

式 5-4 化合物通过胺 5-3 的置换反应按照反应方案 1 的描述制备，其中胺 5-3 相当于 $R^3$-NH。一组代表性的可以购买到或者可以通过文献中的方法制得的式 5-3 的胺包括 1-苯基-哌嗪(Aldrich)、1-吡啶-2-基-哌嗪(Aldrich)、3-哌嗪-1-基-苯并[d]异噁唑(J. Med. Chem. 1986, 29, 359)、3-哌嗪-1-基-苯并[d]异噻唑(J. Med. Chem. 1986, 29, 359)、2-哌嗪-1-基-喹喔啉(J. Med. Chem. 1981, 24, 93)、1-萘-2-基-哌嗪(参见 Tetrahedron Lett. 1994, 35, 7331)和 1-(3,5-二甲基苯基)-哌嗪(参见 Tetrahedron Lett. 1994, 35, 7331)。其它式 5-3 的化合物可以用本领域技术人员熟知

的方法或通过与上述参考文献中描述的方法类似的方法制备。

或者，式 5-4 化合物可以通过将式 5-1 化合物与式 5-5 化合物用以上制备 5-3 所述的条件反应进行制备。式 5-5 化合物可以通过与制备式 1-3 化合物所用的方法类似的方式制备。

其中 X 是氧羰基、亚乙烯基羰基、氧($C_1$-$C_4$)二价烷基羰基、($C_1$-$C_4$)二价烷基羰基、($C_3$-$C_4$)链烯基羰基、硫($C_1$-$C_4$)链烯基羰基、亚乙烯基磺酰基或羰基($C_0$-$C_4$)二价烷基羰基；其中在 X 的定义中的所述氧($C_1$-$C_4$)二价烷基羰基、($C_1$-$C_4$)二价烷基羰基、($C_3$-$C_4$)链烯基羰基和硫($C_3$-$C_4$)链烯基羰基选择性并且彼此独立地被最多两个($C_1$-$C_4$)烷基、苄基或 Ar 取代；在 X 的定义中的所述亚乙烯基磺酰基和所述亚乙烯基羰基选择性并且彼此独立地被最多 3 个($C_1$-$C_4$)烷基、苄基或 Ar 取代的式 5-4 化合物也可以按照以上反应方案 5 制备，其具体描述如下。

其中 X 如上一段中所定义的式 5-4 化合物通过将式 5-5 化合物与其中 $R^9$ 如上所述，X 如上一段中所定义并且 $Lv^3$ 是氯的式 5-1 化合物反应进行制备。反应在无水条件下、在无水碱的存在下进行，所述的碱包括有机胺例如三乙胺、N,N'-二异丙基乙胺和吡啶及其衍生物。反应通常在反应惰性溶剂中进行。优选的溶剂包括卤化碳、脂肪族或芳香族烃、醚、乙酸乙酯、吡啶及其混合物。反应时间为 15 分钟至 24 小时，反应温度为 0℃至 80℃或所用溶剂的回流温度。反应优选在 0℃至室温以及常压下进行。选择性的保护基的脱除按照反应方案 1 中的描述进行。

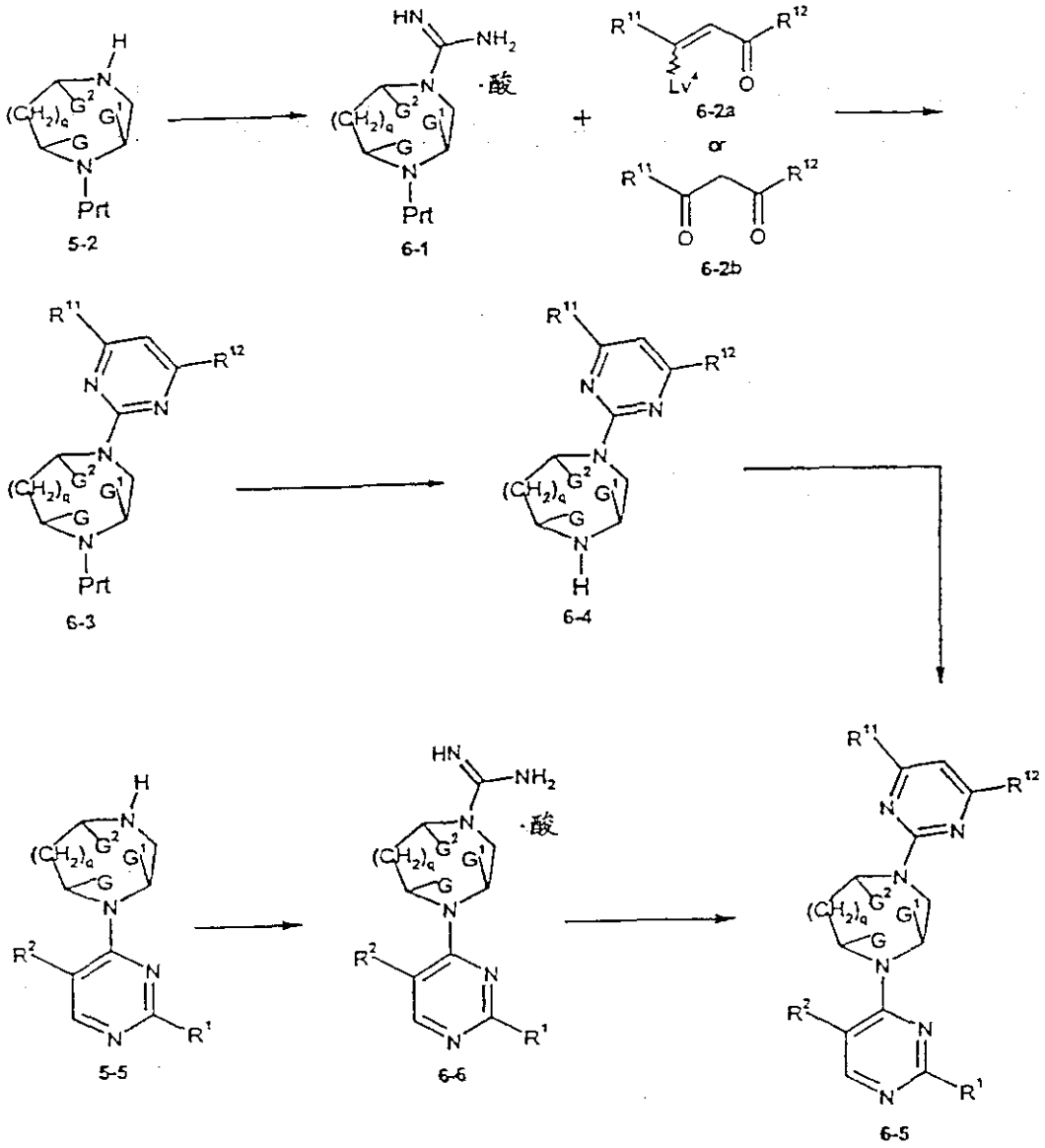
其中 X 是亚乙烯基羰基、氧($C_1$-$C_4$)二价烷基羰基、($C_1$-$C_4$)二价烷基羰基、($C_3$-$C_4$)链烯基羰基、硫($C_2$-$C_4$)链烯基羰基或羰基($C_0$-$C_4$)二价烷基羰基；其中在 X 的定义中的所述氧($C_1$-$C_4$)二价烷基羰基、($C_1$-$C_4$)二价烷基羰基、($C_3$-$C_4$)链烯基羰基和硫($C_2$-$C_4$)链烯基羰基选择性并且彼此独立地被最多两个($C_1$-$C_4$)烷基、苄基或 Ar 取代；在 X 的定义中的所述亚乙烯基羰基选择性并且彼此独立地被最多 3 个($C_1$-$C_4$)烷基、苄基或 Ar 取代的式 5-4 化合物也可以按照以上反应方案 5 制备，其具体描述如下。

式 5-4 化合物通过将式 5-5 化合物与式 $R^9$-X-$Lv^3$ 化合物反应进行制备，其中 $R^9$ 如上所述，X 如前一段所定义，$Lv^3$ 是 OH。反应按照 J. Amer. Chem. Soc. 1996, 118, 4952 的描述在偶联剂的存在下进行，优选二环己基碳二亚胺或 1-(3-二甲氨基丙基)-3-乙基碳二亚胺盐酸盐。反应在反应惰性溶剂中进行。优选的溶剂包括卤化碳、脂肪族或芳香族烃和醚。特别优选的溶剂包括二氯甲烷和氯仿。可以使用的其它偶联剂是本领域技术人员熟知的，其包括但不仅限于，各种膦试剂、氯甲酸乙酯和 N-羟基琥珀酰亚胺。这些试剂和方法记载于“ Compendium of Organic Synthetic Methods ” (I. T. Harrison 和 S. Harrison 编, John Wiley & Sons)。具体的参考文献包括: J. Org. Chem, 1971, 36, 1305; Bull. Soc. Chim. Fr., 1971, 3034; Bull. Chem. Soc. Japan, 1971, 44, 1373; Tetrahedron Lett., 1973, 28, 1595; Tetrahedron Lett., 1971, 26, 2967 和 J. Med. Chem., 1968, 11, 534。选择性的保护基的脱除按照反应方案 1 中的描述进行。

其中 X 是共价键并且 $R^9$ 是($C_3$-$C_7$)环烷基或 $Ar^1$-($C_1$-$C_3$)二价烷基的式 5-4 化合物也可以按照以上反应方案 5 制备，其具体描述如下。

其中 X 是共价键并且 $R^9$ 是($C_3$-$C_7$)环烷基或 $Ar^1$-($C_1$-$C_3$)二价烷基的式 5-4 化合物可以通过将其中 X 是共价键，$R^9$ 是($C_3$-$C_7$)环烷基或 $Ar^1$-($C_1$-$C_3$)二价烷基，$Lv^3$ 是卤素、甲磺酸酯、对甲苯磺酸酯或三氟甲磺酸酯的式 5-1 化合物进行反应制得。反应在无水条件下、在非水碱的存在下进行，所述的碱包括有机胺例如三乙胺、N,N'-二异丙基乙胺和吡啶及其衍生物。反应在反应惰性溶剂中进行。用于该反应的优选的溶剂包括卤化碳、脂肪族或芳香族烃、醚、乙酸乙酯、吡啶及其混合物。反应时间为 15 分钟至 24 小时，反应温度为-20℃至 80℃或所用溶剂的回流温度。反应优选在室温和常压下进行。选择性的保护基的脱除按照反应方案 1 中的描述进行。

反应方案 6




其中 G、$G^1$、$G^2$、q、$R^1$、$R^2$、$R^6$、$R^7$和 $R^8$ 如上所定义的式 6-5 化合物按照以上反应方案 6 的描述进行，具体描述如下。

式 6-1 化合物从式 5-2 的胺制备，其中 Prt 是选自苄基和 $CO_2R^{90}$ 的选择性的胺保护基，其中 $R^{90}$ 选自 $(C_1-C_4)$烷基、$(C_1-C_4)$烯丙基、三氯乙基和被最多两个 $(C_1-C_4)$烷氧基取代的苄基。制备式 6-1 化合物的优选的方法可以参见 Tetrahedron Lett. 1993, 48, 7767 或 J. Org. Chem 1997, 62, 1540。

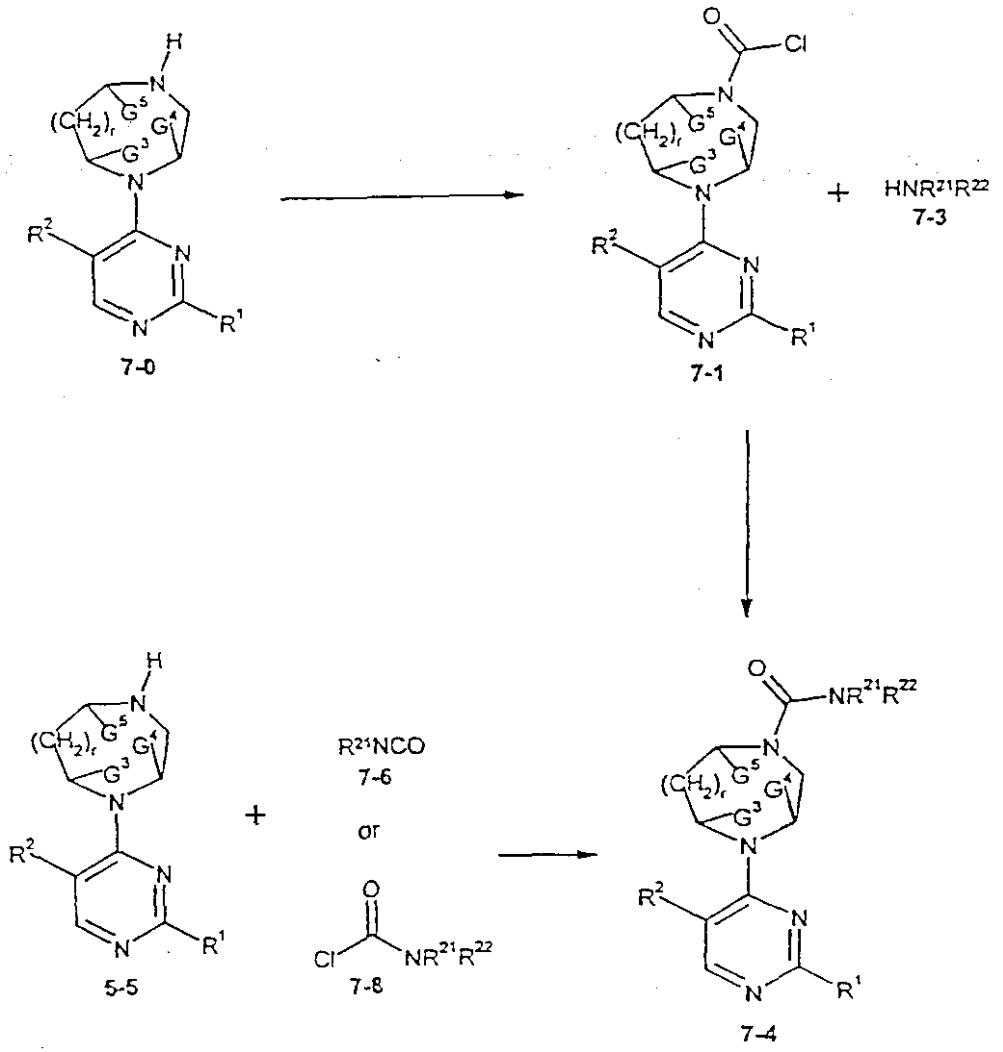
式 6-3 化合物通过将式 6-2b 的β-二酮或β-酮酯(其中 $R^{14}$ 和 $R^{12}$ 彼此独立地按照以上描述被取代)或式 6-2a 的化合物(其中 $Lv^4$ 是，例如羟基、氯或二甲氨基)与式 6-1 的胍缩合进行制备。反应在含水或非水碱、优选氢氧化钾或氢氧化钠、$(C_1-C_4)$-醇钾或醇钠、三乙胺、吡啶、4-二甲氨基吡啶、碳酸钾或碳酸钠或碳酸氢钾或碳酸氢钠的存在下进行。反应在反应惰性溶剂、优选含水溶媒、$(C_1-C_4)$醇、$(C_2-C_6)$二醇、芳香族烃、极性非质子溶剂或其混合物中进行。反应时间为 2 小时至 3 天，反应温度为室温至所用溶剂的回流温度。反应优选在常压下进行，但也可以在最高 250 psi 的压力下进行。

按照以上描述脱除式 6-3 化合物中的选择性的保护基得到式 6-4 化合物。

式 6-5 化合物通过胺 6-4 的置换反应按照反应方案 1 的描述制备，其中胺 6-4 相当于 $R^3$-NH。

或者，式 6-5 化合物可以从式 5-5 化合物通过形成式 6-6 的化合物，或者通过与式 6-2a 或 6-2b 的化合物在以上反应方案 6 所述的条件下反应进行制备。选择性的保护基的脱除按照反应方案 1 的描述进行。式 5-5 化合物按照以上描述制备。

反应方案 7




其中 $G^3$、$G^4$、$G^5$、r、$R^1$、$R^2$、$R^{18}$、$R^{19}$ 和 $R^{20}$ 如上所定义的式 7-4 化合物按照反应方案 7 的描述制备，具体描述如下。

式 7-1 化合物通过将式 7-0 的胺与光气或光气同等物例如三光气反应进行制备。在该反应中也可以使用其中的氯被咪唑基代替了的式 7-1 化合物。该化合物通过将式 7-0 化合物与羰基二咪唑反应制得。反应在无水条件下、在非水碱的存在下进行。优选的该类型的碱包括三乙胺和其它叔胺和吡啶及其衍生物。反应在反应惰性溶剂中、在-78℃至 80℃或所用溶剂的回流温度下进行 15 分钟至 24 小时。用于该反应的优选的溶剂包括卤化碳、脂肪族或芳香族烃、醚、乙酸乙酯、吡

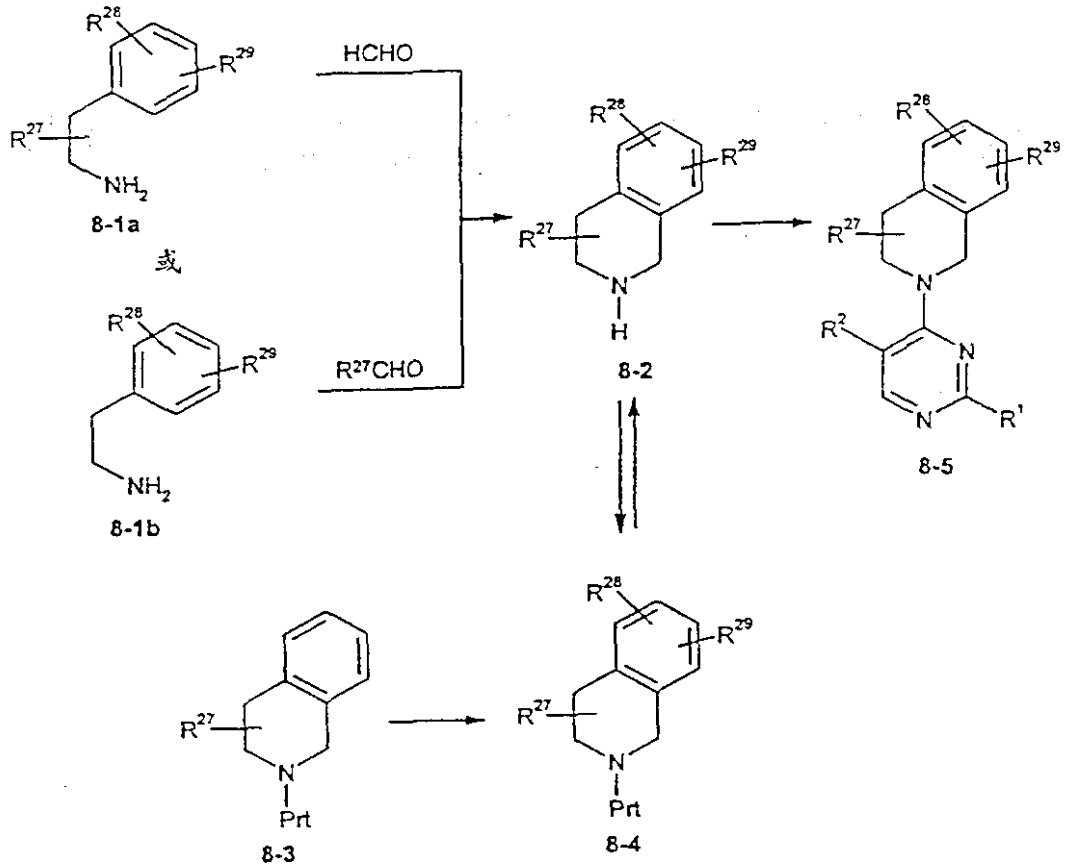
啶及其混合物。反应优选在0℃至室温和常压下进行。

式7-4化合物通过将式7-1的氨基甲酰氯与式7-3的胺反应进行制备，其中 $R^{21}$ 和 $R^{27}$ 如上所定义。反应可以在不含溶剂的条件下进行，或在反应惰性溶剂中进行。优选的溶剂包括含水溶媒、$(C_1-C_4)$醇、$(C_2-C_6)$二醇、芳香族或脂肪族烃、卤化碳、醚、极性非质子溶剂、酮、吡啶或其混合物。反应时间为15分钟至3天，反应温度为0℃至所用溶剂的回流温度。反应优选在常压下进行。本领域技术人员可以理解，可能需要加入碱来完成反应。在这些情况下，优选的碱包括氢氧化钾或氢氧化钠、三乙胺和其它叔胺、吡啶及其衍生物，以及无机碱例如碳酸钠或碳酸钾和碳酸氢钠或碳酸氢钾。$R^1$ 中所含的选择性的羟基保护基的脱除按照反应方案1中所描述的方法进行。

或者，式7-4的化合物可以从式7-0的化合物通过与式7-6的异氰酸酯或式7-8的氨基甲酰氯反应进行制备。所述异氰酸酯是可以购买到的、文献中已知的或是可以在本领域技术人员已知的常规条件下合成的，具体描述参见 March, J. Advanced Oryanic Chemistry, 第3版; John Wiley & Sons Inc.: New York, 1985, 1166页。形成所述异氰酸酯的优选方法是适宜的酰基叠氮的 Curtius 重排。所述氨基甲酰氯用与制备反应方案7中的式7-1化合物所述的类似方法制备。$R^1$ 中所含的选择性的羟基保护基的脱除按照反应方案1中所描述的方法进行。

含有基团 $R^{3c}$ 的式I化合物按照反应方案7中描述的方法用相应的原料和试剂制备。

反应方案 8




式 8-5 化合物按照反应方案 8 的描述制备，具体描述如下。

式 8-2 化合物很容易从式 8-1a 的苯乙胺和甲醛或式 $R^{27}$-CHO 的醛在 Pictet-Spengler 条件下制得。在 Chem. Rev. 1995, 95, 1797 中对 Pictet-Spengler 反应作了综述。也可以采用类似的生成 1,2,3,4-四氢异喹啉的路线，该路线采用 Bischler-Napieralski 反应(参见 March, J. Advanced Organic Chemistry, 第 3 版; John Wiley & Sons.: New York, 1985, 495 中的描述)，随后将形成的亚胺进行常规的还原。

式 8-4 化合物从式 8-3 化合物通过用适宜的亲电试剂进行芳香族亲电取代反应来制备。该类型的反应可以参见 March, J. Advanced Organic Chemistry, 第 3 版; John Wiley & Sons.: New York, 1985, 447-511。

式 8-2 化合物还可以通过脱除保护基从式 8-4 化合物制备。优选

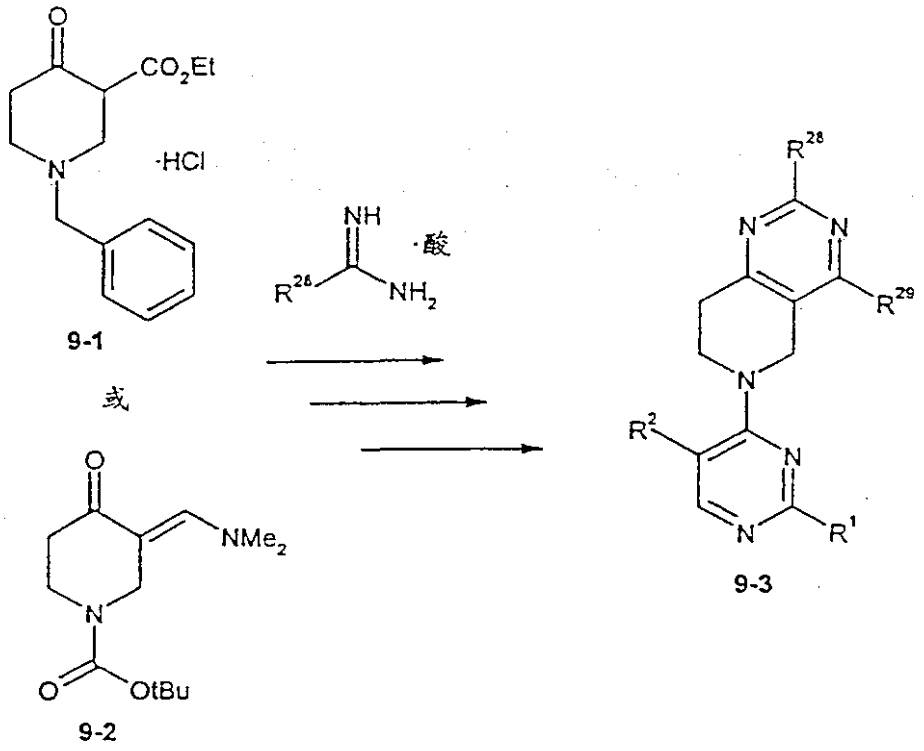
的保护基是三氟乙酰胺，该保护基可以在碱性条件下用无机氢氧化物或碳酸盐反应惰性溶剂中脱除。适宜的溶剂包括($C_1$-$C_4$)醇，优选甲醇。可以选择性地使用一种或多种共溶剂，所述共溶剂优选选自水、四氢呋喃和二氧六环。反应时间为 15 分钟至 24 小时，反应温度为 0℃至 100℃或所用溶剂或溶剂系统的回流温度。反应优选在室温下进行。用于三氟乙酰胺脱保护的其它条件以及其它适宜保护基的脱保护条件可以参见 Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 第 2 版; John Wiley & Sons Inc.: New York, 1991。

式 8-4 化合物通过向式 8-2 的化合物加入保护基进行制备。优选的保护基是三氟乙酰胺或叔丁氧羰基(BOC)。保护基通过将式 8-2 的化合物与三氟乙酰氯或二碳酸二叔丁酯或其等同物在碱、优选三乙胺或哌啶的存在下反应进行连接。反应在反应惰性溶剂中进行。优选的溶剂包括醚例如四氢呋喃、乙醚、二氧六环或二甲氧基乙烷；卤化碳例如二氯甲烷、氯仿或四氯化碳；芳香族或脂肪族烃例如苯、甲苯或己烷。反应时间为 15 分钟至 3 天，反应温度为 0℃至所用溶剂的回流温度。反应优选在常压下进行。用三氟乙酰胺或叔丁氧羰基保护胺的其它条件以及其它适宜的保护基可以参见 Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 第 2 版; John Wiley & Sons Inc.: New York, 1991。

对取代基 $R^{28}$ 和 $R^{29}$ 进行处理以得到具有不同取代的异喹啉化合物。优选采用其中 $R^{23}$ 或 $R^{29}$ 是溴或三氟甲磺酸酯的式 8-4 化合物的过渡金属催化的偶联反应来制备其中 $R^{28}$ 或 $R^{29}$ 如上所述的式 8-4 化合物。该反应按照本领域技术人员熟知的方法进行，具体描述参见 Tetrahedron, 1998, 54, 263 (关于 Stille 和 Suzuki 反应)和 Acc. Chem. Res. 1998, 31, 805 (关于 Buchwald 氨基化反应)。

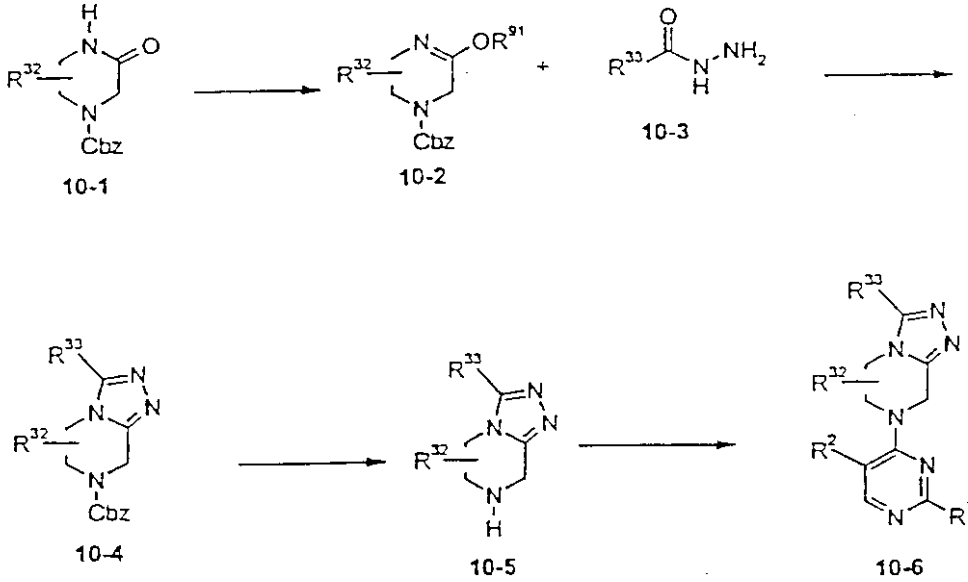
式 8-5 化合物通过胺 8-2 的置换反应按照反应方案 1 的描述制备，其中胺 8-2 相当于 $R^3$-NH。

反应方案 9




式 9-3 化合物按照反应方案 2 中描述的一般方法从 1-苄基-4-氧代-3-哌啶甲酸乙酯盐酸盐(9-1)制备。在某些情况下，当 $R^{29}$ 是 H 时，用 N-叔丁氧羰基-3-(二甲氨基亚甲基)-4-哌啶酮(9-2, Chemical Abstracts 121: 157661)作为原料。

反应方案 10



其中 $R^1$、$R^2$、$R^{32}$和 $R^{33}$如上所定义的式 10-6 化合物按照反应方案 10 的描述制备，更具体的描述如下。

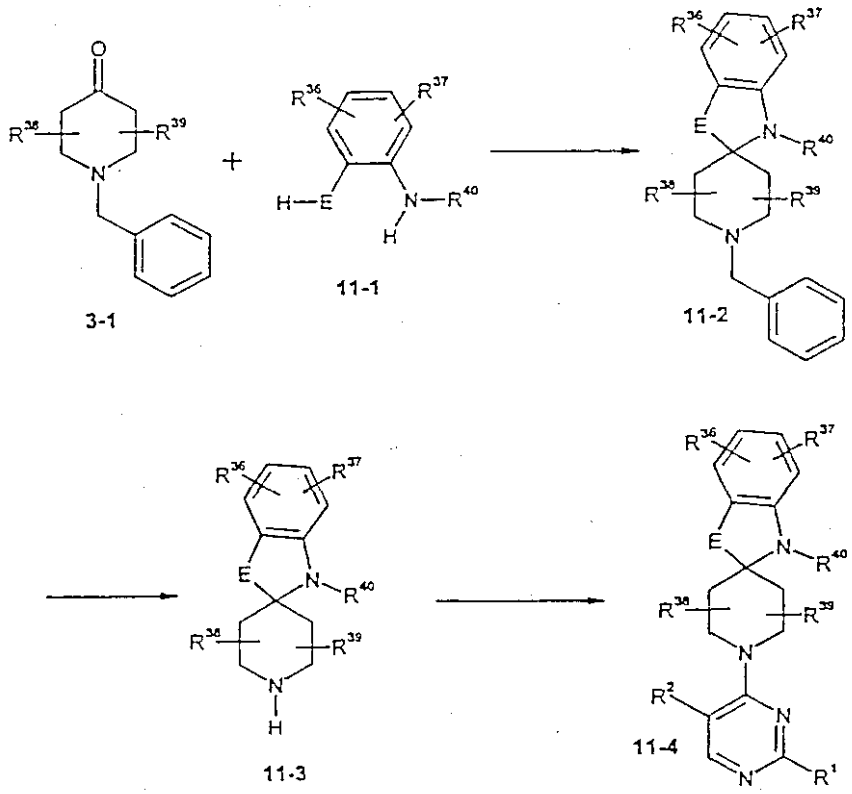
其中 $R^{91}$是($C_1$-$C_4$)烷基的式 10-2 化合物通过将其中 Cbz 是苄氧羰基的式 10-1 化合物与 O-烷基化试剂反应进行制备。优选的式 10-1 化合物是 3-氧代-哌嗪-1-甲酸苄酯。优选的 O-烷基化试剂是三乙基氧鎓四氟硼酸盐。反应在常压下在反应惰性溶剂中进行。优选的溶剂包括芳香族或脂肪族烃、卤化碳和醚。特别优选二氯甲烷。反应时间为 2 小时至 3 天，反应温度为-100℃至室温。

式 10-4 的化合物通过将式 10-2 化合物与式 10-3 化合物缩合进行制备。所述式 10-3 化合物是可购买到的、文献中已知的，或者很容易通过肼和活化的羧酸例如酰氯的常规酰胺化反应制得。该反应是本领域技术人员熟知的。缩合反应优选在常压下进行，但是，如需要，也可以采用最高 250 psi 的较高的压力。反应在反应惰性溶剂中进行，所述溶剂优选选自($C_1$-$C_4$)醇、芳香族或脂肪族烃、极性非质子溶剂、卤化碳和醚或其混合物。反应在室温至 180℃的温度下进行。反应时间为 2 小时至 3 天。

式 10-5 化合物从式 10-4 化合物通过在本领域技术人员熟知的常规条件下的 Cbz 氨基甲酸酯的 Lewis 酸催化裂解或氢解来制备，具体描述参见 Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 第 2 版; John Wiley & Sons Inc.: New York, 1991, 335-338 页。

式 10-6 化合物通过式 10-5 的胺的置换反应按照反应方案 1 的描述制备，其中胺 10-5 相当于 $R^3$-NH。

反应方案 11



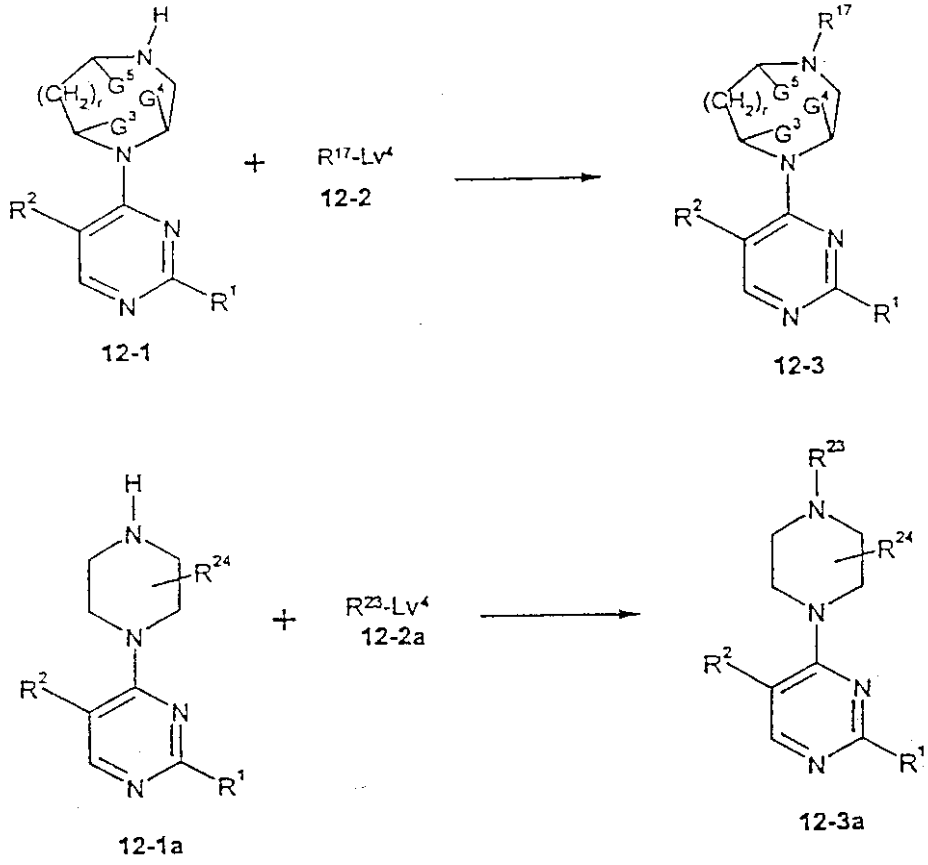

其中 $R^1$、$R^2$、$R^{36}$、$R^{37}$、$R^{38}$、$R^{39}$和 $R^{40}$如上所定义的式 11-4 化合物按照反应方案 11 中的描述制备，更具体的描述如下。

当 $R^{38}$和 $R^{39}$是氢时，将 1-苄基-4-哌啶酮(3-1)(来自 Aldrich)与式 11-1 化合物(可购买到或者是本领域技术人员熟知的)缩合得到式 11-2 化合物。当 $R^{38}$和 $R^{39}$不是氢时，式 3-1 化合物可以按照本领域技术人员熟知的方法制备。反应在常压下、在不含溶剂的条件下或在反应惰性溶剂中进行。优选的溶剂包括($C_1$-$C_4$)醇、芳香族或脂肪族烃、极性非质子溶剂、卤化碳和醚。反应时间为 2 小时至 3 天，反应温度为室温至所用溶剂的回流温度。更具体的条件可以参见 Indian J. Chem. 1976, 14B, 984 和 J. Chem. Soc., Perkin Trans. 1 1984, 2465。

式 11-3 化合物通过按照与以上制备式 2-6 化合物时采用的方法类似的方式从式 11-2 化合物脱除苄基保护基进行制备。

式 11-4 化合物通过式 11-3 的胺的置换反应按照反应方案 1 的描述制备，其中胺 11-3 相当于 $R^3$-NH。

反应方案 12




其中 $R^{17}$ 和 $R^{23}$ 是 $(C_1-C_6)$ 烷氧羰基、$(C_1-C_6)$ 烷基羰基、$Ar^2$-羰基、$(C_1-C_6)$ 烷基磺酰基、$Ar^2$-磺酰基或 $Ar^2$-亚磺酰基的式 12-3 和 12-3a 的化合物按照以上反应方案 12 进行制备，具体描述如下。

其中 $R^{17}$ 和 $R^{23}$ 如上一段所定义的式 12-3 和 12-3a 的化合物分别通过与其中 $Lv^4$ 是氯的式 12-2 和 12-2a 的化合物缩合进行制备。式 12-2 和 12-2a 化合物的例子包括 $(C_1-C_6)$ 烷氧基 COCl、$(C_1-C_6)$ 烷基 COCl、$Ar^2$-COCl、$(C_1-C_6)$ 烷基 $SO_2Cl$、$Ar^2$-$SO_2Cl$ 或 $Ar^2$-SOCl。反应在无水条件下、在非水碱的存在下进行，所述的碱包括有机胺例如三乙胺、N,N'-二异丙基乙胺和吡啶及其衍生物。反应在反应惰性溶剂中进行。用于该反应的优选的溶剂包括卤化碳、脂肪族或芳香族烃、醚、乙酸乙酯、吡啶及其混合物。反应时间为 15 分钟至 24 小时，反应温度为 0℃至 80℃或所用溶剂的回流温度。反应优选在 0℃至室温

以及常压下进行。选择性的保护基的脱除按照反应方案 1 的描述进行。

其中 $R^{17}$和 $R^{23}$是($C_1$-$C_6$)烷基羰基或 $Ar^2$-羰基的式 12-3 和 12-3a 化合物也可以按照以上反应方案 12 进行制备，具体描述如下。

其中 $R^{17}$和 $R^{23}$是($C_1$-$C_6$)烷基羰基或 $Ar^2$-羰基的式 12-3 和 12-3a 化合物通过与其中 $Lv^4$是羟基的式 12-2 或 12-2a 的化合物在偶联剂例如二环己基碳二亚胺或 1-(3-二甲氨基丙基)-3-乙基碳二亚胺盐酸盐的存在下的缩合反应进行制备。反应在反应惰性溶剂中进行。优选的溶剂包括卤化碳、脂肪族/芳香族烃和醚。特别优选的溶剂包括二氯甲烷和氯仿。其它可以使用的偶联剂是本领域技术人员熟知的，其包括但不仅限于，各种膦试剂、氯甲酸乙酯和 N-羟基琥珀酰亚胺。选择性的保护基的脱除按照反应方案 1 中的描述进行。

其中 $R^{17}$是($C_1$-$C_6$)烷基的式 12-3 化合物也可以按照反应方案 12 的描述制备，具体描述如下。

其中 $R^{17}$是($C_1$-$C_6$)烷基的式 12-3 化合物通过将式 12-1 化合物与其中 $R^{17}$是($C_1$-$C_4$)烷基并且 $Lv^4$是 Cl、Br、I、甲磺酰氧基、对-甲苯磺酰氧基或三氟甲磺酰氧基的式 12-2 化合物反应进行制备。反应在无水条件下、在非水碱的存在下进行，所述的碱包括有机胺例如三乙胺、Hunig's 碱和吡啶及其衍生物。反应在反应惰性溶剂中进行。用于该反应的优选的溶剂包括卤化碳、脂肪族或芳香族烃、醚、乙酸乙酯、吡啶及其混合物。反应时间为 15 分钟至 24 小时，反应温度为室温至 80℃或所用溶剂的回流温度。反应优选在室温和常压下进行。

用于上述化合物的原料和反应物也是易得的，或者可由本领域技术人员采用常规的有机合成方法合成。例如，本文中所用的许多化合物与天然化合物有关或者是从天然化合物衍生得到的，这些化合物有很大的科学价值和商业需求，因此许多这样的化合物可以购买到或者在文献中有报道，或者很容易从其它可以获得的物质通过文献中报道的方法制得。

本发明的化合物可以抑制山梨醇脱氢酶的形成，因此可用于治疗

糖尿病并发症，包括但不仅限于糖尿病性肾病、糖尿病神经病、糖尿病性视网膜病、糖尿病性微血管病和糖尿病性大血管病以及糖尿病性心肌病等并发症。本发明的化合物作为药物在哺乳动物(例如人)中治疗疾病(例如本文中详细描述的那些，例如糖尿病并发症如糖尿病性心肌病、糖尿病神经病、糖尿病性肾病、糖尿病性视网膜病、糖尿病性微血管病和糖尿病性大血管病)的用途可以通过本发明式 I 化合物在常规实验中的活性证实。这些实验还提供了将本发明式 I 化合物的活性与其它已知化合物的活性进行比较的方法。这些比较的结果可用于确定在哺乳动物、包括人中治疗所述疾病的剂量水平。

SDH 活性的测量

这些实验使用雄性 Sprague-Dawley 大鼠(350-400g)。通过尾静脉注射链佐星 85mg/kg 在部分大鼠中诱导糖尿病。24 小时后，通过口管饲法向 4 组糖尿病大鼠给予单剂量的本发明式 I 的试验化合物(0.001 至 100mg/kg)。给药 4-6 小时后处死动物并收集血液和坐骨神经。将组织和细胞用 6%高氯酸提取。

通过改良的 R. S. Clements 等的方法(Science, 166: 1007-8, 1969)测定红细胞和神经中的山梨醇。将组织提取液的等分试样加入到试验系统中，系统中各反应物的最终浓度为 0.033M 甘氨酸，pH 9.4，800mM β-烟碱腺嘌呤二核苷酸和 4 单位/mL 山梨醇脱氢酶。室温保温 30 分钟后，在荧光分光光度计上测定样品的荧光，激发光波长 366nm，发射光波长 452nm。减去适当的空白值后，从按照与组织提取液相同的方式处理的山梨醇标准物的线性回归中测定出各样品中山梨醇的量。

通过改良的 M. Ameyama 的方法(Methods in Enzymology, 89: 20-25 (1982))测定果糖。用刃天青代替铁氰化物。将组织提取液的等分试样加入到试验系统中，系统中各反应物的最终浓度为 1.2M 柠檬酸，pH 4.5，13mM 刃天青，3.3 单位/mL 果糖脱氢酶和 0.068% Triton X-100。室温保温 60 分钟后，在荧光分光光度计上测定样品

的荧光，激发光波长 560nm，发射光波长 580nm。减去适当的空白值后，从按照与组织提取液相同的方式处理的果糖标准物的线性回归中测定出各样品中的果糖的量。

通过改良的 U. Gerlach 的方法(Methodology of Enzymatic Analyses, H. U. Bergmeyer 编, 3, 112-117 (1983))测定 SDH 活性。将血清或尿的等分试样加入到试验系统中，系统中各反应物的最终浓度为 0.1M 磷酸钾缓冲液，pH7.4，5mM NAD，20mM 山梨醇和 0.7 单位/mL 山梨醇脱氢酶。室温保温 10 分钟后，于 340nm 下测定样品吸光度的平均改变。SDH 活性用毫 $OD_{340}$ 单位/分钟($OD_{340}$= 340nm 的光密度)表示。

任何醛糖还原酶抑制剂均可作为本发明的第二种化合物(活性物质)用于联合疗法。术语醛糖还原酶抑制剂是指可以抑制由醛糖还原酶催化的葡萄糖向山梨醇的生物转化的化合物。这种抑制作用很容易由本领域技术人员根据常规的试验确定(J. Malone, Diabetes, 29: 861-864, 1980。“红细胞山梨醇，糖尿病控制的指示剂”)。在下文中记载了各种醛糖还原酶抑制剂，其它醛糖还原酶抑制剂是本领域技术人员可以获知的。以下所列的美国专利所公开的内容引入本文作为参考。此外，在括号内记录了通用的化学 USAN 名称或其它命名，以及公开该化合物的适当专利文献。

醛糖还原酶抑制剂在组织中的活性可以通过测定降低组织山梨醇(即，通过阻断醛糖还原酶抑制山梨醇的进一步生产)或降低组织果糖(通过阻断醛糖还原酶抑制山梨醇的生产从而抑制果糖的生产)所需的醛糖还原酶抑制剂的量来确定。虽然不想受到任何具体的理论或机理的束缚，但确信醛糖还原酶抑制剂可以通过抑制醛糖还原酶来预防或减少下文所述的局部缺血性损伤。

因此，可用于本发明的组合物和方法的醛糖还原酶抑制剂的例子包括：

1. 3-(4-溴-2-氟苄基)-3,4-二氢-4-氧代-1-酞嗪乙酸(泊那司他，US 4,251,528)；

2. N-[[(5-三氟甲基)-6-甲氧基-1-萘基]硫代甲基}-N-甲基甘氨酸(托瑞司他, US 4,600,724);

3. 5-[(Z,E)-β-甲基亚肉桂基]-4-氧代-2-硫代-3-噻唑烷乙酸(依帕司他, US 4,464,382, US 4,791,126, US 4,831,045);

4. 3-(4-溴-2-氟苄基)-7-氯-3,4-二氢-2,4-二氧代-1(2H)-喹唑啉乙酸(折那司他, US 4,734,419 和 4,883,800);

5. 2R,4R-6,7-二氯-4-羟基-2-甲基苯并二氢吡喃-4-乙酸(US 4,883,410);

6. 2R,4R-6,7-二氯-6-氟-4-羟基-2-甲基苯并二氢吡喃-4-乙酸(US 4,883,410);

7. 3,4-二氢-2,8-二异丙基-3-氧代-2H-1,4-苯并噁嗪-4-乙酸(US 4,771,050);

8. 3,4-二氢-3-氧代-4-[(4,5,7-三氟-2-苯并噻唑基)甲基]-2H-1,4-苯并噻嗪-2-乙酸(SPR-210, US 5,252,572);

9. N-[3,5-二甲基-4-[(硝基甲基)磺酰基]苯基]-2-甲基-苯乙酰胺(ZD5522, US 5,270,342 和 US 5,430,060);

10. (S)-6-氟螺[苯并二氢吡喃-4,4'-咪唑烷]-2,5'-二酮(索比尼尔, US 4,130,714);

11. d-2-甲基-6-氟-螺(苯并二氢吡喃-4',4'-咪唑烷)-2',5'-二酮(US 4,540,704);

12. 2-氟-螺(9H-芴-9,4'-咪唑烷)-2',5'-二酮(US 4,438,272);

13. 2,7-二氟-螺(9H-芴-9,4'-咪唑烷)-2',5'-二酮(US 4,436,745, US 4,438,272);

14. 2,7-二-氟-5-甲氧基-螺(9H-芴-9,4'-咪唑烷)-2',5'-二酮(US 4,436,745, US 4,438,272);

15. 7-氟-螺(5H-茚并[1,2-b]吡啶-5,3'-吡咯烷)-2',5'-二酮(US 4,436,745, US 4,438,272);

16. d-顺-6'-氯-2,3-二氢-2'-甲基-螺-(咪唑烷-4,4'-4'H-吡

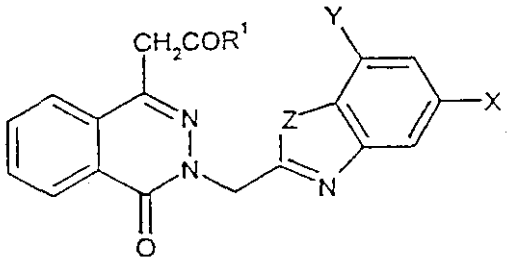
喃并(2,3-b)吡啶)-2,5-二酮(US 4,980,357)；

17. 螺[咪唑烷-4,5'(6H)-喹啉]-2,5-二酮-3'-氯-7,'8'-二氢-7'-甲基-(5'-顺) (US 5,066,659)；

18. (2S,4S)-6-氟-2',5'-二氧代螺(苯并二氢吡喃-4,4'-咪唑烷)-2-甲酰胺(US 5,447,946)；和

19. 2-[(4-溴-2-氟苯基)甲基]-6-氟螺[异喹啉-4(1H),3'-吡咯烷]-1,2',3,5'(2H)-四酮(ARI-509, US 5,037,831)。

其它醛糖还原酶抑制剂包括式ARI的化合物，




ARI

或其可药用盐，其中

式ARI化合物中的Z是O或S；

式ARI化合物中的$R^1$是羟基或是能够在体内脱除而生成其中$R^1$是OH的式ARI化合物的基团；

式ARI化合物中的X和Y相同或不同并且选自氢、三氟甲基、氟和氯。

上述醛糖还原酶抑制剂中的一个优选的亚组包括编号为1、2、3、4、5、6、9、10和17的化合物以及如下式ARI的化合物：

20. 3,4-二氢-3-(5-氟苯并噻唑-2-基甲基)-4-氧代酞嗪-1-基乙酸 [$R^1$= 羟基; X = F; Y = H]；

21. 3-(5,7-二氟苯并噻唑-2-基甲基)-3,4-二氢-4-氧代酞嗪-1-基乙酸 [$R^1$= 羟基; X = Y = F]；

22. 3-(5-氯苯并噻唑-2-基甲基)-3,4-二氢-4-氧代酞嗪-1-基乙酸 [$R^1$= 羟基; X = Cl; Y = H]；

23. 3-(5,7-二氯苯并噻唑-2-基甲基)-3,4-二氢-4-氧代酞嗪-

1-基乙酸[$R^1$= 羟基; X = Y = Cl];

24. 3,4-二氢-4-氧代-3-(5-三氟甲基苯并噁唑-2-基甲基)酞嗪-1-基乙酸 [$R^1$= 羟基; X = $CF_3$; Y = H];

25. 3,4-二氢-3-(5-氟苯并噁唑-2-基甲基)-4-氧代酞嗪-1-基乙酸 [$R^1$= 羟基; X = F; Y = H];

26. 3-(5,7-二氟苯并噁唑-2-基甲基)-3,4-二氢-4-氧代酞嗪-1-基乙酸 [$R^1$= 羟基; X = Y = F];

27. 3-(5-氯苯并噁唑-2-基甲基)-3,4-二氢-4-氧代酞嗪-1-基乙酸 [$R^1$= 羟基; X = Cl; Y = H];

28. 3-(5,7-二氯苯并噁唑-2-基甲基)-3,4-二氢-4-氧代酞嗪-1-基乙酸 [$R^1$= 羟基; X = Y = Cl]; 和

29. 唑泊司他; 1-酞嗪乙酸, 3,4-二氢-4-氧代-3-[[5-(三氟甲基)-2-苯并噻唑基]甲基]- [$R^1$= 羟基; X = 三氟甲基; Y = H]。

在化合物 20-23 和 29 中, Z 是 S。在化合物 24-28 中, Z 是 O。

在上述亚组中, 更优选化合物 20-29, 特别优选 29。

特别优选的醛糖还原酶抑制剂是 1-酞嗪乙酸, 3,4-二氢-4-氧代-3-[[5-(三氟甲基)-2-苯并噻唑基]甲基]-。

术语“羧酸醛糖还原酶抑制剂的酰基”是指含有羧酸基团并且其中的羧酸基团被羰基代替了的上述醛糖还原酶抑制剂。

本发明的醛糖还原酶抑制剂化合物很容易获得, 或者可以由本领域技术人员利用常规的有机合成方法方便地合成, 具体内容可以参见相关的专利说明书。

可以使用对本发明的活性有效量的本发明醛糖还原酶抑制剂。通常, 本发明的醛糖还原酶抑制剂的有效剂量为约 0.1mg/kg/天至 100mg/kg/天单次给药或分多次给药, 优选 0.1mg/kg/天至 20mg/kg/天单次给药或分多次给药。

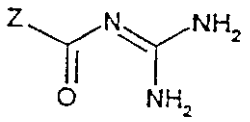
任何钠氢离子交换(NHE-1)抑制剂均可作为本发明的第二种化合物(活性物质)用于联合疗法。术语 NHE-1 抑制剂是指可以抑制钠/质子($Na^+/H^+$)交换转运系统的化合物, 该化合物可用于治疗或预防由于

钠/质子($Na^+/H^+$)交换转运系统的加速所引起或加重的疾病，例如心血管疾病[例如动脉硬化、高血压、心律失常(例如局部缺血性心律失常、由于心肌梗塞引起的心律失常、心肌昏厥、心肌功能障碍、PTCA或溶栓后的心律失常等)、心绞痛、心脏肥大、心肌梗塞、心衰(例如充血性心衰、急性心衰、心脏肥大等)、PTCA、PTCI 后的再狭窄、休克(例如出血性休克、内毒素休克等)]、肾疾病(例如糖尿病、糖尿病性肾病、缺血性急性肾衰等)、与局部缺血或局部缺血再灌注有关的器管疾病[例如与心肌缺血再灌注有关的疾病、急性肾衰或由手术治疗例如冠状动脉旁路移植(CABG)手术、血管手术、器管移植、非心脏的手术或经皮腔内冠状动脉成形术(PTCA)引起的疾病]、脑血管疾病(例如缺血性中风、出血性中风等)、脑缺血疾病(例如与脑梗塞有关的疾病、脑中风后引起的后遗症或脑水肿。NHE-1 抑制剂还可用作冠状动脉旁路移植(CABG)手术、血管手术、经皮腔内冠状动脉成形术(PTCA)、PTCI、器管移植和非心脏的手术过程中的心肌保护剂。NHE-1 抑制剂作为药物在哺乳动物(例如人)中治疗疾病(例如本文中详细描述的疾病，例如在手术过程中的心肌保护或在存在进行性心脏或脑局部缺血事件的患者中的心肌保护或在被诊断为患有冠心病、易患冠心病、心脏功能障碍或心肌昏厥的患者中的长期的心脏保护)的用途可以通过本发明的式 I 化合物在常规的临床前心脏保护试验[参见 Klein, H.等, Circulation 92: 912-917 (1995)中的体内试验; Scholz, W.等, Cardiovascular Research 29: 260-268 (1995)中的离体心脏试验; Yasutake M.等, Am. J. Physiol., 36: H2430-H2440 (1994)中的抗心律失常试验; Kolke 等, J. Thorac. Cardiovasc. Surg. 112: 765-775 (1996)中的 NMR 试验]和以下描述的其它体外和体内试验中的活性来证实。这些实验还提供了将本发明式 I 化合物的活性与其它已知化合物的活性进行比较的方法。这些比较的结果可用于确定在哺乳动物、包括人中治疗所述疾病的剂量水平。

NHE-1 抑制剂公开于美国专利 5,698,581、欧洲专利申请公开号 EP 803501 A1、国际专利申请公开号 WO 94/26709 和

PCT/JP97/04650 中，这些专利申请均引入本文作为参考。这些专利申请中所公开的 NHE-1 抑制剂可用于本发明的联合形式。所述 NHE-1 抑制剂可以按照这些专利申请中的描述进行制备。

优选的 NHE-1 抑制剂包括化合物式 NHE 的化合物，



NHE

其前药或所述化合物或所述前药的可药用盐，其中

式 NHE 化合物中的 Z 是通过碳连接的 5 元、二氮杂、二不饱和环，环中含有两个相邻的氮，所述的环选择性地被最多 3 个彼此独立地选自 $R^1$、$R^2$和 $R^3$的取代基单、二或三取代；

或者

式 NHE 化合物中的 Z 是通过碳连接的 5 元、三氮杂、二不饱和环，所述的环选择性地被最多 2 个彼此独立地选自 $R^4$和 $R^5$的取代基单或二取代；

其中，式 NHE 化合物中的 $R^1$、$R^2$、$R^3$、$R^4$和 $R^5$彼此独立地是氢、羟基-$(C_1-C_4)$烷基、$(C_1-C_4)$烷基、$(C_1-C_4)$烷硫基、$(C_3-C_4)$环烷基、$(C_3-C_7)$环烷基$(C_1-C_4)$烷基、$(C_1-C_4)$烷氧基、$(C_1-C_4)$烷氧基$(C_1-C_4)$烷基、单-N-或二-N,N-$(C_1-C_4)$烷基氨基甲酰基、M 或 M $(C_1-C_4)$烷基，前述的$(C_1-C_4)$烷基部分均选择性地含有 1-9 个氟；所述$(C_1-C_4)$烷基或$(C_3-C_4)$环烷基选择性地被羟基、$(C_1-C_4)$烷氧基、$(C_1-C_4)$烷硫基、$(C_1-C_4)$烷基亚磺酰基、$(C_1-C_4)$烷基磺酰基、$(C_1-C_4)$烷基、单-N-或二-N,N-$(C_1-C_4)$烷基氨基甲酰基或单-N-或二-N,N-$(C_1-C_4)$烷基氨基磺酰基单取代或二取代；并且所述$(C_3-C_4)$环烷基选择性地含有 1-7 个氟；

其中，式 NHE 化合物中的 M 是部分饱和的、完全饱和的或完全不饱和的选择性地含有 1 至 3 个彼此独立地选自氧、硫和氮的杂原子的 5 至 8 元环，或是由两个稠合的部分饱和的、完全饱和的或完全不饱

和的 3 至 6 元环组成的二环，所述 3 至 6 元环彼此独立地选择性地含有 1 至 4 个彼此独立地选自氮、硫和氧的杂原子；

式 NHE 化合物中的所述 M 选择性地在碳或氮上被最多 3 个彼此独立地选自 $R^6$、$R^7$ 和 $R^8$ 的取代基所取代，如果该部分是单环，则在一个环上被取代，如果该部分是二环，则在一个或同时在两个环上被取代，其中，$R^6$、$R^7$ 和 $R^8$ 之一是部分饱和的、完全饱和的或完全不饱和的选择性地含有 1 至 3 个彼此独立地选自氧、硫和氮的杂原子并且选择性地被 $(C_1-C_4)$ 烷基取代的 3 至 7 元环，其它的 $R^6$、$R^7$ 和 $R^8$ 是羟基、硝基、卤素、$(C_1-C_4)$ 烷氧基、$(C_1-C_4)$ 烷氧基羰基、$(C_1-C_4)$ 烷基、甲酰基、$(C_1-C_4)$ 链烷酰基、$(C_1-C_4)$ 链烷酰氧基、$(C_1-C_4)$ 链烷酰氨基、$(C_1-C_4)$ 烷氧羰基氨基、磺酰氨基、$(C_1-C_4)$ 烷基磺酰氨基、氨基、单-N-或二-N,N-$(C_1-C_4)$ 烷基氨基、氨基甲酰基、单-N-或二-N,N-$(C_1-C_4)$ 烷基氨基甲酰基、氰基、巯基、$(C_1-C_4)$ 烷硫基、$(C_1-C_4)$ 烷基亚磺酰基、$(C_1-C_4)$ 烷基磺酰基、单-N-或二-N,N-$(C_1-C_4)$ 烷基氨基磺酰基、$(C_2-C_4)$ 链烯基、$(C_2-C_4)$ 链炔基或 $(C_5-C_7)$ 环烯基，

其中所述的 $(C_1-C_4)$ 烷氧基、$(C_1-C_4)$ 烷基、$(C_1-C_7)$ 链烷酰基、$(C_1-C_4)$ 烷硫基、单-N-或二-N,N-$(C_1-C_4)$ 烷基氨基或 $(C_3-C_7)$ 环烷基 $R^6$、$R^7$ 和 $R^8$ 取代基选择性地被羟基、$(C_1-C_4)$ 烷氧羰基、$(C_3-C_7)$ 环烷基、$(C_1-C_4)$ 链烷酰基、$(C_1-C_4)$ 链烷酰氨基、$(C_1-C_4)$ 链烷酰氧基、$(C_1-C_4)$ 烷氧羰基氨基、磺酰氨基、$(C_1-C_4)$ 烷基磺酰氨基、氨基、单-N-或二-N,N-$(C_1-C_4)$ 烷基氨基、氨基甲酰基、单-N-或二-N,N-$(C_1-C_4)$ 烷基氨基甲酰基、氰基、巯基、硝基、$(C_1-C_4)$ 烷硫基、$(C_1-C_4)$ 烷基亚磺酰基、$(C_1-C_4)$ 烷基磺酰基或单-N-或二-N,N-$(C_1-C_4)$ 烷基氨基磺酰基单取代或选择性地被 1-9 个氟取代。

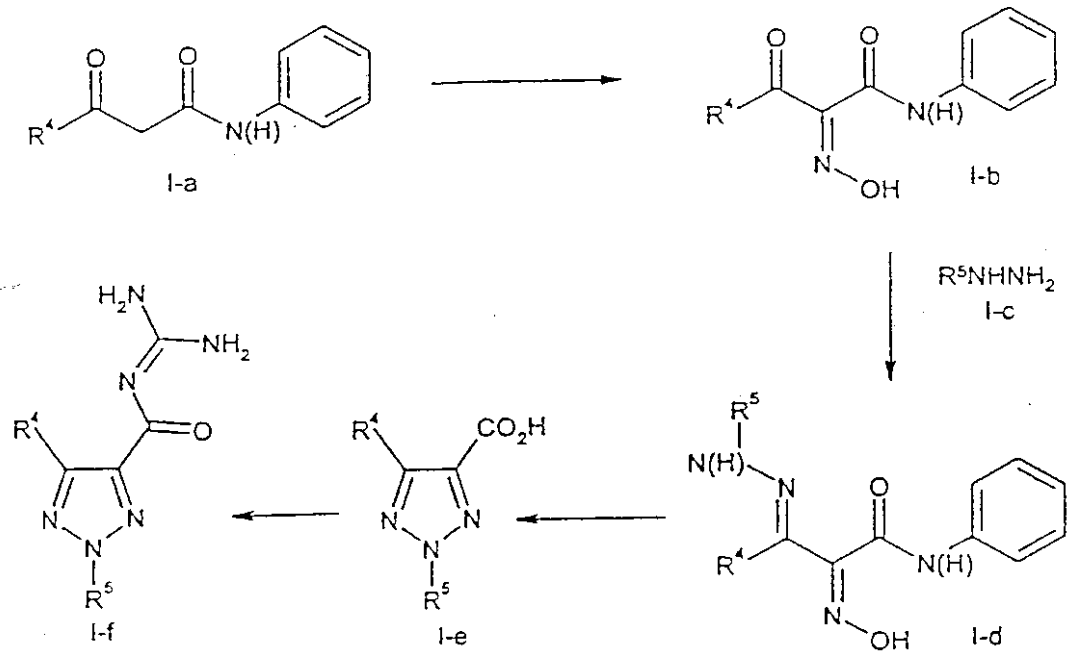
特别优选的 NHE-1 抑制剂包括[1-(8-溴喹啉-5-基)-5-环丙基-1H-吡唑-4-羧基]胍；[1-(6-氯喹啉-5-基)-5-环丙基-1H-吡唑-4-羧基]胍；[1-(吲唑-7-基)-5-环丙基-1H-吡唑-4-羧基]胍；[1-(苯并咪唑-5-基)-5-环丙基-1H-吡唑-4-羧基]胍；[1-(1-异喹啉基)-5-环丙基-1H-吡唑-4-羧基]胍；[5-环丙基-1-(4-喹啉基)-1H-吡唑-4-羧

基]胍；[5-环丙基-1-(喹啉-5-基)-1H-吡唑-4-羰基]胍；[5-环丙基-1-(喹啉-8-基)-1H-吡唑-4-羰基]胍；[1-(吲唑-6-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(吲唑-5-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(苯并咪唑-5-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(1-甲基苯并咪唑-6-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(5-喹啉基)-5-正丙基-1H-吡唑-4 羰基]胍；[1-(5-喹啉基)-5-异丙基-1H-吡唑-4-羰基]胍；[5-乙基-1-(6-喹啉基)-1H-吡唑-4-羰基]胍；[1-(2-甲基苯并咪唑-5-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(1,4-苯并二噁烷-6-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(苯并三唑-5-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(3-氯吲唑-5-基)-5-乙基-1H-吡唑-4-羰基]胍；[1-(5-喹啉基)-5-丁基-1H-吡唑-4-羰基]胍；[5-丙基-1-(6-喹啉基)-1H-吡唑-4-羰基]胍；[5-异丙基-1-(6-喹啉基)-1H-吡唑-4-羰基]胍；[1-(2-氯-4-甲基磺酰基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-三氟甲基-4-氟苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-溴苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氟苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯-5-甲氧基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯-4-甲基氨基磺酰基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2,5-二氯苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2,3-二氯苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯-5-氨基羰基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯-5-氨基磺酰基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氟-6-三氟甲基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯-5-甲基磺酰基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯-5-二甲氨基磺酰基苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-三氟甲基-4-氯苯基)-5-环丙基-1H-吡唑-4-羰基]胍；[1-(2-氯苯基)-5-甲基-1H-吡唑-4-羰基]胍；[5-甲基-1-(2-三氟甲基苯基)-1H-吡唑-4-羰基]胍；[5-乙基-1-苯基-1H-吡唑-4-羰基]胍；[5-环丙基-1-(2-三氟甲基苯基)-1H-吡唑-4-羰基]胍；[5-环丙基-1-苯基-1H-吡唑-4-羰基]胍；[5-环丙基-1-(2,6-二

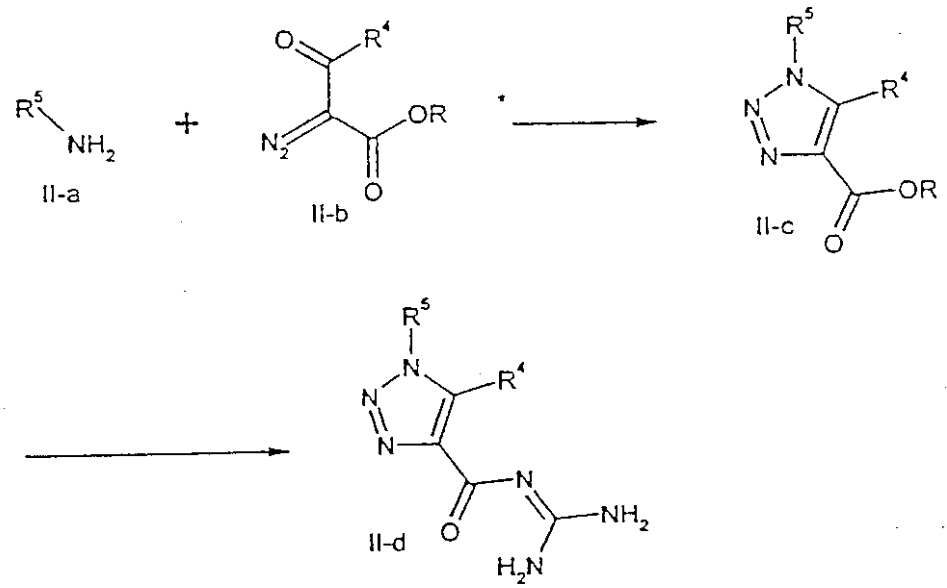
氯苯基)-1H-吡唑-4-羰基]胍或其可药用盐。

在以上两个段落中公开的优选的和特别优选的 NHE-1 抑制剂可以按照国际专利申请号 PCT/IB99/00206 中描述的方法或者按照以下描述进行制备，其中，在以下反应方案和描述中的变量仅指 NHE-1 化合物。

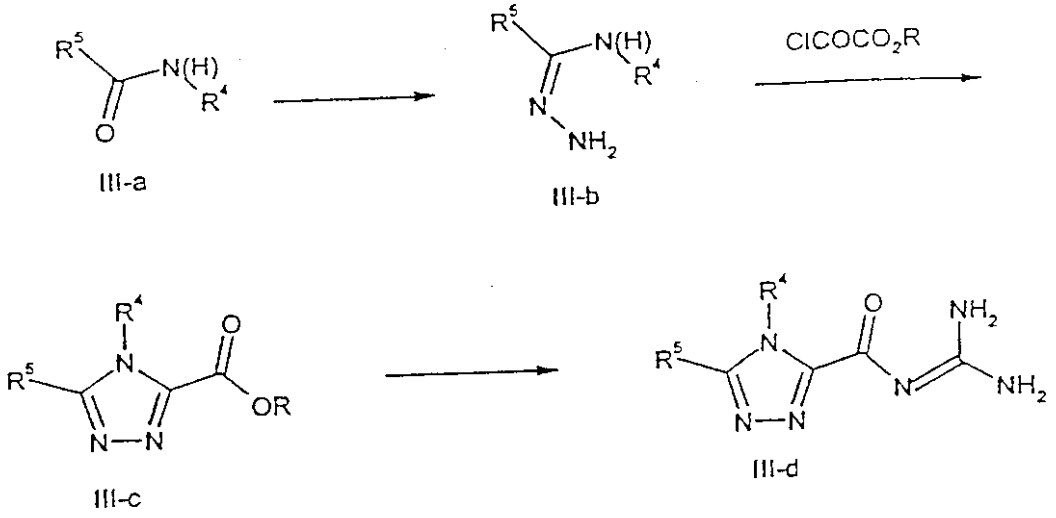
反应方案 I



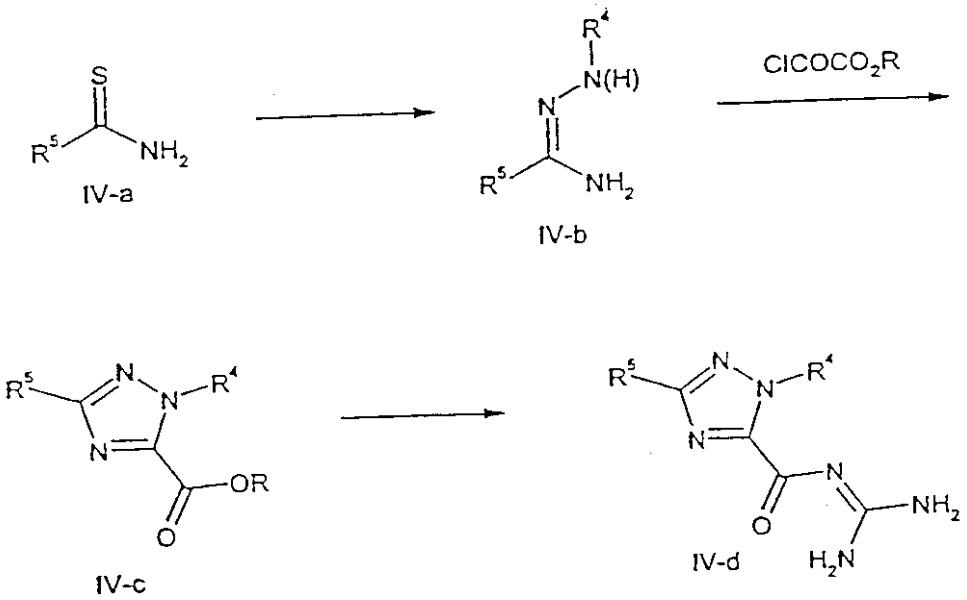

反应方案 II



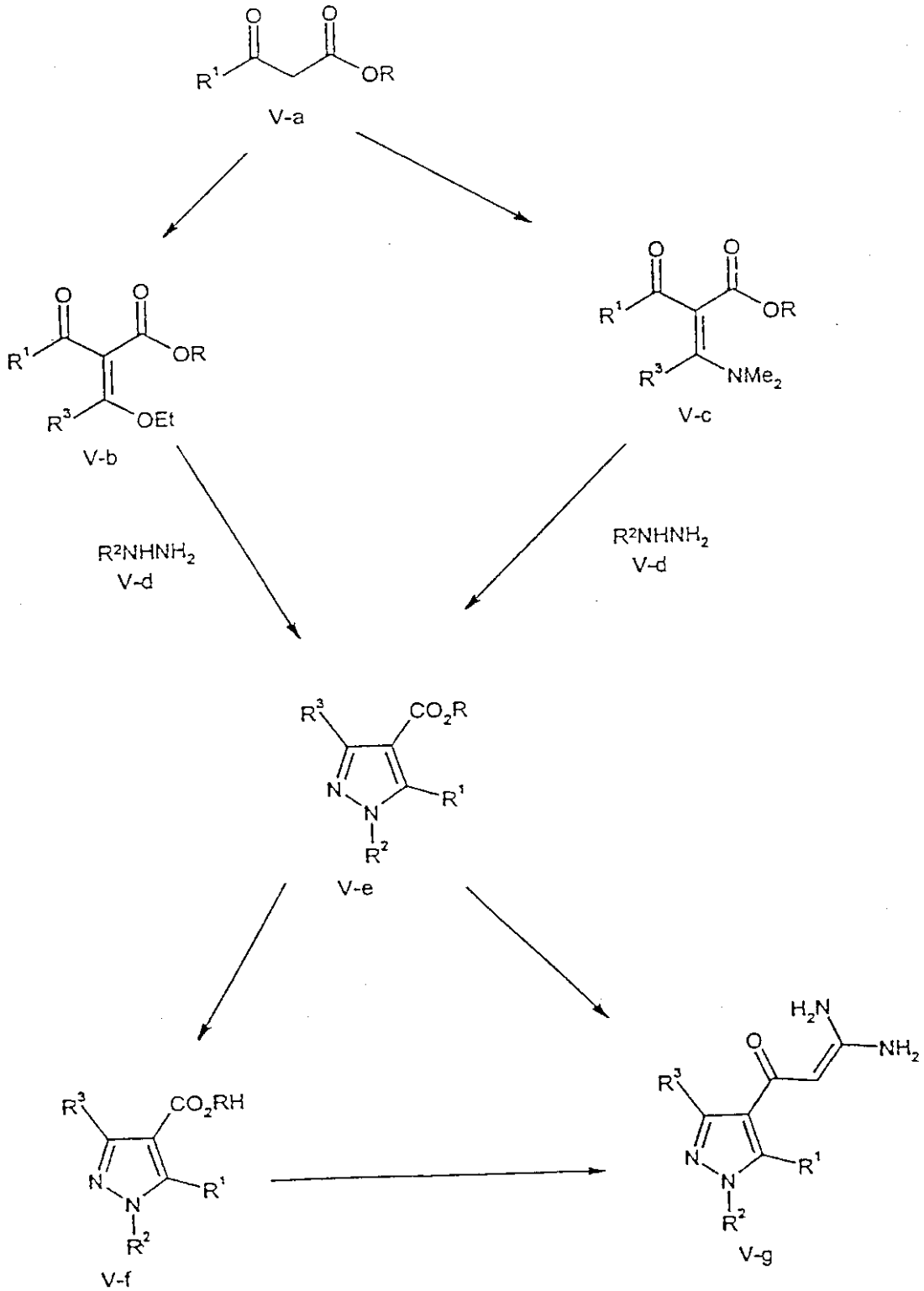
## 反应方案 III



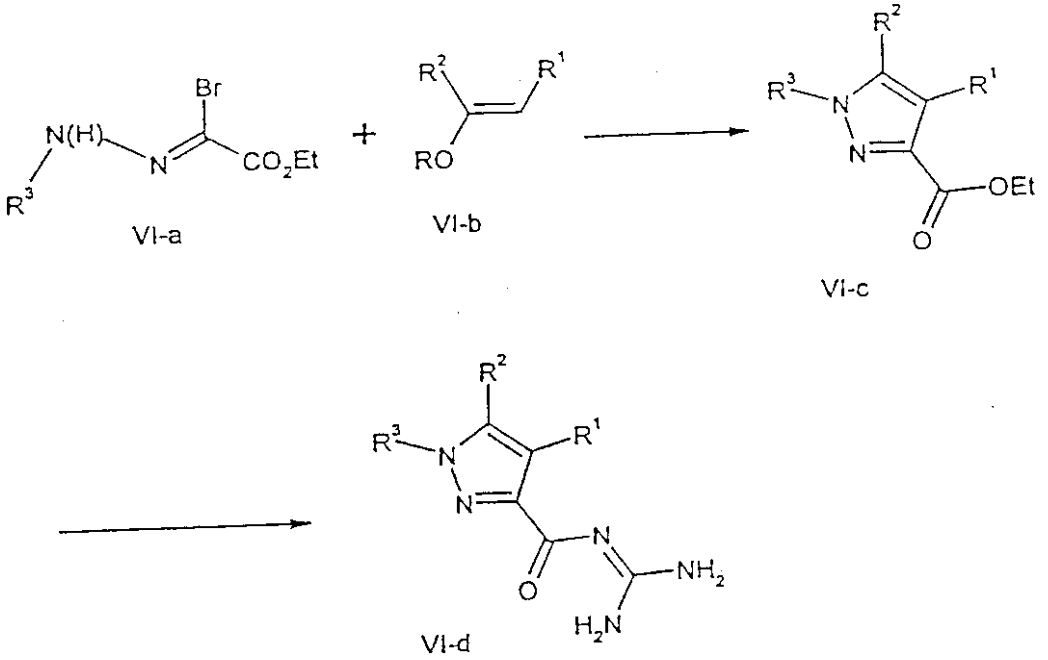

## 反应方案 IV



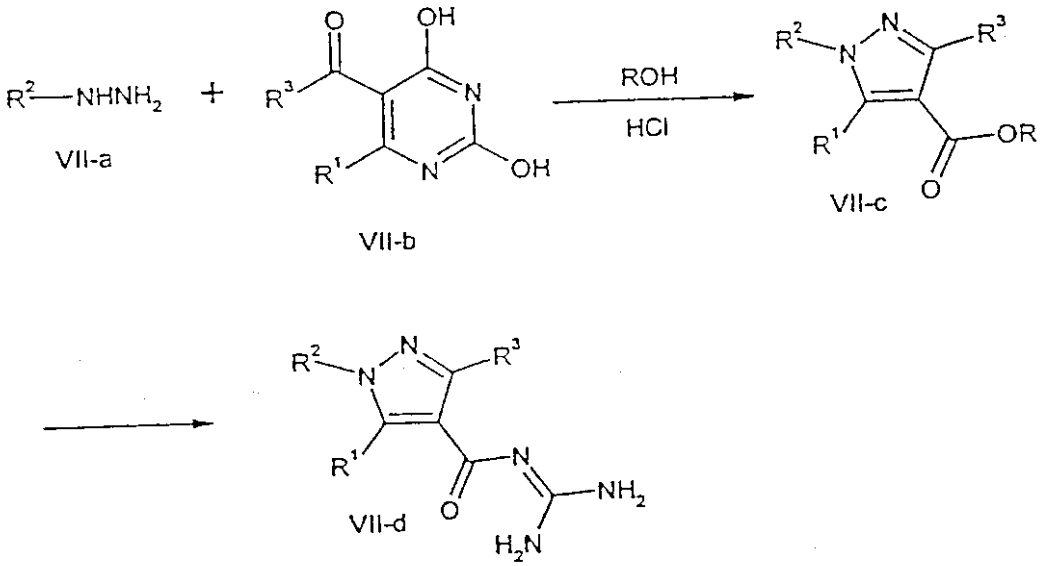
反应方案 V



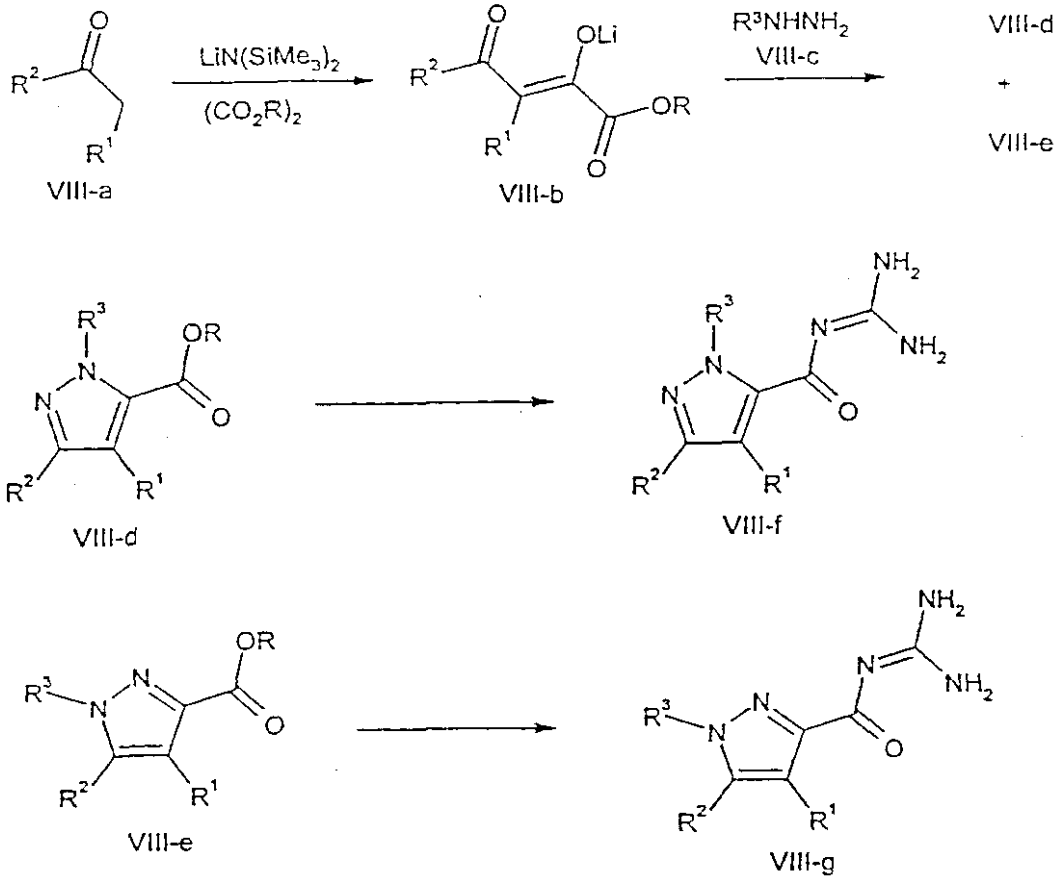
## 反应方案 VI




## 反应方案 VII



反应方案 VIII




根据反应方案 I，将式 I-a 化合物(其中 $R^4$ 如以上式 NHE 化合物中所述)和亚硝酸钠一起溶于或悬浮在碱金属氢氧化物水溶液(例如 1N 氢氧化钠)中，然后将混合物在约 0℃至约 5℃下加入到 pH 值大约为 0 的酸性水溶液(例如 10% v/v 硫酸)中约 30 分钟至 1 小时。将形成的混合物过滤得到式 I-b 的肟。或者，将式 I-a 化合物溶于 1：1 乙酸/丙酸中然后在约 0℃下加入亚硝酸钠。将反应混合物于大约 0℃下搅拌约 2 小时，倒入冰水中然后过滤得到式 I-b 的肟。

将式 I-b 化合物与式 I-c 化合物(其中 $R^5$ 如以上式 NHE 化合物中所述)在质子溶剂溶剂例如乙醇中于约 50℃至约 110℃下反应约 10 分钟至约 1 小时形成式 I-d 的腙。

将式 I-d 的腙环化然后水解成式 I-e 的三唑，反应在醇类溶剂例如 2-乙氧基乙醇中在碱性条件(例如氢氧化钾)下在约 100℃至约 175

℃进行约 1/2 小时至约 2 小时，然后酸化形成式 I-e 的三唑酸。

将式 I-e 的酸与胍在适宜偶联剂的存在下偶联。适宜的偶联剂是可以将羧酸转化成能够在与胺反应时形成酰胺键的活泼物质的偶联剂。

偶联剂可以是在与羧酸和胍混合时能够使该缩合反应以单釜的方式进行的试剂。偶联剂的例子是 1-(3-二甲氨基丙基)-3-乙基碳二亚胺盐酸盐-羟基苯并三唑(EDC/HBT)、二环己基碳二亚胺/羟基苯并三唑(HBT)、2-乙氧基-1-乙氧羰基-1,2-二氢喹啉(EEDQ)和二乙基磷酰基氰化物。偶联反应在过量的胍作为碱的存在下、在惰性溶剂(优选非质子溶剂)中、在约-20℃至约 50℃下进行约 1 至约 48 小时。溶剂的例子包括乙腈、二氯甲烷、二甲基甲酰胺和氯仿或其混合物。

偶联剂还可以是能够将羧酸转化成活化的中间体的物质，可在第一步中分离和/或形成该活化的中间体，然后在第二步中将其与胍反应。这种偶联剂和活化的中间体的例子是用亚硫酰氯或草酰氯形成酰氯、用氰尿酰氟形成酰氟、用氯甲酸烷基酯例如氯甲酸异丁酯或异丙烯酯或丙烷膦酸酐(丙烷膦酸酐，PPA)(使用叔胺碱)形成羧酸的混合酸酐，或用羰基二咪唑形成酰基咪唑。如果偶联剂是草酰氯，优选将少量的二甲基甲酰胺作为共溶剂和另一种溶剂(例如二氯甲烷)一起使用以催化酰氯的形成。该活化的酸衍生物可以通过与过量的胍和适宜的碱在适宜的溶剂中混合进行偶联。适宜的溶剂/碱组合是，例如二氯甲烷、二甲基甲酰胺或乙腈或其混合物和过量的胍作为碱。其它适宜的溶剂/碱组合包括水或($C_1$-$C_5$)醇或其混合物和共溶剂例如二氯甲烷、四氢呋喃或二氧六环和足以消耗掉反应中所释放的酸的碱例如氢氧化钠、氢氧化钾或氢氧化锂。这些偶联剂的使用以及溶剂和温度的适当选择是本领域技术人员熟知的，或者很容易根据文献来确定。用于偶联羧酸的这些以及其它的条件记载于 Houben-Weyl，第 XV 卷，第 11 部分，E. Wunsch 编，G. Theime Verlag，1974，Stuttgart；M. Bodansky，Principes of Peptide Synthesis，Springer-Verlag，Berlin 1984；和 The Peptides，Analysis，Synthesis

and Biology (E. Gross 和 J. Meienhofer 编), 1-5 卷 (Academic Press, NY 1979-1983)。

根据反应方案 II, 将式 II-a 的伯胺(其中 $R^5$ 如以上式 NHE 化合物中所述)与式 II-b 的α-重氮-β-酮基-酯(其中 $R^4$ 如以上式 NHE 化合物中所述, R 是低级烷基)在四氯化钛的存在下按照与 Eguchi S. 等, Synthesis 1993, 793 所述类似的方法反应形成式 II-c 的三唑甲酸酯。将式 II-c 的酯通过与胍在醇类溶剂中在约 60℃至约 110℃的温度下、优选在回流的甲醇中反应 8 至约 20 小时直接转化成酰基胍 II-d。

根据反应方案 III, 将式 III-a 化合物(其中 $R^4$ 和 $R^5$ 如以上式 NHE 化合物中所述)用 Lawesson's 试剂(即, 2,4-二(4-甲氧基苯基)-1,3-二硫杂-2,4-二磷杂环丁烷-2,4-二硫化物)在非质子溶剂例如二甲氧基乙烷中在约 20℃至约 120℃下处理约 1 至 8 小时。将形成的硫酰胺用烷基化试剂例如碘甲烷在极性的惰性溶剂例如丙酮中处理, 通常在室温下处理约 8 小时至约 48 小时。将形成的化合物与无水肼在醇溶剂中在约 0℃至约 25℃下反应约 1 至 8 小时得到式 III-b 化合物(类似于 Doyle 和 Kurzer, Synthesis 1974, 583 中的描述)。

将式 III-b 化合物用单烷基草酰氯在非质子溶剂中在约 25℃至约 50℃的温度下处理约 1 至 8 小时得到其中 R 是低级烷基的式 III-c 的羧酸酯化合物。将式 III-c 的酯直接与胍在醇类溶剂中在约 60℃至约 110℃下、优选在回流的甲醇中偶联 8 至 20 小时制得式 III-d 的三唑羧基胍。

根据反应方案 IV, 将式 IV-a 化合物(其中 $R^5$ 如以上式 NHE 化合物中所述)用碘甲烷在惰性溶剂中处理, 通常在室温下处理约 4 至 24 小时。将形成的化合物与无水 $R^4$-肼(其中 $R^4$ 如以上式 NHE 化合物中所述)在醇类溶剂中约 0℃至约 25℃下反应约 1 至 8 小时得到式 IV-b 的氨基腙化合物(类似于 Doyle 和 Kurzer, Synthesis 1974, 583 中的描述)。

将式 IV-b 化合物用单烷基草酰氯在非质子溶剂中在约 25℃至约

50℃的温度下处理约 1 至 8 小时得到其中 R 是低级烷基的式 IV-c 的羧酸酯化合物。将式 IV-c 的酯直接与胍在醇类溶剂中在约 60℃至约 110℃下、优选在回流的甲醇中偶联 8 至 20 小时制得式 IV-d 的三唑羧基胍。

根据反应方案 V，将式 V-a 化合物(其中 $R^1$ 如以上式 NHE 化合物中所述)与过量的 $(CH_3O)_2C(R^3)N(CH_3)_2$ (N,N-二甲基酰胺二甲缩醛)(其中 $R^3$ 如以上式 NHE 化合物中所述)在不存在或存在酸性催化剂例如对-甲苯磺酸的条件下在约 90℃至约 110℃下混合约 1 至约 2 小时制得以上式 V-c 的化合物。

将式 V-c 化合物与式 V-d 化合物(其中 $R^2$ 如以上式 NHE 化合物中所述)在惰性溶剂例如乙醇中在约 20℃至约 30℃的温度下环化约 5 分钟至约 1 小时，然后加热至约 70℃至约 110℃约 2 小时至约 4 小时形成式 V-f 的吡唑。

或者，根据反应方案 V，将式 V-a 化合物(其中 $R^1$ 如以上式 NHE 化合物中所述)与原酸三乙酯(即，$R^3C(OEt)_3$，其中 $R^3$ 如以上式 NHE 化合物中所述)和乙酸酐在约 120℃至约 150℃的温度下混合约 2 至约 5 小时制得式 V-b 化合物。

将式 V-b 化合物与式 V-d 化合物(其中 $R^2$ 如以上式 NHE 化合物中所述)环化形成式 V-c 的吡唑。

将式 V-c 的吡唑用碱例如氢氧化钠或氢氧化锂在溶剂例如水和/或甲醇和/或 THF 中在室温或升高的温度(例如回流)下水解约 1 小时至约 5 小时制得式 V-f 的酸。

将式 V-f 的酸和胍在以上将式 I-e 的酸和胍偶联时所述的适宜的偶联剂的存在下偶联。在一个实施方案中，将式 V-f 的酸用亚硫酰氯在约 60℃至约 90℃下活化约 15 分钟至约 2 小时。将形成的活化的酰氯与盐酸胍和无机碱(例如氢氧化钠)在无水四氢呋喃和选择性的甲醇和/或水中混合。将溶液加热，通常加热回流约 1 小时至约 8 小时制得式 V-g 化合物。

或者，根据反应方案 V，可将式 V-e 化合物通过多种方法直接转

化成式 V-g 化合物。例如，可将式 V-e 化合物在过量胍的存在下、在极性质子溶剂例如甲醇或异丙醇中在适宜的温度下(通常是回流)加热约 1 至约 72 小时。该转化还可以通过从式 V-e 化合物和过量胍的混合物中在约 1 至约 100mmHg 的压力和约 25℃至约 95℃的温度下反复除去溶剂，例如除去乙醇或甲苯约 4 次来进行。该反应还可以在不含溶剂的条件下，通过将式 V-e 化合物和过量胍的混合物在约 100℃至约 180℃、选择性地在约 1 至约 100mmHg 的压力下加热约 5 分钟至约 8 小时来进行。

根据反应方案 VI，将式 VI-a 化合物(其中 $R^3$ 如以上式 NHE 化合物中所述)与式 VI-b 化合物(其中 $R^1$ 和 $R^2$ 如以上式 NHE 化合物中所述)在非质子溶剂中、在适宜的胺碱例如三乙胺的存在下在约 0℃至约 25℃下反应约 2 小时至约 24 小时形成式 VI-c 化合物。

将形成的式 VI-c 化合物用前面的反应方案中描述的方法之一(例如使用羰基二咪唑的方法)水解和偶联形成式 VI-d 化合物。

根据反应方案 VII，将式 VII-a 的肼(其中 $R^2$ 如以上式 NHE 化合物中所述)与适宜的式 VII-b 的化合物按照 Bajnati, A.和 Hubert-Habart, M.的方法(Bull. Soc. Chim. France 1988, 540)反应形成其中 R 是低级烷基的式 VII-c 的吡唑酯。将形成的吡唑酯用上述的水解和偶联方法转化成式 VII-d 的酰基胍。

根据反应方案 VIII，将式 VIII-a 化合物(其中 $R^2$ 和 $R^1$ 如以上式 NHE 化合物中所述)按照 J. Het. Chem. 1989, 26, 1389 中描述的方法转化成其中 R 是低级烷基的式 VIII-b 的锂盐。将式 VIII-b 的锂盐与式 VIII-c 的肼(其中 $R^3$ 如以上式 NHE 化合物中所述)在惰性溶剂例如乙醇中、在无机酸的存在下在约 20℃至约 30℃的温度下混合约 5 分钟至约 1 小时，然后加热至约 70℃至约 110℃ 2 小时至约 4 小时形成式 VIII-d 和 VIII-e 的吡唑。将式 VIII-d 和 VIII-e 的吡唑分别用上述的水解和偶联方法转化成式 VIII-f 和 VIII-g 的酰基胍。制备本文所述化合物所用的方法可能需要对远端的(remote)功能基(例如式 I 的前体中的伯胺、仲胺、羧基)进行保护。是否需要进行保护取决

于远端功能基的性质和制备方法的条件。本领域技术人员很容易确定是否需要进行保护。所述保护/脱保护方法的使用也是本领域技术人员熟知的。关于保护基及其应用的一般性描述可以参见 T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991。

当本发明的式 I 化合物与 NHE-1 抑制剂联合使用时，可以抑制钠/质子($Na^+/H^+$)交换转运系统，因此可用于治疗或预防由于钠/质子($Na^+/H^+$)交换转运系统的加速所引起或加重的疾病，例如心血管疾病[例如动脉硬化、高血压、心律失常(例如局部缺血性心律失常、由于心肌梗塞引起的心律失常、心肌昏厥、心肌功能障碍、PTCA 或溶栓后的心律失常等)、心绞痛、心脏肥大、心肌梗塞、心衰(例如充血性心衰、急性心衰、心脏肥大等)、PTCA、PTCI 后的再狭窄、休克(例如出血性休克、内毒素休克等)]、肾疾病(例如糖尿病、糖尿病性肾病、缺血性急性肾衰等)、与局部缺血或局部缺血再灌注有关的器管疾病[例如与心肌缺血再灌注有关的疾病、急性肾衰或由手术治疗例如冠状动脉旁路移植(CABG)手术、血管手术、器管移植、非心脏的手术或经皮腔内冠状动脉成形术(PTCA)引起的疾病]、脑血管疾病(例如缺血性中风、出血性中风等)、脑缺血疾病(例如与脑梗塞有关的疾病、脑中风后引起的后遗症或脑水肿)。

优选将本发明的式 I 化合物和 NHE-1 抑制剂联用在冠状动脉旁路移植(CABG)手术、血管手术、经皮腔内冠状动脉成形术(PTCA)、器管移植或非心脏的手术之前、过程中或之后用作心肌保护剂。

优选将本发明的式 I 化合物和 NHE-1 抑制剂联用在存在进行性心脏(急性冠脉综合征，例如心肌梗塞或不稳定型心绞痛)或脑局部缺血事件(例如中风)的患者中用作心肌保护剂。

优选将本发明的式 I 化合物和 NHE-1 抑制剂联用在被诊断为患有冠心病的患者(例如心肌梗塞前或不稳定心绞痛)或处于心肌梗塞高危险性的患者中用作长期的心脏保护剂。

此外，将本发明的式 I 化合物和 NHE-1 抑制剂联用对于细胞增殖

例如成纤维细胞增殖和平滑肌细胞增殖也有很强的抑制作用。因此，本发明的式 I 化合物和本发明的 NHE-1 抑制剂的联合形式是很有价值的治疗剂，可用于其中细胞增殖是主要或次要原因的疾病，因此可用作抗动脉粥样硬化剂、抗糖尿病晚期并发症、癌症、纤维化疾病例如肺纤维化、肝纤维化或肾纤维化、肾小球肾硬化症、器管肥大或增生、特别是前列腺增生或肥大、肺纤维化、糖尿病并发症或 PTCA 后的再狭窄或由于内皮细胞损伤所引起的疾病的药物。

本发明化合物和 NHE-1 抑制剂的联合形式作为药物在哺乳动物(例如人)中治疗疾病(例如本文中详细描述的疾病，例如在手术过程中的心肌保护或在存在进行性心脏或脑局部缺血事件的患者中的心肌保护或在被诊断为患有冠心病、易患冠心病、心脏功能障碍或心肌昏厥的患者中的长期的心脏保护)的用途可以通过所述联合形式在常规的临床前心脏保护试验[参见 Klein, H.等, Circulation 92: 912-917 (1995)中的体内试验; Scholz, W.等, Cardiovascular Research 29: 260-268 (1995)中的离体心脏试验; Yasutake M.等, Am. J. Physiol., 36: H2430-H2440 (1994)中的抗心律失常试验; Kolke 等, J. Thorac. Cardiovasc. Surg. 112: 765-775 (1996)中的 NMR 试验]和以下描述的其它体外和体内试验中的活性来证实。这些实验还提供了将本发明式 I 化合物的活性与其它已知化合物的活性进行比较的方法。这些比较的结果可用于确定在哺乳动物、包括人中治疗所述疾病的剂量水平。

人 NHE-1 抑制活性的测量

测量人 NHE-1 活性和抑制效力的方法是基于 Watson 等所公开的方法(Am. J. Physiol., 24: $G^2$29-$G^2$38, 1991)，在该方法中，测量在细胞内酸化后由 NHE-介导的细胞内 pH 的恢复。因此，将稳定表达人 NHE-1 的成纤维细胞(Counillon, L.等, Mol. Pharmacol., 44: 1041-1045 (1993))置于涂有胶原的 96 孔平板上(50,000/孔)然后在生长培养基(DMEM 高葡萄糖，10%胎牛血清，50u/ml 青霉素和链

霉素)中生长至融合。将融合的平板在 37℃下和 pH 敏感型荧光探针 BCECF (5μM; Molecular Probes, Eugene, OR)一起保温 30 分钟。将含有 BCECF 的细胞在含有酸的培养基(70mM 氯化胆碱, 50mM $NH_4Cl$, 5mM KCl, 1mM $MgCl_2$, 1.8mM $CaCl_2$, 5mM 葡萄糖, 10mM HEPES, pH 7.5)中于 37℃下保温 30 分钟, 然后置于荧光成像平板读数器 (Fluorescent Imaging Plate Reader) (Molecular Devices, CA) 中。用 485nM 的激发波长和 525nM 的发射波长检测 BCECF 荧光。通过迅速将含酸的培养基用恢复培养基(120mM NaCl, 5mM KCl, 1mM $MgCl_2$, 1.8mM $CaCl_2$, 5mM 葡萄糖, 10mM HEPES, pH 7.5)±待测试的联合形式代替来引发细胞内的酸化, 并通过随后的时间依赖性的 BCECF 荧光的增加来监测由 NHE 介导的细胞内 pH 的恢复。本发明式 I 化合物和 NHE-1 抑制剂的联合形式的效力以减少细胞内 pH 的恢复达 50%时的浓度($IC_{50}$)来计算。在这些条件下, 参比 NHE 抑制剂阿米洛利和 HOE-642 对人 NHE-1 的 $IC_{50}$ 值分别为 50μM 和 0.5μM。

作为背景资料, 应当注意, 在冠状动脉再灌注后的短时间心肌缺血可以防止心脏发生随后的严重心肌缺血(Murry 等), Circulation 74: 1124-1136, 1986)。

本发明式 I 化合物和 NHE-1 抑制剂的联合形式在预防由于局部缺血发作所引起的心脏组织损伤中的治疗作用可以参照 Liu 等描述的体外试验(Cardiovasc. Res., 28: 1057-1061, 1994)按照本文中的描述来证实。心脏保护作用(表现为梗塞心肌的减少)可以在药理学上用腺苷受体激动剂在用作心肌缺血预适应体外模型的离体的、逆行灌注的兔心脏中引发(Liu 等, Cardiovasc. Res., 28: 1057-1061,1994)。下述的体外试验证实, 当向兔子的离体心脏给药时, 试验化合物或者在该情况下的待测试的联合形式(即, 式 I 化合物和 NHE-1 拮抗剂的联合形式)也可以在药理学上引发心脏保护作用, 即减少心肌梗塞的面积。将待测试的联合形式的效果与局部缺血预适应和 A1/A3 腺苷激动剂, APNEA ($N^6$-[2-(4-氨基苯基)乙基]腺苷, 已证实其可以在兔离体心脏中在药理学上引发心脏保护作用, Liu 等,

Cardiovasc. Res., 28: 1057-1061, 1994)进行比较。具体的方法如下所述。

这些实验所用的方法基本按照 Liu 等, Cardiovasc. Res., 28: 1057-1061, 1994 的描述进行。将雄性新西兰白兔(3-4 kg)用戊巴比妥钠麻醉(30mg/kg, i.v.)。在达到深度麻醉后(通过缺乏眼的瞬目反射来确定), 对动物进行插管并用正压呼吸器通入 100% $O_2$。进行左胸廓切开术, 暴露心脏, 在左冠状动脉的隆凸支上绕一个松的动脉夹(2-0 丝), 距离心脏尖端约 2/3 的距离。从胸内取出心脏并迅速(<30 秒)安装在 Langendorff 装置上。将心脏用改良的 Krebs 溶液(NaCl 118.5mM, KCl 4.7mM, $MgSO_4$ 1.2mM, $KH_2PO_4$ 1.2mM, $NaHCO_3$ 24.8mM, $CaCl_2$ 2.5mM 和葡萄糖 10mM)在 80mmHg 的恒压下于 37℃以非循环的方式进行逆行灌注。通过通入 95% $O_2$/5% $CO_2$ 将灌注液的 pH 保持在 7.4-7.5。通过用加热的水箱控制生理溶液和灌注管及离体心脏周围水夹套的温度对心脏温度进行严格地控制。通过插入到左心室内并且通过不锈钢管与压力传感器相连的乳胶气囊来测定心率和左心室压。将心室内的气囊充气以产生 80-100mmHg 的心脏收缩压和≤10mmHg 的舒张压。用内联的流量探头连续监测总的冠脉流量并用心脏的重量标准化。

使心脏平衡 30 分钟, 在这段时间内, 心脏必需显示在以上所列参数范围内的稳定的左心室压。如果在 30 分钟的局部缺血期之前的任何时间心率降至了 180bpm 以下, 则在实验的剩余时间内用心脏起博器将心率控制在大约 200bpm。通过完全停止心脏灌注(完全缺血)5 分钟然后再灌注 10 分钟来引发局部缺血预适应。通过系紧环绕冠状动脉支的动脉夹来产生局部缺血。在 30 分钟的局部缺血后, 将动脉夹放松并对心脏再灌注 120 分钟。

通过以预定的浓度从 30 分钟局部缺血期的 30 分钟之前开始输注待测试的联合形式(即, 式 I 化合物和 NHE-1 抑制剂的联合形式)并持续至 120 分钟的再灌注期结束来诱导药理学的心脏保护。接受待测试的联合形式的心脏不经历局部缺血预适应期。将参比化合物 APNEA

(500nM)灌注通过不接受试验化合物心脏 5 分钟的时间，灌注在 30 分钟局部缺血期的 10 分钟之前结束。

在 120 分钟的再灌注期结束时，将冠状动脉动脉夹系紧，将 0.5%硫酸锌镉荧光颗粒的悬浮液(1-10μM, Duke Scientific Corp. Palo Alto, CA)灌注通过心脏；这可以染色所有的心肌，但梗塞发展的危险区域(危险区域)除外。从 Langendorff 装置上取下心脏，蘸干，用铝箔包裹然后于-20℃保存过夜。第二天，将心脏从心室的一端至另一端切成 2mm 的横向切片。将切片用 1%氯化三苯基四氮唑(TTC)在磷酸盐缓冲盐水中于 37℃染色 20 分钟。由于 TTC 可与活的组织(含有 NAD-依赖型脱氢酶)反应，该染色可以区分活的组织(红色染色)和死亡的组织(未染色的梗塞组织)。用预先校准的图象分析仪计算各左心室切片的梗塞面积(未染色)和危险面积(无荧光颗粒)。为了用不同心脏之间危险区域的差异将局部缺血性损伤标准化，将数据以梗塞面积比危险面积的比值(%IA/AAR)来表示。所有数据均用平均值±SE 来表示，并用 Mann-Whitney 非参数试验进行统计学比较，用 Bonferroni 校正进行多重比较。当 $p < 0.05$ 时认为是显著性的。

以上体外试验的结果证实，本发明化合物和 NHE-1 抑制剂的联合形式与对照组相比具有明显的心脏保护作用。

本发明式 I 化合物和 NHE-1 抑制剂的联合形式在预防由于局部缺血发作之外的其它原因引起的心脏组织损伤中的治疗作用也可以参照 Liu 等的描述(Circulation, Vol. 84: 350-356, 1991)通过本文中详细描述的方法在体内证实。该体内试验测试试验用联合方式(即式 I 化合物加 NHE-1 抑制剂)相对于接受盐水载体的对照组的心脏保护作用。心脏保护作用(表现为梗塞心肌的减少)可以在药理学上通过静脉内给药腺苷受体激动剂在作为心肌缺血预适应原位模型进行研究的完整的、麻醉的兔子中引发(Liu 等, Circulation 84: 350-356, 1991)。该体内试验测试本发明的式 I 化合物和 NHE-1 抑制剂的联合形式在向完整的、麻醉的兔子胃肠外给药时，是否可以在药理学上诱导心脏保护作用，即减少心肌梗塞的面积。可将本发明式 I 化合物和

NHE-1 抑制剂的联合形式的效果与使用 A1 腺苷激动剂 $N^6$-1-(苯基-2R-异丙基)腺苷(PIA，已证实其可以在原位研究的完整的麻醉的兔子中在药理学上诱导心脏保护作用，Liu 等，Circulation 84：350-356，1991)的局部缺血预适应进行比较。所用方法如下所述。

手术：将雄性的新西兰白兔(3-4kg)用戊巴比妥钠麻醉(30mg/kg，i.v.)。通过腹侧中线颈部切口术进行气管切开术，然后将兔子用正压呼吸器用 100%氧气换气。在左颈静脉内放置导管用于给药，在左颈动内放置导管用于血压测量。然后通过左胸廓切开术暴露心脏并在左冠状动脉的隆凸支上绕一个松的动脉夹(00 丝)。通过将动脉夹拉紧并在适当的位置夹住引起局部缺血。将动脉夹放松使受影响的区域再灌注。通过青紫来证实心肌缺血；通过反应性充血来证实再灌注。

方法：当动脉压和心率稳定了至少 30 分钟后，开始试验。通过将冠状动脉闭合 5 分钟然后再灌注 10 分钟来诱导局部缺血预适应。通过输注待测试的联合形式(即本发明的式 I 化合物和 NHE-1 抑制剂的联合形式)例如 5 分钟的时间并在 10 分钟后进行进一步的处理或者通过输注腺苷激动剂 PIA (0.25mg/kg)来诱导药理学上的预适应。在局部缺血预适应、药理学预适应或没有进行适应(未适应，载体对照)后，将动脉闭合 30 分钟然后再灌注 2 小时以诱导心肌梗塞。将待测试的联合形式和 PIA 溶于盐水或其它适宜的载体，然后分别以 1 至 5mg/kg 进行给药。

染色(Liu 等，Circulation 84：350-356，1991)：在 2 小时的再灌注期结束时，迅速取出心脏，悬挂在 Langendorff 装置上，用加热至体温(38℃)的生理盐水冲洗 1 分钟。用丝制的缝线作为动脉夹然后系紧以闭合动脉，用灌注液输注 0.5%硫酸锌镉荧光颗粒(1-10μm，Duke Scientific Corp. Palo Alto，CA)的悬浮液以染色除危险区域(无荧光的心室)之外的所有心肌。然后将心脏迅速冷冻并于-20℃存放过夜。第二天，将心脏切成 2mm 的切片并用 1%氯化三苯基四氮唑(TTC)染色。由于 TTC 可与活的组织反应，该染色可以区分活的(红色染色)组织和死亡的组织(未染色的梗塞组织)。用预先校准的图象分析仪计

算各左心室切片的梗塞面积(未染色)和危险面积(无荧光颗粒)。为了用不同心脏之间危险区域的差异将局部缺血性损伤标准化，将数据以梗塞面积比危险面积的比值(%IA/AAR)来表示。所有数据均用平均值±SEM 来表示，并用单因素 ANOVA 或 Mann-Whitney 非参数试验进行统计学比较。当 $p < 0.05$ 时认为是显著性的。

可以用科技文献中报道的方法来测试本发明式 I 化合物和 NHE-1 抑制剂的联合形式在非心脏组织例如脑或肝脏中减轻或预防局部缺血性损伤的用途。在该试验中，可将本发明式 I 化合物和 NHE-1 抑制剂的联合形式通过优选的途径和给药载体在优选的给药时间进行给药，给药时间可以在局部缺血事件之前、在局部缺血事件过程中、在局部缺血事件之后(再灌注期间)或在任何下述实验阶段的过程中。

NHE-1 抑制剂和本发明式 I 化合物的联合形式在减轻局部缺血性脑损伤中的有益效果可以采用 Park 等的方法(Ann. Neurol. 1988; 24: 543-551)在哺乳动物中证实。根据 Park 等的方法，将成年的雄性 Sprague Dawley 大鼠先用 2%氟烷麻醉，然后用含有 0.5-1%氟烷的一氧化二氮-氧气混合物(70%: 30%)进行机械换气。然后进行气管切开术。调整呼吸机的每次输出量将动脉二氧化碳张力保持在约 35mmHg 并保持适当的动脉氧($PaO_2$>90mmHg)。可以通过直肠温度计监测体温，如需要，可以通过外部的加热将动物保持在正常体温。然后在手术显微镜下对动物进行颞下的颅骨切除术以暴露左大脑中动脉(MCA)的主干，然后将暴露的动脉用微两极凝结法闭合以在大脑皮质和基底核产生大的局部缺血性损伤。在 MCA 闭合 3 小时后，将大鼠用 2%氟烷深度麻醉然后进行胸廓切开术以向左心室输注肝素化的盐水。通过右心房的切口收集流出液。在用盐水冲洗之后，用约 200mL 40%甲醛、冰乙酸和无水甲醇溶液(FAM; 1: 1: 8, v/v/v)冲洗，然后将动物杀头并将头在固定液中放置 24 小时。然后取出大脑，切开，包埋在石蜡中然后切片(每个大脑约 100 片 0.2mm 的切片)。然后将切片用苏木精-曙红染色或用甲酚紫和 Luxol 固蓝联合进行染色，然后用预先校准的图象分析仪通过光学显微镜识别并定量局部缺血性损伤。将

局部缺血的体积和面积用绝对单位($mm^3$ 和 $mm^2$)和总检测区域的百分比来表示。治疗组大鼠的脑切片和安慰剂处理的对照组大鼠的脑切片相比，相对或绝对局部缺血性损伤面积或体积的减少证实了本发明的组合物和方法减轻由 MCA 闭合引起的局部缺血性脑损伤的效果。

可用于证实本发明减轻局部缺血性脑损伤的有益效果的其它方法包括如下文献中公开的方法 Nakayama 等，Neurology 1988,, 38: 1667-1673; Memezawa 等，Stroke 1992, 23: 552-559; Folbergrova 等，Proc. Nat. Acad. Sci. 1995, 92: 5057-5059; 和 Gotti 等，Brain Res. 1990, 522: 290-307。

本发明的组合物和方法减轻局部缺血性肝损伤的有益效果可以用例如 Yokoyama 等的方法(Am. J. Physiol. 1990; 258: G564-G570)在哺乳动物中证实。按照 Yokoyama 等的方法，将禁食的成年雄性 Sprague Dawiey 大鼠用戊巴比妥钠(40mg/kg i.p.)麻醉，然后将动物切开气管并用室内的空气进行机械换气。切除肝脏然后置于保持恒温(37℃)的环境室中，然后以 15cm $H_2O$ 的恒定压力将改良的、不含血红蛋白的 Krebs-Henseleit 缓冲液(单位 mM: 118 NaCl, 4.7 KCl, 27 $NaHCO_3$, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 $KH_2PO_4$, 0.05 EDTA 和 11mM 葡萄糖，加 300 U 肝素)灌注通过门静脉。通过向缓冲液中通入 95% $O_2$-5%$CO_2$ 将灌注液的 pH 保持在 7.4。将各肝脏以 20ml/分钟的流速以一次性通过的方式灌注 30 分钟的冲洗和平衡期(缺血前期)，然后是 2 小时的整体缺血期，然后是在与缺血前期相同的条件下的 2 小时的再灌注期。在缺血前期、闭合性局部缺血期之后立即以及在 2 小时的再灌注期的每隔 30 分钟收集灌注液的等分试样(20mL)。分析灌注液样品中的肝细胞酶，例如天冬氨酸氨基转移酶(AST)、丙氨酸氨基转移酶(ALT) 和乳酸脱氢酶(LDH)，用这些酶定量反应在该过程中的局部缺血性肝损伤的程度。灌注液中的 AST、ALT 和 LDH 活性可以通过多种方法测定，例如 Nakano 等(Hepatology 1995; 22: 539-545)所报道的使用自动 Kodak Ektachem 500 分析仪的反射计方法。治疗组大鼠的灌注的肝脏和安慰剂处理的对照组大鼠的灌注的肝脏在闭合

期之后立即和/或在局部缺血后-再灌注期过程中肝细胞酶释放的减少证实了本发明的组合物和方法减轻由闭合引起的局部缺血性肝损伤的效果。

可用于证实本发明的组合物和方法在减轻局部缺血性肝损伤中的有益效果的其它方法和参数包括 Nakano 等所公开的那些(Hepatology 1995; 22: 539-545)。

可以使用任意糖原磷酸化酶抑制剂作为本发明的第二种化合物。术语糖原磷酸化酶抑制剂是指可以减轻、阻止或消除糖原磷酸化酶的酶催化作用的任何物质或试剂或各种物质和/或试剂的任意组合。目前已知的糖原磷酸化酶的酶催化作用是通过催化糖原大分子和无机磷酸盐的可逆的反应将糖元降解成葡萄糖-1-磷酸和比最初的糖原大分子短了一个葡萄糖残基的糖原大分子(糖原分解的向前方向)。该作用很容易由本领域技术人员按照常规的试验(例如下文中描述的试验)进行测定。在如下公开的 PCT 专利申请中公开了各种这样的化合物: PCT 申请公开号 WO 96/39384 和 WO 96/39385。但是, 其它的糖原磷酸化酶抑制剂也是本领域技术人员熟知的。

式 I 化合物、其前药、式 I 化合物和醛糖还原酶抑制剂的交互前药、上述物质的可药用盐以及含有式 I 化合物、其前药或所述化合物或所述前药的可药用盐和(a)醛糖还原酶抑制剂、其前药或所述醛糖还原酶抑制剂或所述前药的可药用盐、(b) NHE-1 抑制剂、其前药或所述 NHE-1 抑制剂或所述前药的可药用盐或糖原磷酸化酶抑制剂、其前药或所述糖原磷酸化酶抑制剂或所述前药的可药用盐的药物组合物在下文中统称为“本发明的活性化合物和组合物”。

本发明的活性化合物和组合物可以通过各种常规的给药途径向所需的个体进行给药, 包括口服、胃肠外和局部给药。通常, 可将式 I 化合物及其可药用盐以约 0.001 至约 100mg/kg、优选约 0.01 至 10mg/kg 所治疗患者的体重/天的剂量以单一或分开的剂量进行胃肠外给药。式 I 化合物和醛糖还原酶抑制剂的交互前药通常以约 0.001 至约 100mg/kg、优选约 0.01 至 10mg/kg 所治疗患者的体重/天的剂量

以单一或分开的剂量进行口服或胃肠外给药。含有式 I 化合物和醛糖还原酶抑制剂的组合物通常以约 0.001 至约 100mg 各活性成分(即，式 I 化合物和醛糖还原酶抑制剂)/kg 所治疗患者的体重、优选约 0.01 至 10mg/kg/天的剂量口服或胃肠外给药。含有式 I 化合物和 NHE-1 抑制剂的组合物通常以约 0.001 至约 100mg 所述式 I 化合物/kg 所治疗患者的体重/天和约 0.001 至约 100mg/kg/天 NHE-1 抑制剂的剂量口服或胃肠外给药。特别优选的剂量包含约 0.01 至 10mg/kg/天所述的式 I 化合物和约 0.01 至 50mg/kg/天所述的 NHE-1 抑制剂。含有式 I 化合物和糖元磷酸化酶抑制剂的组合物通常以约 0.001 至 100mg 所述式 I 化合物/kg 所治疗患者的体重/天和约 0.005 至约 50mg/kg/天所述糖原磷酸化酶抑制剂的剂量口服或胃肠外给药，优选 0.01 至 10mg/kg/天所述式 I 化合物和 0.01 至 25mg/kg/天所述糖原磷酸化酶抑制剂，首选 0.01 至 10mg/kg 天所述式 I 化合物和 0.1 至 15mg/kg/天所述糖原磷酸化酶抑制剂。但是，根据所治疗个体的病情可能需要对剂量进行一些改变。无论如何，应由负责给药的人来确定对于具体个体的适宜剂量。

本发明的活性化合物和组合物可以单独给药或者与可药用载体混合以单个或多个剂量给药。适宜的药物载体包括惰性固体稀释剂或填料、无菌水溶液和各种有机溶剂。药物组合物通过将本发明的活性式I化合物和可药用载体混合制得，然后很容易以各种剂量形式例如片剂、散剂、锭剂、糖浆、可注射溶液等剂型给药。如需要，这些药物组合物可以含有其它成分，例如矫味剂、粘合剂、赋形剂等。因此，对于口服给药，可以采用含有各种赋形剂如柠檬酸钠、碳酸钙和磷酸钙以及各种崩解剂例如淀粉、藻酸和某些复合硅酸盐及粘合剂如聚乙烯吡咯烷酮、蔗糖、明胶和阿拉伯胶的片剂。此外，润滑剂如硬脂酸镁、十二烷基硫酸钠和滑石也经常用于片剂的制备。相同类型的固体组合物还可用作软和硬明胶胶囊的填料。就此而言，优选的材料包括乳糖以及高分子量的聚乙二醇。当需要用含水混悬液和/或酏剂进行口服给药时，可将其中的活性成分与各种甜味剂或矫味剂、着色剂或染

料以及(如果需要的话)乳化剂或助悬剂和稀释剂如水、乙醇、丙二醇、甘油及它们的混合物进行混合。

对于胃肠外给药，可以采用本发明的活性化合物和组合物在芝麻油或花生油、含水丙二醇或无菌水溶液中的溶液。如需要，应将所述含水溶液进行适当地缓冲，并将液体稀释剂首先用足够的盐或葡萄糖调至等渗。这些含水溶液特别适于静脉内、肌肉内、皮下和腹膜内给药的目的。就此而言，所用的无菌含水溶媒很容易通过本领域技术人员熟知的常规技术获得。

可将本发明的式 I 化合物通过能够将本发明的化合物优先输送到所需的组织(例如神经、肾、视网膜和/或心脏组织)的各种方法来给药。这些方法包括口服途径、胃肠外、十二指肠内的途径等。通常，可将本发明的化合物以单一(例如每天一次)或多剂量或通过连续输注进行给药。

含有式 I 化合物和 NHE-1 抑制剂的联合形式的本发明组合物可用于例如减轻或尽可能地减少由于局部缺血事件(例如心肌梗塞)引起的对易受局部缺血/再灌注损伤的组织(例如心、脑、肺、肾、肝、肠、骨骼肌、视网膜)的损伤。因此，该组合物可用于在有局部缺血(例如心肌缺血)危险性的患者中预防性地阻止、即(前瞻性或预防性的)延缓或阻止组织损伤(例如心肌组织) 。

通常，本发明的式 I 化合物可以口服或胃肠外(例如静脉内、肌肉内、皮下或髓内)给药。也可以采用局部给药，例如，当患者患有胃肠疾病或者当首选将药物涂抹在组织或器管表面时，这可由主治医师来确定。

化合物的给药量和给药时间取决于所治疗的患者、疾病的严重程度、给药方式以及处方医师的判断。因此，由于患者之间的差异，以下给出的剂量是指导性的，医师可以确定药物的剂量以达到医师认为的适于患者的治疗。在考虑所需的治疗程度时，医师必需平衡各种因素，例如患者的年龄、是否有先前存在的疾病以及是否存在其它疾病。

因此，例如，在一种给药方式中，可将本发明的式 I 化合物在临手术前(例如在手术如心脏手术前的 24 小时内)、在手术过程中或手术后(例如在手术后的 24 小时内)在有心肌缺血的危险性时给药。还可将本发明的式 I 化合物以长期的每天给药的方式给药。

本发明的化合物通常以含有至少一种本发明的式 I 化合物和可药用载体或稀释剂的药物组合物的形式给药。因此，可将本发明的式 I 化合物以任何常规的口服、胃肠外、直肠或经皮剂量形式单独或一起给药。

对于经皮(例如局部)给药，可以制备与上述胃肠外溶液相似的稀的无菌含水或部分含水的溶液(通常约为 0.1%至 5%浓度)。

制备含有一定量活性成分的各种药物组合物的方法是已知的，或者根据本文公开的内容对于本领域技术人员是显而易见的。关于制备药物组合物的方法的例子可以参见 Remington's Pharmaceutical Sciences, Mack 出版公司, Easton, Pa., 第 19 版(1995)。

本发明的药物组合物可以含有例如 0.0001%-95%本发明的化合物。不论怎样，用于给药的组合物或制剂均应含有可以有效治疗所治疗患者的疾病/病症的一定量的本发明化合物。

本发明的联合形式的两种不同的化合物可以同时或以任何顺序依次共同给药，或以含有式 I 化合物和上述醛糖还原酶抑制剂或上述糖原磷酸化酶抑制剂或心血管药物的单一的药物组合物形式给药。

由于本发明涉及用可以分别进行给药的活性成分的联合形式来治疗本文所述的疾病/病症，因此，本发明还涉及将独立的药物组合物以药盒的形式合并。该药盒包含两种独立的药物组合物：式I化合物、其前药或所述化合物或前药的可药用盐以及上述的第二种化合物。该药盒含有用于包含独立的组合物的装置，例如容器、分开的小瓶或分开的锡箔包装。药盒中通常含有将各独立的成分进行给药的指导。当所述独立的组分优选以不同的剂型(例如口服和胃肠外)、以不同的给药间隔施用或者当需要由处方医生确定组合中的每个组分的用量时，药盒的形式是特别有利的。

所述药盒的一个实例是所谓的凸泡包装。凸泡包装是包装工业熟知的，并被广泛用于包装药物单位剂量形式(片剂、胶囊等)。凸泡包装通常由相对较硬材料的薄片组成，其上覆盖有优选是透明塑料材料的箔。在包装过程中，在塑料箔上形成凹穴。所述凹穴与待包装片剂或胶囊的大小和形状相同。然后，将片剂或胶囊放在凹穴中，并在与凹穴形成相反的表面，将相对较硬材料的薄片与塑料箔密封。结果，片剂或胶囊被密封在塑料箔和所述薄片之间的凹穴内。优选所述薄片的强度是：用手压在凹穴上时可在凹穴处的薄片形成开口，这样可从凸泡包装中取出片剂或胶囊。然后经所述开口取出所述片剂或胶囊。

还可在药盒上提供记忆辅助装置，例如在片剂或胶囊旁边的数字，该数字与应当摄取片剂或胶囊的给药方案的天数相对应。所述记忆辅助装置的另一实例是印在卡上的日历，例如“第一周，星期一、星期二…等…，第二周，星期一、星期二…”等。记忆辅助装置的其它改变形式是显而易见的。“每日剂量”可以是单个片剂或胶囊或是需要在一天内摄入的多个片剂或胶囊。此外，式I化合物的每日剂量还可由一粒片剂或胶囊组成，而第二种化合物的每日剂量可由数粒片剂或胶囊组成，反之亦然。记忆辅助装置应说明这些情况。

本发明的另一具体实施方案提供了一种分散器，该分散器被设计成可以按照其使用顺序每次分散一个每日剂量。优选在分散器上配有记忆辅助装置，从而更有利于遵从给药方案。所述记忆辅助装置的一个实例是一个机械计数器，该计数器显示已经分散的每日剂量数。所述记忆辅助装置的另一个实例是一个与液晶读数器相连的以电池为能源的微芯片记忆装置，或可发声的提醒信号装置，所述装置可读出上一次服药的日期和/或提醒下一次服药日期。

本发明的式 I 化合物通常以适当的制剂进行给药。以下制剂的例子仅仅是说明性的，并非想要限定本发明的范围。

在以下制剂中，“活性成分”是指本发明的化合物。

制剂 1：明胶胶囊

用如下成分制备硬明胶胶囊：

| 成分 | 含量(mg/胶囊) |
|---|---|
| 活性成分 | 0.25-100 |
| 淀粉，NF | 0-650 |
| 淀粉，可流动的粉末 | 0-50 |
| 聚硅氧烷液体 350 厘沲 | 0-15 |

用如下成分制备片剂：

制剂 2：片剂

| 成分 | 含量(mg/片) |
|---|---|
| 活性成分 | 0.25-100 |
| 微晶纤维素 | 200-650 |
| 煅烧二氧化硅 | 10-650 |
| 硬脂酸 | 5-15 |

将各成分混合然后压制成片剂。

或者，可以按照如下描述制备每片含有 0.25-100mg 活性成分的片剂：

制剂 3：片剂

| 成分 | 含量(mg/片) |
|---|---|
| 活性成分 | 0.25-100 |
| 淀粉 | 45 |
| 微晶纤维素 | 35 |
| 聚乙烯吡咯烷酮(10%水溶液) | 4 |
| 羧甲基纤维素钠 | 4.5 |
| 硬脂酸镁 | 0.5 |
| 滑石 | 1 |

将活性成分、淀粉和纤维素压过 45 目美国筛然后充分混合。将聚乙烯吡咯烷酮溶液与得到的粉末混合，然后将其压过 14 目美国筛。将形成的颗粒于 50-60℃干燥然后压过 18 目美国筛。将羧甲基淀粉钠、硬脂酸镁和滑石预先压过 60 目美国筛，然后加入到颗粒中，在混合后，在压片机中压制成片剂。

按照如下描述制备含有 0.25-100mg 活性成分/5mL 药物的混悬液：

制剂 4：混悬液

| 成分 | 含量(mg/5mL) |
|---|---|
| 活性成分 | 0.25-100mg |
| 羧甲基纤维素钠 | 50mg |
| 糖浆 | 1.25mg |
| 苯甲酸溶液 | 0.10mL |
| 矫味剂 | 适量 |
| 着色剂 | 适量 |
| 纯净水至 | 5mL |

将活性成分压过 45 目美国筛然后与羧甲基纤维素钠和糖浆混合形成均匀的糊状物。将苯甲酸溶液、矫味剂和着色剂用一部分水稀释然后在搅拌下加入。然后加入足够量的水达到所需的体积。制备含有如下成分的气雾剂溶液：

制剂 5：气雾剂

| 成分 | 含量(%重量) |
|---|---|
| 活性成分 | 0.25 |
| 乙醇 | 25.75 |
| 抛射剂 22（氯二氟甲烷） | 74.00 |

将活性成分与乙醇混合然后将混合物加入到一部分抛射剂 22 中，冷却至 30℃，然后转移到填充装置中。然后在不锈钢容器中加够所需的量并用剩余的抛射剂稀释。然后在容器上安装阀门。栓剂的制备如下：

制剂 6：栓剂

| 成分 | 含量(mg/栓剂) |
|---|---|
| 活性成分 | 250 |
| 饱和脂肪酸甘油酯 | 2,000 |

将活性成分通过 60 目美国筛然后悬浮在预先用最少的所需热量熔融的饱和脂肪酸甘油酯中。然后将混合物倒入标称容量为 2g 的栓剂模

具中然后冷却。

静脉内制剂的制备如下：

制剂 7：静脉内溶液

| 成分 | 量 |
|---|---|
| 活性成分 | 25mg-10,000mg |
| 等渗盐水 | 1,000mL |

将上述成分的溶液向患者静脉内给药。

上述活性成分还可以是药物的联合形式。

## 一般实验方法

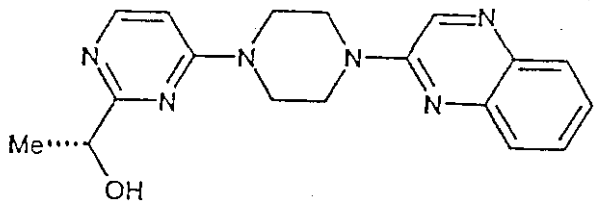
熔点用 Thomas-Hoover 毛细管熔点仪测定，未校正。$^1$H NMR 波谱在 Bruker AM-250 (Bruker Co., Billerica, Massachusetts)、Bruker AM-300、Varian XL-300 (Varian Co., Palo Alto, California)或 Varian Unity 400 上在约 23℃下在 250、300 或 400MHz 测得。化学位移以相对于残留的氯仿(7.26 ppm)、二甲亚砜(2.49 ppm)或甲醇(3.30 ppm)作为内参物的 ppm (δ)表示。峰形和峰的描述如下：s，单峰；d，二重峰；t，三重峰；q，四重峰；m，多重峰；c，复合的；br，宽峰；app，表观的。低分辨质谱在热喷雾(TS)条件下在 Fisons(现在的 Micromass) Trio 1000 质谱仪(Micromass Inc., Beverly, Massachusetts)上、在化学解离(CI)条件下在 Hewlett Packard 5989A 粒子束质谱仪(Hewlett Packard Co., Palo Alto, California)上或在常压化学解离(APCI)条件下在 Fisons (现在的 Micromass) Platform II 光谱计上测得。旋光度在 Perkin-Elmer 241 MC 旋光计(Perkin-Elmer, Norwalk, Connecticut)上用 1dcm 的标准路径长度在约 23℃下在指定的浓度和指定的溶剂中测得。

液相柱色谱用指定溶剂的强制流动(快速色谱)在 Baker 硅胶(40μm, J. T. Baker, Phillipsburg, New Jersey)或硅胶 60 (EM Sciences, Gibbstown, New Jersey)在玻璃柱中进行或用低的

氮气或空气压力在 Flash 40™ 或 Flash 12™ (Biotage, Charlottesville, Virginia) 药筒中进行。径向色谱用 Chromatron (Hanison Research, Palo Alto, California) 进行。术语“浓缩”和“蒸发”是指用旋转蒸发仪在水流抽气机的压力或在用 Buchi B-171 Vacobox (Brinkmann Instruments, Inc., Westbury, New York)或 Buchi B-177 Vacobox 产生的类似的压力下在小于或等于 50℃的浴温下蒸除溶剂。需要使用压力在 1 大气压以上的氢气的反应用 Parr 氢气装置(Parr Instrument Co., Moline, Illinois)进行。若无另外说明，试剂均来自商业途径。缩写“d”、“h”和“min”分别表示“天”、“小时”和“分钟”。

实施例 1

(R)-1-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇



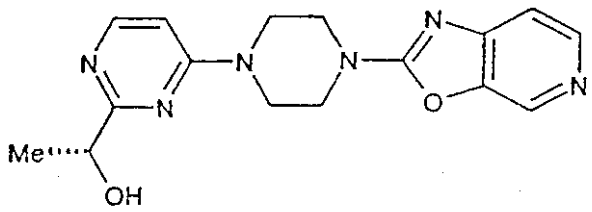

步骤 A: 乙酸(R)-1-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯。向乙酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 5 的方法制备，7.3g，36.2mmol)的异丙醇(240mL)溶液中依次加入三乙胺(10.1mL，72.4mmol)和 2-(1-哌嗪基)喹喔啉(10.1g，47.1mmol；J. Med. Chem. 1981，24，93)。将该混合物室温搅拌过夜然后浓缩。将残余物用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(5 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(2%甲醇/氯仿)得到 12.4g (91%)黄色泡沫状的实施例 1，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$，250MHz) δ 8.61 (s，1H)，8.27 (d，1H)，7.91 (dd，1H)，7.72 (dd，1H)，7.61 (td，1H)，7.44 (td，1H)，6.43 (d，1H)，5.70 (q，1H)，3.96-3.84 (c，

8H), 2.18 (s, 3H), 1.61 (d, 3H); MS (CI/$NH_3$) 379 ($MH^+$)

步骤 B: (R)-1-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇。向乙酸(R)-1-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 1, 步骤 A 的方法制备, 14.1g, 37.2mmol)的 3: 1: 1 四氢呋喃/水/甲醇混合物(375mL)的溶液中加入水合氢氧化锂(4.7g, 112mmol)。将该混合物室温搅拌 1 小时 45 分钟, 浓缩然后用氯仿萃取(6 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(2 次; 2%甲醇/氯仿), 在用己烷研制后得到 11.3g (90%)浅黄色固体状标题化合物。mp: 106.5-108℃; $^1H$ NMR ($CDCl_3$, 250MHz) δ 8.62 (s, 1H), 8.26 (d, 1H), 7.92 (dd, 1H), 7.72 (dd, 1H), 7.61 (td, 1H), 7.44 (td, 1H), 6.45 (d, 1H), 4.75 (m, 1H), 3.95-3.85 (c, 8H), 1.54 (d, 3H); MS (CI/$NH_3$) 337 ($MH^+$); $[\alpha]_D$ +15.3 (c 2.3, MeOH)。

## 实施例 2

(R)-1-[4-(4-噁唑并[5,4-c]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇



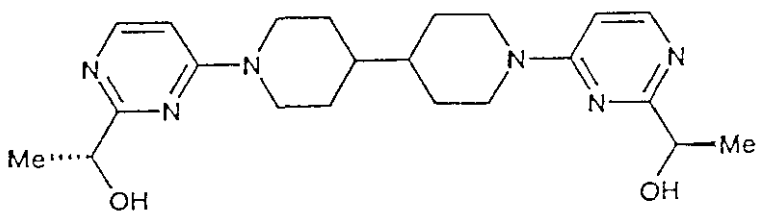

步骤 A: 丁酸(R)-1-[4-(4-噁唑并[5,4-c]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]乙酯。向 2-(1-哌嗪基)噁唑并[5,4-c]吡啶(775mg, 3.8mmol; J. Org. Chem. 1995, 60, 5721)的异丙醇(38mL)溶液中依次加入丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备, 868mg, 3.8mmol)和三乙胺(1.6mL, 11.4mmol)。将该混合物回流搅拌过夜, 冷却至室温然后蒸发。将残余物用饱和碳酸氢钠水

溶液稀释然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(2 次；3%甲醇/氯仿，然后是 6→8%甲醇/乙酸乙酯，此处的箭头符号→是指梯度)得到 1.2g (79%)浅黄色油状的实施例 2，步骤 A 的标题化合物，其在放置后固化。$^1$H NMR ($CDCl_3$, 250MHz) δ 8.57 (s, 1H), 8.39 (d, 1H), 8.28 (d, 1H), 7.30 (d, 1H), 6.44 (d, 1H), 5.70 (q, 1H), 3.85 (s, 8H), 2.42 (t, 2H), 1.78-1.61 (c, 2H), 1.60 (d, 3H), 0.98 (t, 3H)；MS (APCI) 397 ($MH^+$)。

步骤 B：(R)-1-[4-(4-噁唑并[5,4-c]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇。向丁酸(R)-1-[4-(4-噁唑并[5,4-c]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 2，步骤 A 的方法制备，1.2g, 3.0mmol)的甲醇(30mL)溶液中加入碳酸钾(823mg, 6.0mmol)。将该混合物室温搅拌 5 小时，用饱和氯化铵水溶液稀释，浓缩然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(6%甲醇/氯仿)，在用己烷研制后得到 915mg (94%)白色固体状标题化合物。mp：181-183℃；$^1$H NMR ($CDCl_3$, 300MHz) δ 8.54 (d, 1H), 8.35 (d, 1H), 8.25 (d, 1H), 7.27 (dd, 1H), 6.44 (d, 1H), 4.71 (q, 1H), 4.25 (br s, 1H), 3.86-3.83 (c, 8H), 1.50 (d, 3H)；MS (APCI) 327 ($MH^+$)；$[\alpha]_D$ +15.3 (c 0.5, MeOH)。

## 实施例 3

1R-(4-{1'-[2-(1R-羟基-乙基)-嘧啶-4-基]-[4,4']联哌啶-1-基}-嘧啶-2-基)乙醇。



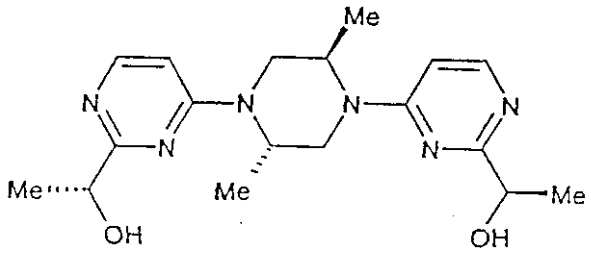
将(R)-1-(4-氯-嘧啶-2-基)-乙醇(按照制备例 10 的方法制备，100mg，0.63mmol)、4,4'-联哌啶二盐酸盐(76mg，0.32mmol)和三乙胺(0.44mL，3.2mmol)在异丙醇(3mL)中的混合物回流过夜然后冷却至室温。将反应混合物用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(4 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(Biotage Flash 40S™，5%甲醇/氯仿)得到 110mg (85%)白色固体状标题化合物。mp：144-153℃，$^1$H NMR ($CDCl_3$，400MHz) δ 8.14 (d，2H)，6.36 (d，2H)，4.67 (q，2H)，4.53-4.28 (c，4H)，2.84 (t，4H)，1.82 (d，4H)，1.49 (d，6H)；1.43-1.40 (c，2H)，1.30-1.18 (c，4H)；MS (APCI) 413 ($MH^+$)；$[\alpha]_D$ +22.6 (c 1.0，MeOH)。

## 实施例 4 至 8

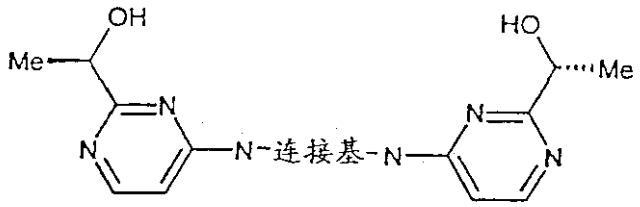
实施例 4 至 8 按照与实施例 3 类似的方式从适宜的原理制得。

## 实施例 4

1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇



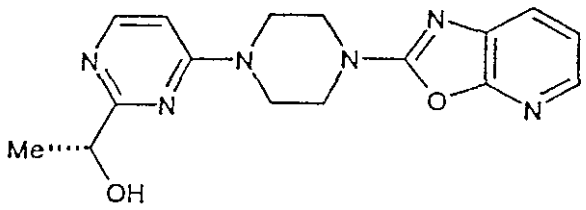

mp：153-155℃，$^1$H NMR ($CDCl_3$，400MHz) δ 8.23 (d，2H)，6.40 (d，2H)，4.71 (m，2H)，4.28 (dd，2H)，3.51-3.45 (c，4H)，1.51 (d，6H)，1.23 (d，6H)；MS (APCI) 359 ($MH^+$)；$[\alpha]_D$ +18.6 (c 1.2，$CHCl_3$)。




| 实施例 | N-连接基-N | (℃) | MS(MH$^+$) |
|---|---|---|---|
| 5 | N,N'-乙二胺 | 141-143 | 333 |
| 6 | [1,4]二氮杂环庚烷 | 136-138 | 345 |
| 7 | 4,4'-亚乙基联哌啶 | | 441 |
| 8 | 甲基-哌啶-4-基甲基-胺 | | 373 |

实施例 9

(R)-1-[4-(4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇




步骤 A: 2-(1-哌嗪基)噁唑并[5,4-b]吡啶。将 2-(甲硫基)噁唑并[5,4-b]吡啶(9.2g, 55.5mmol; J. Org. Chem. 1995, 60, 5721)和哌嗪(23.9g, 277mmol)和少量乙酸乙酯(用于将化合物从烧瓶壁上洗下)一起于 90℃加热 1.5 小时。将反应混合物冷却至室温，用约 20%的饱和碳酸氢钠水溶液稀释然后用氯仿萃取(4 次)。将合并的有机萃取液用饱和碳酸氢钠水溶液洗涤(1 次)，用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(3→5%甲醇/氯仿+ 1%氢氧化铵)得到 9.1g (81%)黄白色固体状实施例 9，步骤 A 的标题化合物。$^1$H NMR

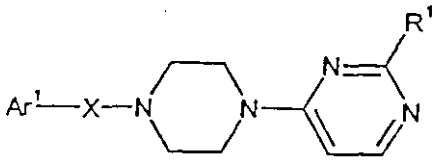
($CDCl_3$, 300MHz) δ 7.92 (dd, 1H), 7.55 (dd, 1H), 7.10 (dd, 1H), 3.74-3.70 (c, 4H), 3.02-2.97 (c, 4H); MS (APCI) 205 ($MH^+$)。

步骤 B: 丁酸(R)-1-[4-(4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]乙酯。向丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备, 6.8g, 29.9mmol)和三乙胺(12.5mL, 89.6mmol)的异丙醇(100mL)溶液中加入 2-(1-哌嗪基)噁唑并[5,4-b]吡啶(按照实施例 9, 步骤 A 的方法制备, 6.1g, 29.9mmol)。将混合物回流搅拌过夜, 冷却至室温然后蒸发。将残余物用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(1.5→2%甲醇/氯仿)得到 11.1g (94%)黄色油状实施例 9, 步骤 B 的标题化合物, 其在放置后固化。$^1H$ NMR ($CDCl_3$, 250MHz) δ 8.28 (d, 1H), 7.97 (dd, 1H), 7.60 (dd, 1H), 7.25 (dd, 1H), 6.44 (d, 1H), 5.70 (q, 1H), 3.85 (app s, 8H), 2.42 (t, 2H), 1.78-1.61 (c, 2H), 1.60 (d, 3H), 0.98 (t, 3H); MS (APCI) 397 ($MH^+$)。

步骤 C: (R)-1-[4-(4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇。向丁酸(R)-1-[4-(4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 9, 步骤 B 的方法制备, 11.0g, 27.6mmol)的二氧六环(11.5mL)溶液中加入浓盐酸(23mL, 276mmol)。将混合物室温搅拌过夜, 用 6N 氢氧化钠水溶液中和然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(3.5%甲醇/氯仿)得到 8.4g (93%)白色固体状标题化合物。mp: 153-156℃; $^1H$ NMR ($CDCl_3$, 300MHz) δ 8.25 (d, 1H), 7.95 (dd, 1H), 7.58 (dd, 1H), 7.15 (dd, 1H), 6.45 (d, 1H), 4.72 (q, 1H), 4.25 (br s, 1H), 3.85-3.82 (c, 8H), 1.51 (d, 3H); MS (CI/$NH_3$) 327 ($MH^+$); $[\alpha]_D$ +16.1 (c 1.0, MeOH)。

## 实施例 10 至 15

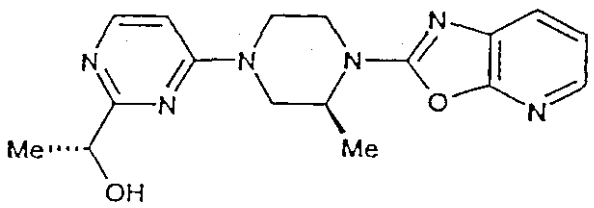
实施例 10 至 15 按照与实施例 9 类似的方法从适宜的原料制备。



| 实施例 | X-Ar¹ | R¹ | mp(℃) | MS(MH⁺) |
|---|---|---|---|---|
| 10 | 噁唑并[4,5-c]吡啶-2-基 | (R)-CH(CH₃)OH | 178-180 | 327 |
| 11 | 噁唑并[5,4-c]吡啶-2-基 | -C(CH₃)₂OH | 181-184 | 341 |
| 12 | 噁唑并[5,4-c]吡啶-2-基 | (±)-CH(CH₃)OH | 153-158 | 327 |
| 13 | 噁唑并[5,4-c]吡啶-2-基 | (S)-CH(CH₃)OH | 175-179 | 327 |
| 14 | 喹喔啉基-2-基 | (±)-CH(CH₃)OH | 102-105 | 337 |
| 15 | (5-碘)-苯并噁唑-2-基 | (R)-CH(CH₃)OH | | 452 |

## 实施例 16

1R-[4-(3S-甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇



步骤 A: (S)-2-(4-苄基-2-甲基-哌嗪-1-基)-噁唑并[5,4-b]吡啶。将 2-(甲硫基)噁唑并[5,4-b]吡啶(44g, 264mmol; J. Org. Chem. 1995, 60, 5721)和(S)-1-苄基-3-甲基-哌嗪(25g, 132mmol; J.

Org. Chem. 1995, 60, 4177)的混合物于 130℃搅拌 3 天，冷却至室温然后通过快速柱色谱纯化(17→83%乙酸乙酯/己烷)得到 30g (74%)深黄色油状实施例 16，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 7.89 (d, 1H), 7.53 (d, 1H), 7.34-7.25 (c, 5H), 7.10 (dd, 1H), 4.45 (m, 1H), 4.11 (d, 1H), 3.59 (d, 1H), 3.52-3.45 (c, 2H), 2.90 (d, 1H), 2.73 (d, 1H), 2.32 (dd, 1H), 2.21 (td, 1H), 1.41 (d, 3H); MS (APCI) 309 ($MH^+$)。

步骤 B: (S)-2-(2-甲基-哌嗪-1-基)-噁唑并[5,4-b]吡啶。向(S)-2-(4-苄基-2-甲基-哌嗪-1-基)-噁唑并[5,4-b]吡啶(按照实施例 16，步骤 A 的方法制备，30g，97mmol)的甲醇(970mL)溶液中加入氯化氢(5.85M 的甲醇溶液，20mL，116mmol)、甲酸铵(122g，1.95mol)和 10%钯碳(60g，200 wt%)。将该混合物回流搅拌 50 分钟，冷却然后用硅藻土过滤。将滤液浓缩，用饱和碳酸氢钠水溶液稀释然后依次用氯仿(1 次)和 10%异丙醇/氯仿萃取(4 次)。将合并的有机萃取液用硫酸钠干燥，过滤然后蒸发得到 16g (76%)绿色油状实施例 16，步骤 B 的标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 7.89 (m, 1H), 7.53 (m, 1H), 7.09 (m, 1H), 4.42 (m, 1H), 4.11 (d, 1H), 3.35 (td, 1H), 3.09-3.03 (c, 2H), 2.85 (d, 1H), 2.82 (td, 1H), 1.38 (d, 3H); MS (APCI) 219 ($MH^+$)。

步骤 C: 丁酸 1R-[4-(3S-甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯。将(S)-2-(2-甲基-哌嗪-1-基)-噁唑并[5,4-b]吡啶(按照实施例 16，步骤 B 的方法制备，10g，45.9mmol)、丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，9.5g，41.7mmol)和三乙胺(17.3mL，125mmol)在异丙醇(230mL)中的混合物加热回流 30 小时，冷却至室温，用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(4 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(1.5%甲醇/氯仿)得到 16g (93%)黄色油状的实施例 16，步骤 C 的标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.23 (d, 1H), 7.93 (dd, 1H), 7.57 (d, 1H), 7.13 (dd, 1H), 6.39 (d, 1H),

5.67 (q, 1H), 4.61 (m, 1H), 4.42 (m, 1H), 4.28 (m, 1H), 4.18 (dt, 1H), 3.51 (td, 1H), 3.41 (dd, 1H), 3.17 (td, 1H), 2.39 (t, 2H), 1.72-1.59 (c, 2H), 1.57 (d, 3H), 1.30 (d, 3H), 0.95 (t, 3H); MS (APCI) 411 ($MH^+$)。

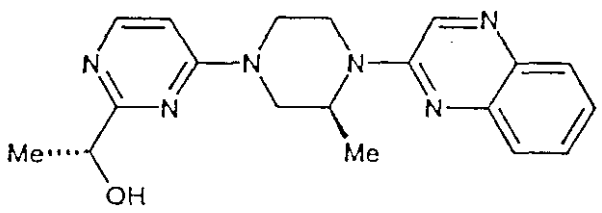
步骤 D: 1R-[4-(3S-甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇。将丁酸 1R-[4-(3S-甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 16, 步骤 C 的方法制备, 16g, 39.0mmol)和碳酸钾(10.8g, 78.1mmol)在甲醇(195mL)中的混合物室温搅拌 4 小时, 用饱和碳酸氢钠水溶液稀释, 然后依次用氯仿(1 次)和 10%异丙醇/氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(1→2.5%甲醇/氯仿)得到白色泡沫, 将其用乙醚/氯仿重结晶得到 8.9g (67%)白色固体状标题化合物。mp: 147-149℃; $^1H$ NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 1H), 7.94 (dd, 1H), 7.58 (d, 1H), 7.14 (dd, 1H), 6.42 (d, 1H), 4.72 (m, 1H), 4.64 (m, 1H), 4.42 (m, 1H), 4.32 (m, 1H), 4.25 (d, 1H), 4.21 (dt, 1H), 3.54 (td, 1H), 3.46 (dd, 1H), 3.24 (td, 1H), 1.51 (d, 3H), 1.33 (d, 3H); MS (APCI) 411 ($MH^+$); $[\alpha]_D$ +70.4 (c 1.1, MeOH)。

## 实施例 17 至 25

实施例 17 至 25 按照与实施例 16 类似的方法从适宜的原料制备。

## 实施例 17

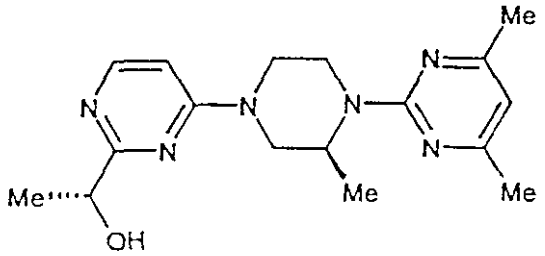
1R-[4-(3S-甲基-4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇



$^1$H NMR ($CDCl_3$, 400MHz) δ 8.56 (d, 1H), 8.23 (d, 1H), 7.89 (d, 1H), 7.69 (d, 1H), 7.59 (t, 1H), 7.41 (t, 1H), 6.42 (d, 1H), 4.78 (m, 1H), 4.73 (m, 1H), 4.43 (m, 1H), 4.38-4.23 (c, 2H), 3.64-3.52 (c, 2H), 3.38 (m, 1H), 1.52 (d, 3H), 1.30 (d, 3H); MS (APCI) 351 ($MH^+$); $[\alpha]_D$ +57.0 (c 1.2, $CHCl_3$)。

## 实施例 18

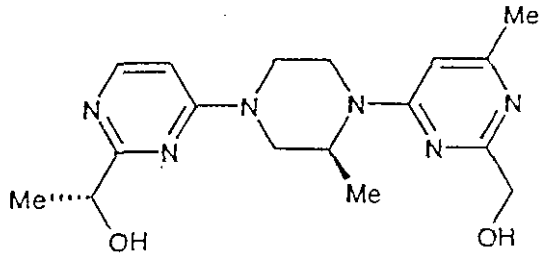
1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




$^1$H NMR ($CDCl_3$, 400MHz) δ 8.18 (d, 1H), 6.37 (d, 1H), 6.30 (s, 1H), 5.04 (m, 1H), 4.70 (q, 1H), 4.60 (dt, 1H), 4.37 (br s, 1H), 4.36-4.12 (c, 2H), 3.40 (dd, 1H), 3.34 (td, 1H), 3.16 (td, 1H), 2.28 (s, 6H), 1.51 (d, 3H), 1.16 (d, 3H); MS (APCI) 329 ($MH^+$); $[\alpha]_D$ +78.8(c 1.6, MeOH)。

## 实施例 19

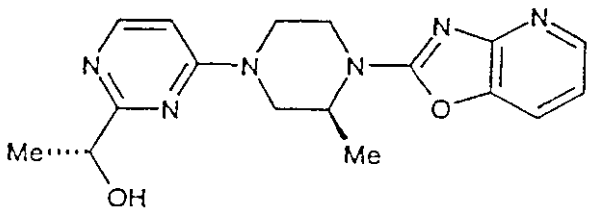
1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



$^1$H NMR ($CDCl_3$, 400MHz) δ 8.23 (d, 1H), 6.38 (d, 1H), 6.23 (s, 1H), 4.71 (q, 1H), 4.58 (s, 3H), 4.36-4.18 (c, 4H), 3.86 (br s, 1H), 3.57 (dd, 1H), 3.46 (td, 1H), 3.32 (td, 1H), 2.38 (s, 3H), 1.51 (d, 3H), 1.22 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ +72.6 (c 1.1, MeOH)。

实施例 20

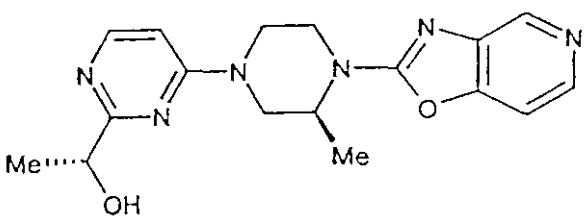
1R-[4-(3S-甲基-4-噁唑并[4,5-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇




mp: 158-161℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.22-8.15 (c, 2H), 7.40 (dd, 1H), 6.86 (dd, 1H), 6.40 (d, 1H), 4.65 (m, 1H), 4.61 (m, 1H), 4. 44-4.20 (c, 3H), 4.18 (dt, 1H), 3.50 (td, 1H), 3.41 (dd, 1H), 3.19 (td, 1H), 1.45 (d, 3H), 1.26 (d, 3H); MS (APCI) 341 ($MH^+$); $[\alpha]_D$ +58.2 (c 1.1, MeOH)。

实施例 21

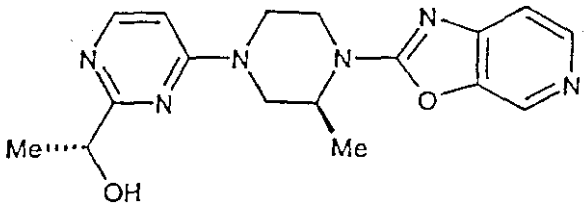
1R-[4-(3S-甲基-4-噁唑并[4,5-c]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇



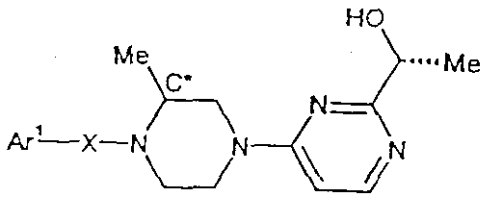
$^1$H NMR ($CDCl_3$, 400MHz) δ 8.68 (d, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 7.25 (dd, 1H), 6.42 (d, 1H), 4.71 (m, 1H), 4.60 (m, 1H), 4.42 (m, 1H), 4.32-4.23 (c, 2H), 4.17 (dt, 1H), 3.56 (td, 1H), 3.47 (dd, 1H), 3.24 (td, 1H), 1.51 (d, 3H), 1.32 (d, 3H); MS (APCI) 341 ($MH^+$); $[\alpha]_D$+57.9 (c 1.6, MeOH)。

实施例 22

1R-[4-(3S-甲基-4-噁唑并[5,4-c]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇



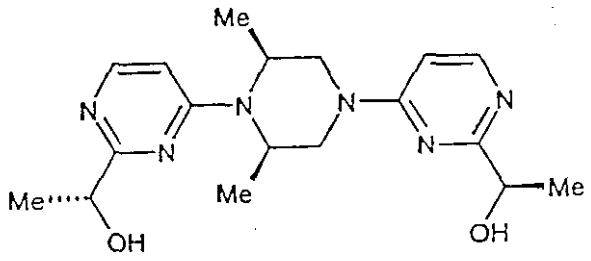

$^1$H NMR ($CDCl_3$, 400MHz) δ 8.56 (s, 1H), 8.37 (d, 1H), 8.25 (d, 1H), 7.29 (d, 1H), 6.43 (d, 1H), 4.72 (m, 1H), 4.65 (m, 1H), 4.45 (m, 1H), 4.29 (m, 1H), 4.26-4.20 (c, 2H), 3.58 (td, 1H), 3.48 (dd, 1H), 3.26 (td, 1H), 1.51 (d, 3H), 1.34 (d, 3H); MS (APCI) 341 ($MH^+$); $[\alpha]_D$ +61. 1 (c 1. 0, MeOH)。




| 实施例 | X-$Ar^1$ | C* | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|
| 23 | 喹喔啉基-2-基 | R | | 351 |
| 24 | (2-[$C(CH_3)_2OH$])-嘧啶-4-基 | S | | 359 |
| 25 | 苯并噁唑-2-基 | S | | 340 |

## 实施例 26

1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}嘧啶-2-基)-乙醇




方法 1：向丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4 的方法制备，72.8g，238mmol)和三乙胺(50mL，357mmol)的异丙醇(793mL)溶液中加入丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，54.3g，238mmol)。将该混合物回流搅拌 12 小时然后浓缩。将残余物溶于 3：1：1 四氢呋喃/甲醇/水的混合物(1200mL)并加入水合氢氧化锂(60g. 1.43mol)。将该混合物室温搅拌 2.5 小时，部分浓缩，用饱和碳酸氢钠水溶液稀释并用 10%异丙醇/氯仿萃取(6 次)。将合并的有机萃取液用硫酸钠干燥，过滤然后蒸发。将残余物用 1：1 乙酸乙酯/甲醇(1100mL)稀释然后室温搅拌 1 稀释。过滤收集沉淀并将滤液浓缩至约 850mL。1 小时后，又有沉淀生成并过滤收集该沉淀。将滤液部分浓缩并加入乙酸乙酯。1 小时，再次形成沉淀并过滤收集该沉淀。将该过程再重复一次，总共得到 65.9g (77%)白色固体状标题化合物。mp：163-164.5℃；$^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.74-4.70 (c, 2H), 4.70-4.50 (c, 2H), 4.50-4.30 (c, 2H), 4.30 (d, 1H), 4.27 (d, 1H), 3.31 (dt, 2H), 1.51 (d, 6H), 1.26 (d, 6H)；MS (APCI) 359 ($MH^+$)；$[\alpha]_D$ +42.3 (c 1.0, MeOH)。

方法 2，步骤 A：丁酸 1R-(4-{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基哌嗪-1-基}-嘧啶-2-基)-乙酯。向(R)-2-(1-丁

酰氧基-乙基)-3H-嘧啶 4-酮(828g, 3.9mol)的二氯甲烷(50L)溶液中加入三乙胺(576mL, 4.1mol)并将形成的溶液冷却至 5℃。缓慢加入三氟甲磺酸酐(729mL, 4.3mol)的二氯甲烷(6L)溶液，使内部温保持在 10℃以下。加料结束后，通过 TLC 判断反应是否完成，然后加入水(5.3L)终止反应。将有机层分离，用水(20L)和饱和碳酸氢钠水溶液(20L)洗涤，用硫酸钠干燥。将该溶液缓慢加入到丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯二苯甲酰基-L-酒石酸盐(按照制备例 15 的方法制备，2.49 kg, 3.75mol)和三乙胺(1.6L, 11.6mol)的二甲基乙酰胺(18L)溶液中，保持内部温度在 10℃以下。将形成的溶液于 10℃搅拌 12 小时，然后用乙酸乙酯(40L)和水(27L)稀释。分出水层并将有机层用水(40L)洗涤两次，用盐水(20L)洗涤一次，然后用硫酸钠干燥。将得到的溶液部分浓缩(8L)，然后加入己烷(23L)。使形成的悬浮液成粒 12 小时，然后用棉花过滤。将固体真空干燥(40℃)得到 1178g (63%)白色固体状实施例 26，方法 2，步骤 A 的标题化合物。该化合物的 $^1$H NMR 和 MS 数据与实施例 266 的一致。

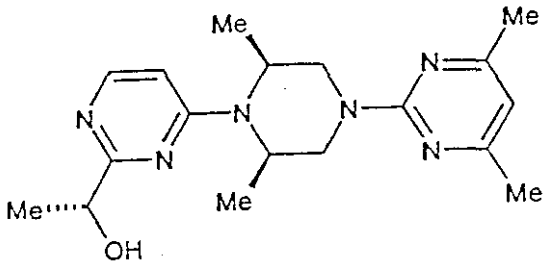
方法 2，步骤 B: 1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇。向丁酸 1R-(4-{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酯(按照实施例 26，方法 2，步骤 A 的方法制备，1140g, 2.28mol)的异丙醇(11.4L)溶液中于室温下加入 40%氢氧化钾水溶液(800mL)。将形成的溶液搅拌 16 小时然后用水(5L)和二氯甲烷(4L)稀释。将有机层分离并将水层用二氯甲烷(4L)萃取。将合并的有机层用 1M 氢氧化钠水溶液(10L)洗涤两次，然后用水(5L)洗涤两次，部分浓缩(5L)，用乙酸乙酯(4L)稀释，然后再次部分浓缩(6L)。加入己烷(10L)并将形成的浆液回流搅拌 12 小时，冷却至室温然后过滤。将得到的固体真空干燥得到 758g (93%)白色固体状标题化合物。该化合物的 mp、$^1$H NMR、MS 和旋光数据与实施例 26，方法 1 的一致。

## 实施例 27 至 62

实施例 27 至 62 按照与实施例 26 类似的方法从适宜的原料制备。

### 实施例 27

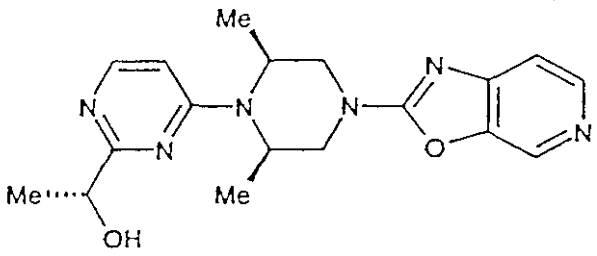
1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}乙醇



mp: 150.5-152℃; $^1$H NMR ($CD_3OD$, 300MHz) δ 8.14 (d, 1H), 6.62 (d, 1H), 6.46 (d, 1H), 6.40 (s, 1H), 4.83 (d, 2H), 4.72-4.52 (c, 3H), 3.30 (dd, 2H), 2.28 (s, 6H), 1.46 (d, 3H), 1.23 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +12.0 (c 1.3, MeOH)。

### 实施例 28

1R-[4-(2R,6S-二甲基-4-噁唑并[5,4-c]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇

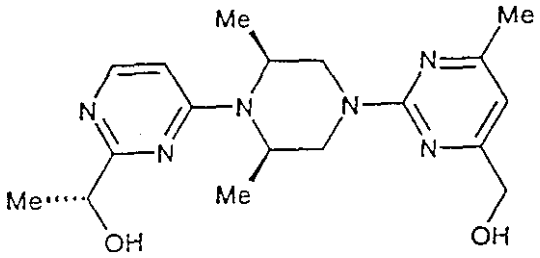


$^1$H NMR ($CD_3OD$, 300MHz) δ 8.53 (d, 1H), 8.28 (d, 1H), 8.20 (d, 1H), 7.34 (dd, 1H), 6.68 (d, 1H), 4.90-4.72 (c, 2H),

4.69 (q, 1H), 4.32 (d, 2H), 3.56 (dd, 2H), 1.47 (d, 3H), 1.33 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +8.1 (c 1.3, MeOH)。

## 实施例 29

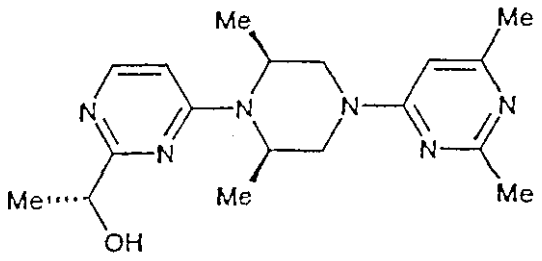
1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




mp: 139-141 ℃; $^1H$ NMR ($CD_3OD$, 300MHz) δ 8.24 (d, 1H), 6.51 (d, 1H), 6.38 (s, 1H), 4.90 (m, 1H), 4.84 (d, 2H), 4.77-4.53 (c, 2H), 4.55 (s, 2H), 3.24 (dd, 2H), 2.37 (s, 3H), 1.61 (d, 3H), 1.32 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +14.8 (c 1.0, MeOH)。

## 实施例 30

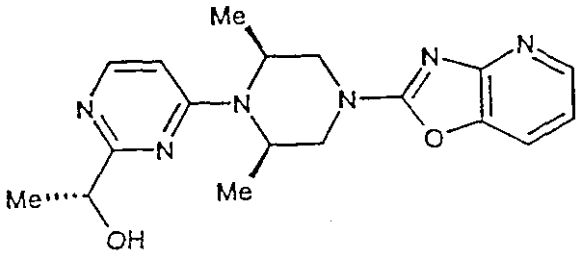
1R-{4-[4-(2,6-二甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



$^1$H NMR ($CDCl_3$, 300MHz) δ 8.22 (d, 1H), 6.36 (d, 1H), 6.26 (s, 1H), 4.71 (m, 1H), 4.65-4.50 (c, 2H), 4.42-4.28 (c, 3H), 3.24 (dd, 2H), 2.49 (s, 3H), 2.35 (s, 3H), 1.52 (d, 3H), 1.26 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +11.4 (c 0.8, MeOH)。

## 实施例 31

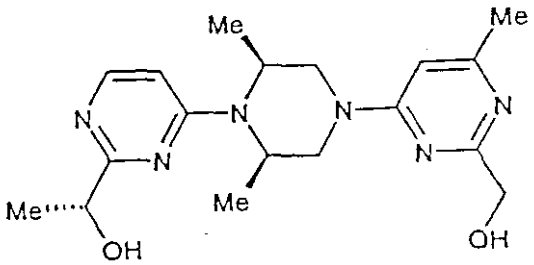
1R-[4-(2R,6S-二甲基-4-噁唑并[4,5-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇




mp: 231-233℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.26-8.23 (c, 2H), 7.47 (d, 1H), 6.94 (dd, 1H), 6.39 (d, 1H), 4.75-4.53 (c, 2H), 4.72 (q, 1H), 4.35 (d, 1H), 4.28 (m, 1H), 3.44 (dd, 2H), 1.51 (d, 3H), 1.34 (d, 6H); MS (APCI) 355 ($MH^+$); $[\alpha]_D$ +8.0 (c 0.8, MeOH)。

## 实施例 32

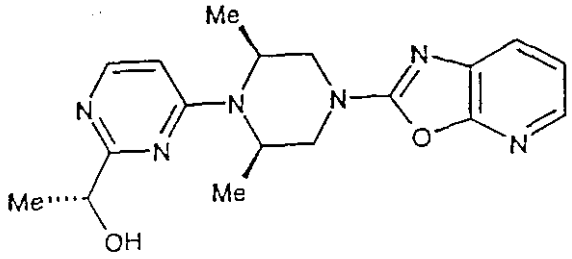
1R-{4-[4-(2-羟甲基-6-甲基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



$^1$H NMR ($CD_3OD$, 300MHz) δ 8.16 (d, 1H), 6.66 (s, 1H), 6.63 (d, 1H), 4.85-4.63 (c, 2H), 4.67 (q, 1H), 4.58 (d, 2H), 4.50 (s, 2H), 3.26 (dd, 2H), 2.35 (s, 3H), 1.46 (d, 3H), 1.24 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +11.8 (c 0.9, MeOH)。

## 实施例 33

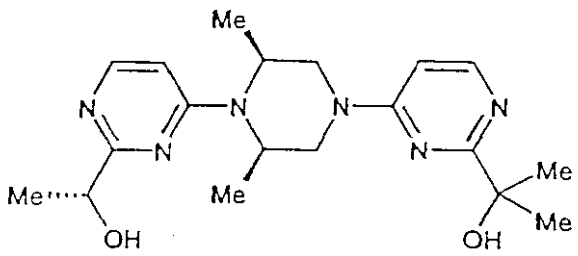
1R-[4-(2R,6S-二甲基-4-噁唑并[5,4-b]吡啶-2-基-哌嗪-1-基)-嘧啶-2-基]-乙醇




mp: 204-207 ℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.25 (d, 1H), 7.95 (dd, 1H), 7.59 (dd, 1H), 7.15 (dd, 1H), 6.39 (d, 1H), 4.80-4.57 (c, 2H), 4.73 (q, 1H), 4.30 (d, 2H), 3.42 (dd, 2H), 1.51 (d, 3H), 1.35 (d, 6H); MS (APCI) 355 ($MH^+$); $[\alpha]_D$ +7.5 (c 0.7, MeOH)。

## 实施例 34

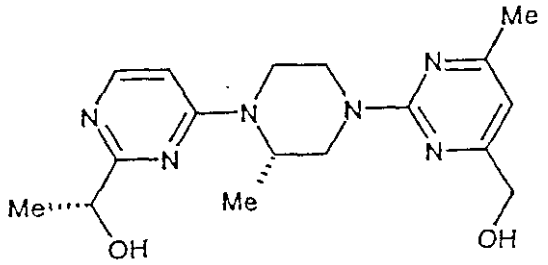
2-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-丙-2-醇



mp: 138-140℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.23 (d, 2H), 6.45 (d, 1H), 6.36 (d, 1H), 4.86 (s, 1H), 4.70 (m, 1H), 4.67-4.33 (c, 4H), 4.30 (d, 1H), 3.31 (dd, 2H), 1.53 (s, 6H), 1.51 (d, 3H), 1.25 (d, 6H); MS (APCI) 373 ($MH^+$); $[\alpha]_D$ +15.5 (c 1.2, MeOH)。

实施例 35

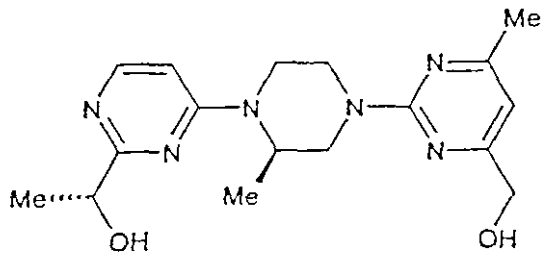
1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-2S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




$^1$H NMR ($CDCl_3$, 400MHz) δ 8.18 (d, 1H), 6.36 (d, 1H), 6.32 (s, 1H), 4.69 (q, 1H), 4.60-4.53 (c, 3H), 4.52 (s, 2H), 4.38-4.18 (c, 2H), 3.63 (m, 1H), 3.40-3.29 (c, 2H), 3.24 (m, 1H), 2.32 (s, 3H), 1.49 (d, 3H), 1.20 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ +66.5 (c 1.0, MeOH)。

实施例 36

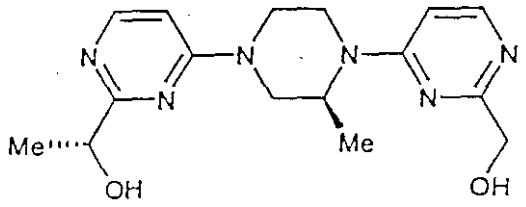
1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-2R-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



$^1$H NMR ($CDCl_3$, 400MHz) δ 8.21 (d, 1H), 6.37 (d, 1H), 6.33 (s, 1H), 4.72 (m, 1H), 4.67-4.54 (c, 3H), 4.54 (s, 2H), 4.34 (d, 1H), 4.20 (d, 1H), 3.58 (br s, 1H), 3.42-3.32 (c, 2H), 3.26 (td, 1H), 2.34 (s, 3H), 1.51 (d, 3H), 1.21 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ -35.0 (c 1.1, MeOH)。

实施例 37

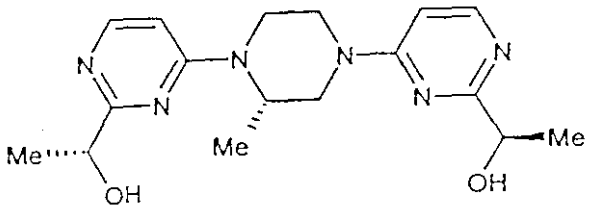
1R-{4-[4-(2-羟甲基-嘧啶-4-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




mp: 178-181 ℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.23 (d, 2H), 6.38 (d, 2H), 4.60 (q, 1H), 4.60 (s, 2H), 4.56 (m, 1H), 4.28-4.15 (c, 4H), 3.72 (br s, 1H), 3.58 (dd, 1H), 3.48 (m, 1H), 3.33 (td, 1H), 1.51 (d, 3H), 1.23 (d, 3H); MS (APCI) 331 ($MH^+$); $[\alpha]_D$ +88.9 (c 1.1, MeOH)。

实施例 38

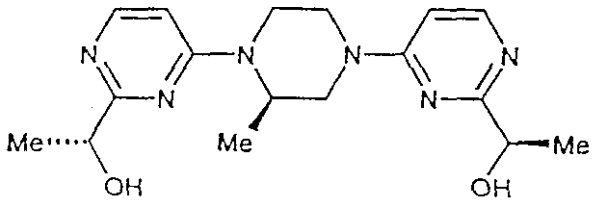
1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2S-甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇



mp: 158-160℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 2H), 6.39 (d, 1H), 6.38 (d, 1H), 4.71 (m, 2H), 4.55 (br s, 1H), 4.32-4.16 (c, 5H), 3.60 (dd, 1H), 3.48 (td, 1H), 3.38 (td, 1H), 1.52 (d, 6H), 1.24 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ +82.5 (c 1.0, MeOH)。

实施例 39

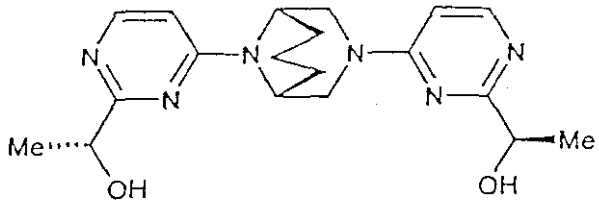
1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R-甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇




mp: 155-157℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 2H), 6.39 (d, 1H), 6.38 (d, 1H), 4.73 (m, 2H), 4.58 (br s, 1H), 4.32-4.16 (c, 5H), 3.59 (dd, 1H), 3.50 (m, 1H), 3.38 (m, 1H), 1.52 (d, 6H), 1.25 (d, 3H); MS (APCI) 345 ($MH^+$); $[\alpha]_D$ -30.4 (c 0.9, MeOH)。

实施例 40

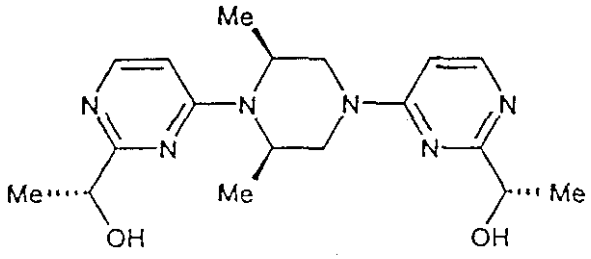
1R-(4-{3-[2-(1R-羟基-乙基)-嘧啶-4-基]-3,9-二氮杂-二环[3.3.1]壬-9-基}-嘧啶-2-基)-乙醇



mp: 151-158℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 2H), 6.42 (d, 1H), 6.41 (d, 1H), 4.72 (m, 2H), 4.48-4.18 (c, 2H), 4.29 (dd, 2H), 3.28 (d, 2H), 2.03 (m, 1H), 1.98-1.82 (c, 4H), 1.58 (m, 1H), 1.51 (d, 3H), 1.50 (d, 3H); MS (APCI) 371 ($MH^+$); $[\alpha]_D$ +27.6 (c 0.9, MeOH)。

## 实施例 41

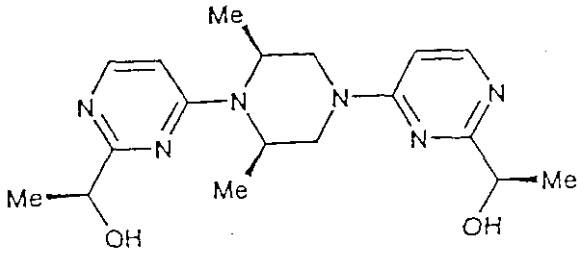
1R-(4-{4-[2-(1S-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇




mp: 222-223.5℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.75-4.51 (c, 4H), 4.50-4.30 (c, 4H), 3.31 (dt, 2H), 1.51 (d, 6H), 1.26 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ -3.4 (c 0.5, $CHCl_3$)。

## 实施例 42

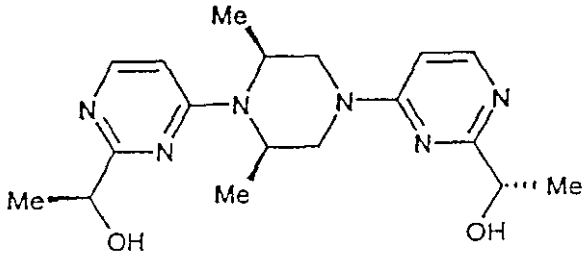
1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇



mp: 224-226℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.76-4.51 (c, 4H), 4.50-4.23 (c, 4H), 3.33 (dt, 2H), 1.51 (d, 6H), 1.25 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +64.2 (c 0.5, $CHCl_3$)。

## 实施例 43

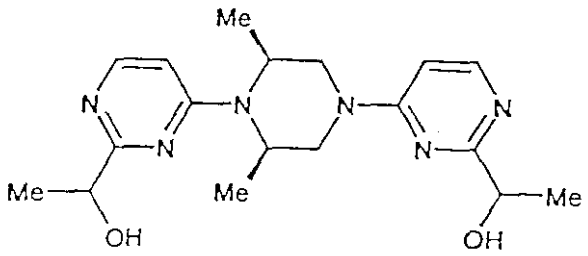
1S-(4-{4-[2-(1S-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇




mp: 164-165.5℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.75-4.51 (c, 4H), 4.50-4.23 (c, 4H), 3.47-3.28 (c, 2H), 1.51 (d, 6H), 1.25 (d, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ -43.8 (c 1.0, MeOH)。

## 实施例 44

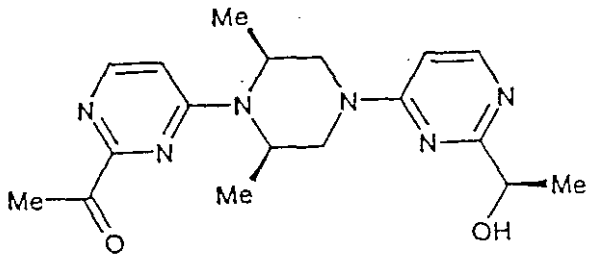
1RS-(4-{4-[2-(1RS-羟基-乙基)-嘧啶-4-基]-2R*,6S*-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇



mp: 180-186 ℃ ; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.24 (d, 1H), 8.23 (d, 1H), 6.46 (d, 1H), 6.36 (d, 1H), 4.75-4.51 (c, 4H), 4.51-4.31 (c, 4H), 3.47-3.28 (c, 2H), 1.51 (d, 6H), 1.25 (d, 6H); MS (APCI) 359 ($MH^+$)。

实施例 45

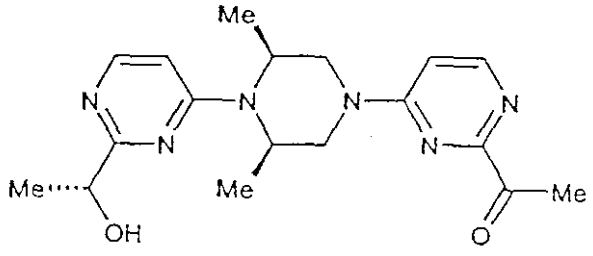
1-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶 2-基)-乙酮




mp: 123-127 ℃ ; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.41 (d, 1H), 8.24 (d, 1H), 6.56 (d, 1H), 6.47 (d, 1H), 4.75-4.53 (c, 3H), 4.52-4.28 (c, 2H), 4.26 (m, 1H), 3.36-3.29 (c, 2H), 2.68 (s, 3H), 1.51 (d, 3H), 1.28 (d, 6H); MS (APCI) 357 ($MH^+$); $[\alpha]_D$+ 19. 4 (c 1.0, MeOH)。

实施例 46

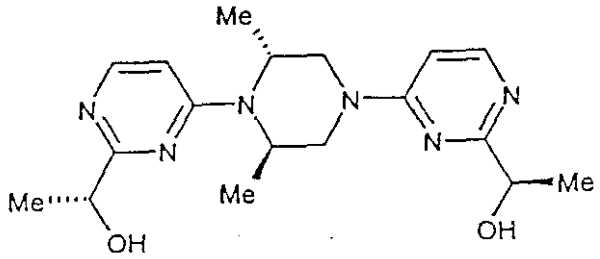
1-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酮



mp: 150-164℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.40 (d, 1H), 8.24 (d, 1H), 6.66 (d, 1H), 6.37 (d, 1H), 4.74-4.52 (c, 3H), 4.51-4.31 (c, 2H), 4.29 (m, 1H), 3.36 (dd, 2H), 2.69 (s, 3H), 1.51 (d, 3H), 1.27 (d, 6H); MS (APCI) 357 ($MH^+$); $[\alpha]_D$ +21. 8 (c 1.1, MeOH)。

实施例 47

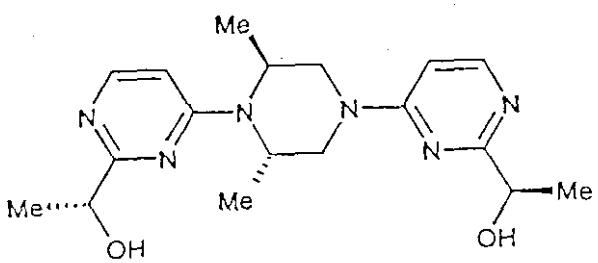
1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6R-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇




mp: 168-171℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.27 (d, 1H), 8.23 (d, 1H), 6.33 (d, 1H), 6.30 (d, 1H), 4.78-4.69 (c, 2H), 4.68-4.28 (c, 5H), 3.83-3.69 (c, 2H), 3.54 (m, 1H), 1.53 (d, 3H), 1.52 (d, 3H), 1.43-1.22 (c, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$+92.2 (c 0.5, MeOH)。

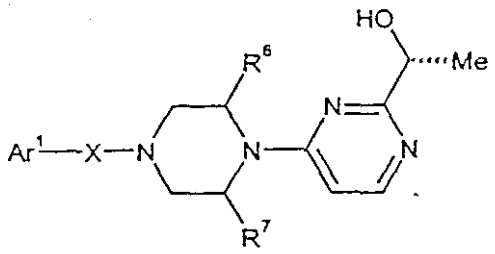
实施例 48

1R-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2S,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇

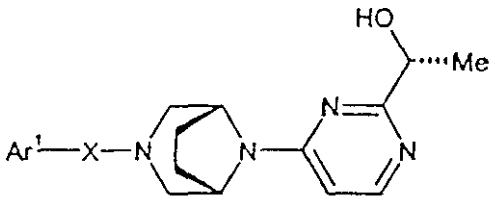


mp: 168-178℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.26 (d, 1H), 8.23 (d, 1H), 6.32 (d, 1H), 6.29 (d, 1H), 4.78-4.68 (c, 2H), 4.65-4.27 (c, 5H), 3.82-3.71 (c, 2H), 3.55 (m, 1H), 1.52 (d, 3H), 1.51 (d, 3H), 1.43-1.20 (c, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ -32. 4 (c 0.7, MeOH).

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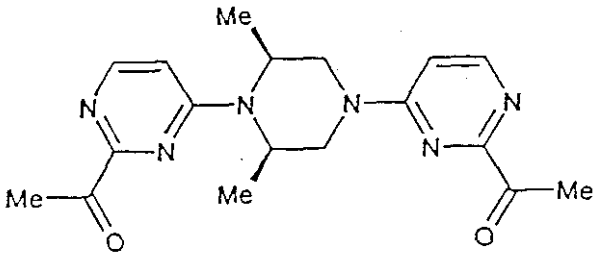

| 实施例 | X-Ar$^1$ | R$^6$ | R$^7$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 49 | 苯并噁唑-2-基 | (R)-Me | (S)-Me | | 354 |
| 50 | 苯并噻唑-2-基 | (R)-Me | (S)-Me | | 370 |
| 51 | 噁唑并[4,5-c]吡啶-2-基 | (R)-Me | (S)-Me | | 355 |
| 52 | 喹喔啉基-2-基 | (R)-Me | H | | 351 |
| 53 | 喹喔啉基-2-基 | (S)-Me | H | | 351 |
| 54 | 喹喔啉基-2-基 | (R)-Me | (S)-Me | | 365 |
| 55 | (4,6-二甲基)-嘧啶-2-基 | H | H | 132-133 | 315 |
| 56 | (4,6-二甲基)-嘧啶-2-基 | (S)-Me | H | | 329 |
| 57 | (2,6-二甲基)-嘧啶-4-基 | H | H | 125.5-127 | 314 |
| 58 | (2-羟甲基)-嘧啶-4-基 | (S)-Me | H | 146-148 | 331 |
| 59 | (2-羟甲基)-嘧啶-4-基 | (R)-Me | (S)-Me | 168-171 | 345 |
| 60 | (2-羟甲基-6-甲基)-嘧啶 4-基 | (S)-Me | H | | 345 |



| 实施例 | X-Ar¹ | mp(℃) | MS(MH⁺) |
|---|---|---|---|
| 61 | (4-羟甲基-6-甲基)-嘧啶-2-基 | | 357 |
| 62 | (R)-[2-(1-羟基-乙基)]-嘧啶-4-基 | | 357 |

## 实施例 63

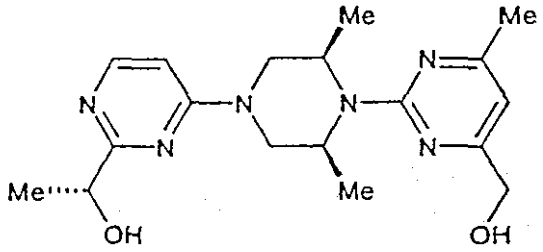
1-{4-[4-(2-乙酰基-嘧啶-4-基)-2R*,6S*-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酮



将 1S-(4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙醇(按照实施例 42 的方法制备，1.05g，2.93mmol)和氧化锰(IV) (5.15g，59.3mmol)在二氯乙烷(28mL)中的混合物加热回流 7 小时，用硅藻土过滤(热过滤)。将滤液浓缩然后通过快速柱色谱纯化(Flash 40M™，5%甲醇/氯仿)得到 0.67g (64%)白色固体状标题化合物。mp: > 235℃(分解)；$^1$H NMR ($CDCl_3$，400MHz) δ 8.42 (d, 1H)，8.41 (d, 1H)，6.68 (d, 1H)，6.57 (d, 1H)，4.81-4.36 (c, 4H)，3.39 (dd, 2H)，2.69 (s, 3H)，2.68 (s, 3H)，1.29 (d, 6H)；MS (APCI) 355 ($MH^+$)。

实施例 64

1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




步骤 A: 丁酸 1R-{4-[4-(叔丁氧羰基氨基-叔丁氧羰基亚氨基-甲基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。于 0℃下，向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备，10g，32.7mmol)、N,N'-二(叔丁氧羰基)硫脲(8.6g，32.7mmol；Synth. Commun. 1993，23，1443)和三乙胺(9.0mL，65.4mmol)在二甲基甲酰胺(110mL)中的混合物中加入氯化汞(II) (9.8g，36.0mmol)。将该混合物升温至室温搅拌过夜，用乙酸乙酯稀释，用水(3 次)和盐水(1 次)洗涤。将有机相用硫酸钠干燥，过滤然后蒸发得到 17.9g (100%)黄色泡沫状实施例 64，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$，300MHz) δ 9.61 (s，1H)，8.19 (d，1H)，6.37 (d，1H)，5.66 (q，1H)，4.51-4.14 (c，4H)，3.36-3.23 (c，2H)，2.37 (t，2H)，1.75-1.60 (c，2H)，1.55 (d，3H)，1.49 (s，9H)，1.46 (s，9H)，1.28 (d，3H)，1.26 (d，3H)，0.94 (t，3H)；MS (APCI) 549 ($MH^+$)。

步骤 B: 丁酸 1R-[4-(4-亚氨基氨基甲酰基(Carbamimidoyl)-3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯三氟乙酸盐。将丁酸 1R-{4-[4-(叔丁氧羰基氨基-叔丁氧羰基亚氨基-甲基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 64，步骤 A 的方法制备，17.9g，32.7mmol)在 3：1 二氯甲烷/三氟乙酸混合物(300mL)中的混合物室温搅拌过夜然后浓缩得到约 36g 油状的实施例 64，步骤

B 的标题化合物并将其直接使用。$^1$H NMR ($CD_3OD$, 400MHz) δ 8.24 (d, 1H), 7.25 (d, 1H), 5.69 (q, 1H), 4.19-4.10 (c, 4H), 3.79-3.42 (c, 2H), 2.45 (t, 2H), 1.67-1.45 (c, 2H), 1.63 (d, 3H), 1.32-1.25 (c, 6H), 0.95 (t, 3H); MS (APCI) 349 ($MH^+$)。

步骤 C: 1R-{4-[4-(4-甲氧基甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。将金属钠(3.8g, 160mmol)加入到异丙醇(160mL)中并加热回流至所有的金属被消耗掉制得 1M 异丙醇钠的异丙醇溶液。向回流的异丙醇钠/异丙醇溶液中加入丁酸 1R-[4-(4-亚氨基氨基甲酰基-3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯三氟乙酸盐(按照实施例 64, 步骤 B 的方法制备, 32.7mmol, 理论值), 1 小时后加入 1-甲氧基-戊烷-2,4-二酮(21.2g, 163mmol; J. Am. Chem. Soc. 1944, 22, 2092)。12 小时后, 补加异丙醇钠(1M 的异丙醇溶液, 65mL, 65mmol)。回流过夜后, 将反应混合物冷却至室温然后用水(100mL)稀释。加入水合氢氧化锂(6.9g, 163mmol)并将该混合物搅拌 3 小时, 浓缩并用 10%异丙醇/氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(1→2.5%甲醇/氯仿)得到 10.5g (87%, 2 步)黄色固体状实施例 64, 步骤 C 的标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.18 (d, 1H), 6.54 (s, 1H), 6.43 (d, 1H), 5.00-4.94 (c, 2H), 4.69 (m, 1H), 4.37-4.34 (c, 2H), 4.33 (s, 2H), 3.45 (s, 3H), 3.29-3.23 (c, 2H), 2.33 (s, 3H), 1.51 (d, 3H), 1.20 (s, 6H); MS (APCI) 373 ($MH^+$)。

步骤 D: 1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。向 1R-{4-[4-(4-甲氧基甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇(按照实施例 64, 步骤 C 的方法制备, 8.0g, 21.5mmol)的二氯甲烷(150mL)溶液中于 0℃下加入三溴化硼(1M 的二氯甲烷溶液, 64.3mL, 64.3mmol)。将该混合物升温至室温并搅拌过夜, 然后小心地加入饱

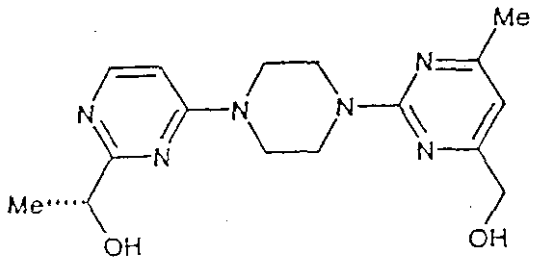
和碳酸氢钠水溶液终止反应。分液并将水相用 10%异丙醇/氯仿萃取(3 次)。将合并的有机萃取液用盐水洗涤(1 次)，用硫酸钠干燥，过滤然后蒸发。将得到的固体在乙酸乙酯中回流然后过滤(热过滤)。重复该过程并将合并的滤液浓缩至最小的体积。室温放置过夜后，过滤收集黄褐色的固体。将得到的滤液再次放置过夜得到另一批所需产物，总共得到 6.0g (78%)黄褐色固体状的标题化合物。mp: 149-151℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.19 (d, 1H), 6.45 (d, 1H), 6.32 (s, 1H), 5.02-4.96 (c, 2H), 4.71 (q, 1H), 4.53 (s, 2H), 4.50-4.23 (c, 2H), 3.31-3.25 (c, 2H), 2.33 (s, 3H), 1.51 (d, 3H), 1.23 (s, 6H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +18.9 (c 1.1, MeOH)。

## 实施例 65 至 74

实施例 65 至 74 按照与实施例 64 类似的方式从适宜的原料制备。

### 实施例 65

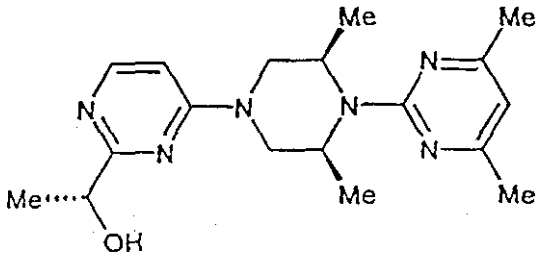
(R)-1-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇




mp: 139-140 ℃; $^1$H NMR ($CDCl_3$, 300MHz) δ 8.21 (d, 1H), 6.41 (d, 1H), 6.37 (s, 1H), 4.71 (m, 1H), 4.54 (s, 2H), 4.32 (d, 1H), 4.02-3.93 (c, 4H), 3.78-3.68 (c, 4H), 3.65 (br s, 1H), 2.34 (s, 3H), 1.19 (d, 3H); MS (TS) 331 ($MH^+$); $[\alpha]_D$ +21.6 (c 2.0, MeOH)。

## 实施例 66

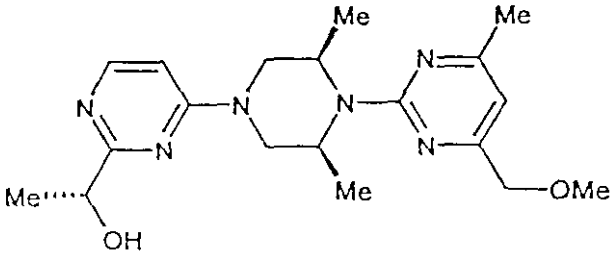
1R-{4-[4-(4,6-二甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




mp: 141.5-142.5℃; $^1$H NMR ($CDCl_3$, 400MHz) δ 8.17 (d, 1H), 6.43 (d, 1H), 6.28 (s, 1H), 5.03-4.97 (c, 2H), 4.70 (q, 1H), 4.44-4.18 (c, 2H), 3.32-3.20 (c, 2H), 2.27 (s, 6H), 1.50 (d, 3H), 1.20 (d, 6H); MS (APCI) 343 ($MH^+$); $[\alpha]_D$ +19.2 (c 1.1, MeOH)。

## 实施例 67

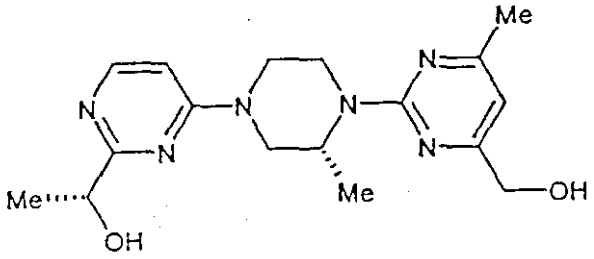
1R-{4-[4-(4-甲氧基甲基-6-甲基-嘧啶-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




$^1$H NMR ($CDCl_3$, 400MHz) δ 8.18 (d, 1H), 6.55 (s, 1H), 6.43 (d, 1H), 5.02-4.93 (c, 2H), 4.69 (m, 1H), 4.43-4.20 (c, 2H), 4.36 (d, 1H), 4.33 (s, 2H), 3.46 (s, 3H), 3.30-3.21 (c, 2H), 2.34 (s, 3H), 1.51 (d, 3H), 1.20 (d, 6H); MS (APCI) 373 ($MH^+$); $[\alpha]_D$ +16.0 (c 0.9, MeOH)。

## 实施例 68

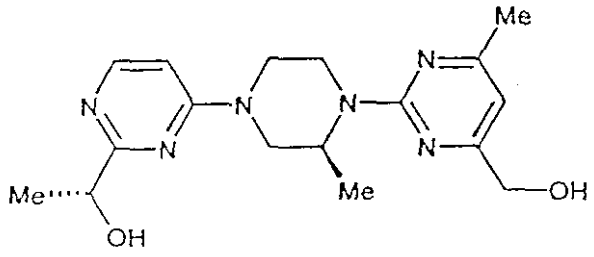
1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3R-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



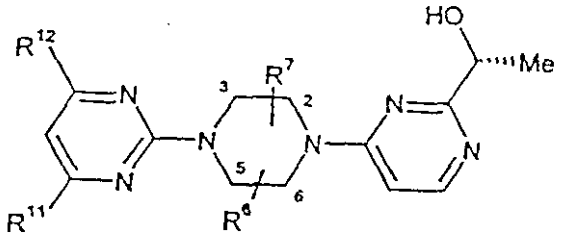

$^1$H NMR ($CDCl_3$, 400MHz) δ 8.17 (d, 1H), 6.36 (d, 1H), 6.32 (s, 1H), 4.98 (m, 1H), 4.69 (q, 1H), 4.58 (dt, 1H), 4.51 (s, 2H), 4.37-4.11 (c, 3H), 3.62 (br s, 1H), 3.48-3.36 (c, 2H), 3.18 (td, 1H), 2.31 (s, 3H), 1.49 (d, 3H), 1.17 (s, 3H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ -40.6 (c 1.0, MeOH)。

## 实施例 69

1R-{4-[4-(4-羟甲基-6-甲基-嘧啶-2-基)-3S-甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



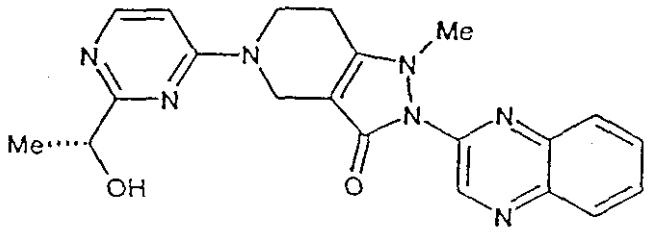

$^1$H NMR ($CDCl_3$, 400MHz) δ 8.17 (d, 1H), 6.36 (d, 1H), 6.33 (s, 1H), 4.99 (m, 1H), 4.69 (q, 1H), 4.58 (m, 1H), 4.52 (s, 2H), 4.40-4.11 (c, 3H), 3.60 (br s, 1H), 3.45-3.34 (c, 2H), 3.19 (td, 1H), 2.32 (s, 3H), 1.49 (d, 3H), 1.16 (s, 3H); MS (APCI) 359 ($MH^+$); $[\alpha]_D$ +68.1 (c 0.7, MeOH)。



| 实施例 | $R^{11}$ | $R^{12}$ | $R^7$ | $R^6$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|---|
| 70 | H | OH | 3R-Me | 5S-Me | | 331 |
| 71 | Me | OH | 3R-Me | 5S-Me | 231-232 | 345 |
| 72 | Ph | OH | 3R-Me | 5S-Me | | 407 |
| 73 | Me | 乙氧基甲基 | 3R-Me | 5S-Me | | 387 |
| 74 | Me | 乙氧基甲基 | 2R-Me | 6S-Me | 106-108 | 387 |

实施例 75

(R)-5-[2-(1-羟基-乙基)-嘧啶-4-基]-1-甲基-2-喹喔啉-2-基-1,2,4,5,6,7-六氢-吡唑并[4.3-c]吡啶-3-酮



步骤 A: 3-氧代-2-喹喔啉-2-基-1,2,3,4,6,7-六氢-吡唑并[4,3-c]吡啶-5-甲酸叔丁酯。向 4-氧代-哌啶-1,3-二甲酸 1-叔丁酯 3-乙酯(500mg, 1.84mmol; Tetrahedron 1994, 50, 515)的甲苯(10mL)溶液中加入喹喔啉-2-基-肼(295mg, 1.85mmol; Heterocycles 1985, 23, 2603)。将混合物回流搅拌过夜，冷却至室温，浓缩，然后通过快速柱色谱纯化(25→75%乙酸乙酯/己烷)得到 600mg (89%)浅

橙色固体状实施例 75，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$, 250MHz, 5: 1 互变异构体的混合物) δ 11.94 (br s, 0.83H), 10.16 (s, 0.17H), 9.57 (s, 0.83H), 8.13 (dd, 1H), 7.91-7.69 (c, 3H), 4.45 (s, 1.66H), 4.33 (s, 0.34H), 3.79-3.72 (c, 2H), 2.82-2.72 (c, 2H), 1.52 (s, 9H); MS (APCI) 368 ($MH^+$)。

步骤 B: 1-甲基-3-氧代-2-喹喔啉-2-基-1,2,3,4,6,7-六氢-吡唑并[4,3-c]吡啶-5-甲酸叔丁酯。0℃下，向 3-氧代-2-喹喔啉基-2-基-1,2,3,4,6,7-六氢-吡唑并[4,3-c]吡啶-5-甲酸叔丁酯(按照实施例 75，步骤 A 的方法制备，250mg, 0.68mmol)的二甲基甲酰胺(2mL)溶液中在氮气氛下搅拌下加入氢化钠(60%矿物油分散液，41mg, 1.02mmol)。10 分钟后，加入碘甲烷(51μL, 0.82mmol)。将混合物于 0℃搅拌 2 小时，加入饱和碳酸氢钠水溶液终止反应然后用乙酸乙酯萃取(4 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(40%乙酸乙酯/己烷)得到 164mg (63%)黄色泡沫状实施例 75，步骤 B 的标题化合物。$^1$H NMR ($CDCl_3$, 250MHz) δ 9.71 (s, 1H), 8.15 (dd, 1H), 8.02 (m, 1H), 7.80-7.70 (c, 2H), 4.29 (s, 2H), 4.14 (t, 2H), 3.79 (s, 3H), 2.72-2.67 (c, 2H), 1.50 (s, 9H); MS (APCI) 382 ($MH^+$)。

步骤 C: 1-甲基-2-喹喔啉-2-基-1,2,4,5,6,7-六氢-吡唑并[4,3-c]吡啶-3-酮盐酸盐。向 1-甲基-3-氧代-2-喹喔啉-2-基-1,2,3,4,6,7-六氢-吡唑并[4,3-c]吡啶-5-甲酸叔丁酯(按照实施例 75，步骤 B 的方法制备，279mg, 7.3mmol)的甲醇(6mL)溶液中加入氯化氢(5.85M 的甲醇溶液，1.25mL, 7.3mmol)。将该混合物于 60℃加热 30 分钟，冷却至室温然后浓缩得到 249mg (>100%)深红色固体状实施例 75，步骤 C 的标题化合物。$^1$H NMR ($CD_3OD$, 250MHz) δ 9.45 (s, 1H), 8.13 (dd, 1H), 8.05 (m, 1H), 7.91-7.83 (c, 2H), 4.05 (s, 2H), 3.64 (t, 2H), 3.56 (s, 3H), 3.12 (t, 2H); MS (APCI) 282 ($MH^+$)。

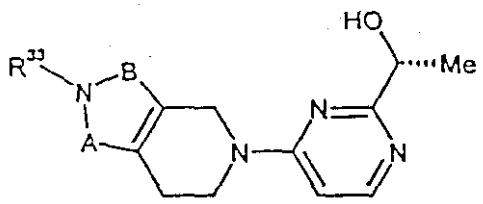
步骤 D: 丁酸(R)-1-[4-(1-甲基-3-氧代-2-喹喔啉-2-基-1,2,3,4,6,7-六氢-吡唑并[4,3-c]吡啶-5-基)-嘧啶-2-基]-乙酯。向 1-甲基-2-喹喔啉-2-基-1,2,4,5,6,7-六氢-吡唑并[4,3-c]吡啶-3-酮盐酸盐(按照实施例 75, 步骤 C 的方法制备, 175mg, 0.55mmol)和丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备, 126mg, 0.55mmol)的异丙醇(6mL)溶液中加入三乙胺(230μL, 1.66mmol)。将该混合物加热回流过夜, 冷却至室温然后蒸发。将残余物用饱和碳酸氢钠水溶液稀释并用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(1.5%甲醇/氯仿)得到 248 mg (95%)黄色油状实施例 75, 步骤 D 的标题化合物。$^1$H NMR ($CDCl_3$, 250MHz) δ 9.70 (s, 1H), 8.29 (d, 1H), 8.15 (dd, 1H), 8.03 (m, 1H), 7.82-7.70 (c, 2H), 6.48 (d, 1H) 5.72 (q, 1H), 4.36 (s, 2H), 4.35-4.15 (c, 2H), 3.42 (s, 3H), 2.77-2.82 (c, 2H), 2.43 (t, 2H), 1.79-1.60 (c, 2H), 1.61 (d, 3H), 0.99 (t, 3H); MS (APCI) 474 ($MH^+$)。

步骤 E: (R)-5-[2-(1-羟基-乙基)-嘧啶-4-基]-1-甲基-2-喹喔啉-2-基-1,2,4,5,6,7-六氢-吡唑并[4,3-c]吡啶-3-酮。向丁酸(R)-1-[4-(1-甲基-3-氧代-2-喹喔啉-2-基-1,2,3,4,6,7-六氢-吡唑并[4,3-c]吡啶-5-基)-嘧啶-2-基]-乙酯(按照实施例 75, 步骤 D 的方法制备, 248mg, 0.52mmol)在 5: 2 甲醇/四氢呋喃混合物(7mL)中的溶液中加入碳酸钾(218mg, 1.57mmol)。将混合物室温搅拌过夜然后蒸发。将残余物用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发, 然后通过快速柱色谱纯化(1.5→3%甲醇/氯仿)得到 150mg (71%)白色固体状标题化合物。mp: 217-219℃(分解); $^1$H NMR ($CDCl_3$, 250MHz) δ 9.66 (s, 1H), 8.25 (d, 1H), 8.12 (dd, 1H), 7.99 (m, 1H), 7.68-7.78 (c, 2H), 6.47 (d, 1H), 4.72 (q, 12H), 4.32 (s, 2H), 4.19-4.14 (c, 3H), 3.41 (s, 3H), 2.80 (t, 2H), 1.51

(d, 3H); MS (APCI) 404 ($MH^+$); $[\alpha]_D$ +13.4 (c 1.5, $CHCl_3$)。

实施例 76 和 77

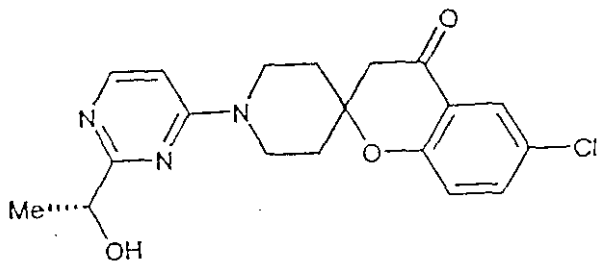
实施例 76 和 77 按照与实施例 75 类似的方法从适宜的原料制备。




| 实施例 | A | $R^{33}$ | B | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 76 | N-Me | 苯并噻唑-2-基 | CO | 176-178 | 409 |
| 77 | CO | 喹喔啉基-2-基 | N-Me | 201-204(分解) | 404 |

实施例 78

(R)-6-氯-1'-[2-(1-羟基-乙基)-嘧啶-4-基]-螺[苯并二氢吡喃-2,4'-哌啶]-4-酮




步骤 A: 6-氯-螺[苯并二氢吡喃-2,4'-哌啶]-4-酮盐酸盐。向 1'-苄基-6-氯-螺[苯并二氢吡喃-2,4'-哌啶]-4-酮(300mg, 0.88mmol, Chem. Pharm. Bull. 1981, 29, 3494)的丙酮(5mL)溶液中于 0℃下加入氯甲酸 1-氯乙酯(0.29mL, 2.64mmol)。将该混合物升温至室

温，搅拌过夜然后浓缩。将残余物通过快速柱色谱纯化(10→20%乙酸乙酯/己烷)得到中间体氨基甲酸酯，将其在甲醇(3mL)中回流 1 小时。将反应混合物蒸发得到 149mg (59%)无色固体状实施例 78，步骤 A 的题化合物。$^1$H NMR ($CD_3OD$, 250MHz) δ 7.77 (d, 1H), 7.58 (dd, 1H), 7.15 (d, 1H), 3.33 (被掩盖的, 4H), 2.90 (s, 2H), 2.46-2.20 (c, 2H), 2.04-1.81 (c, 2H); MS (APCI) 252, 254 ($MH^+$)。

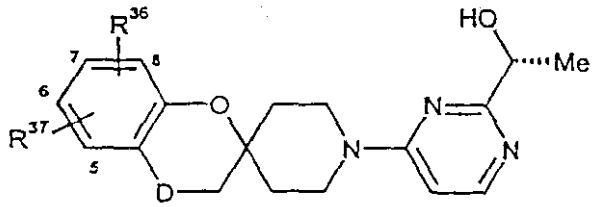
步骤 B: (R)-1'-[2-(1-丁酰氧基-乙基)-嘧啶-4-基]-6-氯-螺[苯并二氢吡喃-2,4'-哌啶]-4-酮。向 6-氯-螺[苯并二氢吡喃-2,4'-哌啶]-4-酮盐酸盐(按照实施例 78，步骤 A 的方法制备，175mg, 0.61mmol)的异丙醇(5mL)溶液中依次加入丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，160mg, 0.70mmol)和三乙胺(0.29mL, 2.1mmol)。将该混合物回流搅拌 1.5 小时，浓缩然后通过快速柱色谱纯化(1%甲醇/氯仿)得到 270mg (100%)黄色油状实施例 78，步骤 B 的标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.19 (d, 1H), 7.83 (d, 1H), 7.44 (dd, 1H), 6.97 (d, 1H), 6.37 (d, 1H), 5.64 (q, 1H), 4.18 (app s, 2H), 3.34 (t, 2H), 2.72 (s, 2H), 2.37 (t, 2H), 2.10 (d, 2H), 1.71-1.60 (c, 4H), 1.55 (d, 3H), 0.94 (t, 3H); MS (APCI) 444, 446 ($MH^+$)。

步骤 C: (R)-6-氯-1'-[2-(1-羟基-乙基)-嘧啶-4-基]-螺[苯并二氢吡喃-2,4'-哌啶]-4-酮。将(R)-1'-[2-(1-丁酰氧基-乙基)-嘧啶-4-基]-6-氯-螺[苯并二氢吡喃-2,4'-哌啶]-4-酮(按照实施例 78，步骤 B 的方法制备，270mg, 0.61mmol)和水合氢氧化锂(80mg, 1.83mmol)在 3: 1: 1 四氢呋喃/甲醇/水混合物(5mL)中的混合物室温搅拌 1.5 小时。蒸除有机溶剂并将残余物用氯仿萃取(4 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(乙酸乙酯)得到 41mg (18%)红色泡沫状标题化合物。$^1$H NMR ($CDCl_3$, 300MHz) δ 8.19 (d, 1H), 7.82 (d, 1H), 7.44 (dd, 1H), 6.96 (d, 1H), 6.40 (d, 1H), 4.65 (q, 1H), 4.20 (app s,

2H), 3.42-3.32 (c, 2H), 2.73 (s, 2H), 2.14 (d, 2H), 1.67 (td, 2H), 1.48 (d, 3H); MS (APCI) 374, 376 ($MH^+$); $[\alpha]_D$ +12.6 (c 0.5, MeOH)。

## 实施例 79 至 85

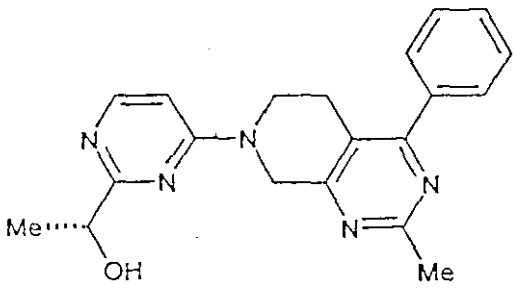
实施例 79 至 85 按照与实施例 78 类似的方法从适宜的原料制备。




| 实施例 | $R^{36}$ | $R^{37}$ | D | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 79 | 6-Ph | H | $CH_2$ | | 402 |
| 80 | 6-Ph | H | CHOH | | 418 |
| 81 | 6-Ph | H | CO | | 416 |
| 82 | 6-OMe | H | CO | 156.5-157.5 | 370 |
| 83 | 7-Br | H | CO | | 418, 420 |
| 84 | 5-Cl | 6-Cl | CO | | 408,410 |
| 85 | 6-OMe | 7-OMe | CO | | 400 |

## 实施例 86

(R)-1-[4-(2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶-7-基)-嘧啶-2-基]-乙醇



步骤 A：7-苄基-2-甲基-5,6,7,8-四氢-3H-吡啶并[3,4-d]嘧啶-4-酮。将金属钠(5.7g，247mmol)溶于无水乙醇(141mL)制备乙醇钠的乙醇溶液。当金属完全溶解后，依次加入 1-苄基-3-氧代-4-哌啶甲酸乙酯盐酸盐(21g，70.5mmol)和乙脒盐酸盐(13.3g，141mmol)。将该混合物回流搅拌 1 小时，冷却至室温然后浓缩。将残余物溶于少量水然后用冰乙酸将 pH 调至约 7。滤出形成的黄色沉淀，用水洗涤(3 次)，晾干 2 小时，然后真空干燥过夜得到 17.1g (95%)黄色固体状实施例 86，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$，250MHz) δ 7.35-7.25 (c，5H)，3.70 (s，2H)，3.42 (s，2H)，2.73-2.64 (c，2H)，2.64-2.60 (c，2H)，2.41 (s，3H)；MS (APCI) 256 ($MH^+$)。

步骤 B：7-苄基-4-氯-2-甲基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶。将 7-苄基-2-甲基-5,6,7,8-四氢-3H-吡啶并[3,4-d]嘧啶-4-酮(按照实施例 86，步骤 A 的方法制备，17.1g，67.0mmol)悬浮在三氯氧磷(66mL，335mmol)。将该混合物回流搅拌 1 小时，冷却至室温，蒸发然后用甲苯带走溶剂。将残余物小心地用冰/水/氯仿稀释然后分液。将水相用氯仿萃取(3 次)并将合并的有机萃取液用饱和碳酸氢钠水溶液(1 次)和水(1 次)洗涤，用硫酸钠干燥，过滤然后蒸发得到棕色油状实施例 86，步骤 B 的标题化合物，其不经纯化直接用于随后的步骤。$^1$H NMR ($CDCl_3$，250MHz) δ 7.36-7.23 (c，5H)，3.73 (s，2H)，3.63 (s，2H)，2.63 (app s，4H)，2.36 (s，3H)；MS (APCI) 274，276 ($MH^+$)。

步骤 C：7-苄基-2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶。向 1,4-二苯基膦基丁烷(1.43g，3.35mmol)的甲苯(50mL)悬浮液中加入二(苄腈)氯化钯(II) (1.28g，3.35mmol)。将该混合物室温搅拌 25 分钟，然后加入到 7-苄基-4-氯-2-甲基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶(按照实施例 86，步骤 B 的方法制备，67.0mmol，估算的)和苯基硼酸(10.6g，87.1mmol)在无水乙醇(40mL)、甲苯(175mL)和 2N 碳酸钠水溶液(33.5mL)的混合物中的悬浮液中。将该

混合物回流搅拌 6.5 小时，冷却至室温然后搅拌约 2.5 天，然后用硅藻土垫过滤。将滤液浓缩并将残余物用水稀释然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(45→50%乙酸乙酯/己烷)得到 16.5g (78%，两步)黄色油状实施例 86，步骤 C 的标题化合物。$^1$H NMR ($CDCl_3$，250MHz) δ 7.57-7.54 (c，2H)，7.48-7.24 (c，8H)，3.71 (app s，4H)，2.85 (t，2H)，2.71-2.67 (c，2H)，2.69 (s，3H)；MS (APCI) 316 ($MH^+$)。

步骤 D：2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶。通过将氯化氢(1.9M 的甲醇溶液，31.1mL，51.1mmol)加入到 7-苄基-2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶(按照实施例 86，步骤 C 的方法制备，16.5g，52.2mmol)的甲醇(75mL)溶液中就地形成 7-苄基-2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶盐酸盐。室温搅拌 10 分钟后，有沉淀生成，加入甲醇(100mL)形成均相的溶液。向该混合物中加入 10%钯碳(3.3g，20 wt%)在甲醇中的浆液，然后加入甲酸铵(16.5g，261mmol)。将该混合物回流搅拌 5 小时，冷却至室温然后用硅藻土过滤。将滤液蒸发，用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(3%甲醇/氯仿+1%氢氧化铵)得到 6.7g (57%)黄白色固体状实施例 86，步骤 D 的标题化合物和 2.4g (19%)黄色胶状 7-甲酰基-2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶。将 7-甲酰基副产物用氯化氢的甲醇溶液于室温下处理过夜，然后用水处理并进行柱色谱得到另外 1.4g (12%)实施例 86，步骤 D 的标题化合物。$^1$H NMR ($CDCl_3$，250MHz) δ 7.55-7.40 (c，5H)，4.09 (s，2H)，3.05 (t，2H)，2.75 (t，2H)，2.79 (s，3H)；MS (APCI) 226 ($MH^+$)。

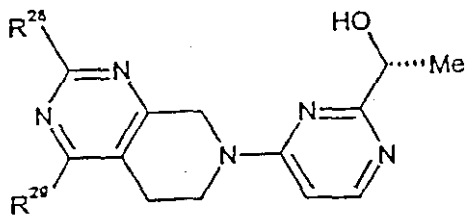
步骤 E：丁酸(R)-1-[4-(2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶-7-基)-嘧啶-2-基]-乙酯。向 2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶(按照实施例 86，步骤 D 的方法制备，

6.8g, 30.0mmol)的异丙醇(125mL)溶液中依次加入丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备, 6.8g, 30mmol)和三乙胺(12.5mL, 89.9mmol)。将该混合物回流搅拌 8 小时, 冷却至室温过夜然后蒸发。将残余物用饱和碳酸氢钠水溶液稀释并用乙酸乙酯萃取(3 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(2%甲醇/乙酸乙酯)得到 11.0g (88%)黄色油状实施例 86, 步骤 E 的标题化合物。$^1$H NMR ($CDCl_3$, 250MHz) δ 8.28 (d, 1H), 7.62-7.40 (c, 5H), 6.45 (d, 1H), 5.69 (q, 1H), 4.78 (s, 2H), 3.93 (app s, 2H), 2.95 (t, 2H), 2.77 (s, 3H), 2.40 (t, 2H), 1.77-1.63 (c, 2H), 1.60 (d, 3H), 0.98 (t, 3H); MS (APCI) 418 ($MH^+$)。

步骤 F: (R)-1-[4-(2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶-7-基)-嘧啶-2-基]-乙醇。向丁酸(R)-1-[4-(2-甲基-4-苯基-5,8-二氢-6H-吡啶并[3,4-d]嘧啶-7-基)-嘧啶-2-基]-乙酯(按照实施例 86, 步骤 E 的方法制备, 11.0g, 26.4mmol)的二氧六环(13mL)溶液中加入浓盐酸(22mL, 264mmol)。将混合物室温搅拌过夜, 冷却至 0℃, 缓慢 6N 氢氧化钠水溶液进行中和, 然后用乙酸乙酯萃取(4 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发然后通过快速柱色谱纯化(2→5%甲醇/乙酸乙酯)得到油, 将其用己烷研制得到 8.0g (88%)白色固体状标题化合物。mp: 114-116℃; $^1$H NMR ($CD_3OD$, 250MHz) δ 8.26 (d, 1H), 7.62-7.47 (c, 5H), 6.52 (d, 1H), 4.79 (s, 2H), 4.66 (q, 1H), 4.24 (br s, 1H), 3.90-3.80 (c, 2H), 2.95 (t, 2H), 2.70 (s, 3H), 1.49 (d, 3H); MS (APCI) 348 ($MH^+$), $[\alpha]_D$ +15.6 (c 1.0, MeOH)。

实施例 87 至 100

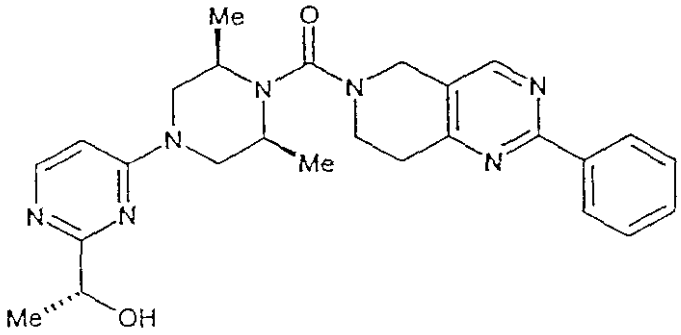
实施例 87 至 100 按照与实施例 86 类似的方法从适宜的原料制备。



| 实施例 | $R^{29}$ | $R^{28}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|
| 87 | H | Ph | 72-74 | 334 |
| 88 | Ph | H | | 334 |
| 89 | Ph | Et | | 362 |
| 90 | Ph | $NH_2$ | 225-228(分解) | 349 |
| 91 | Ph | Ph | 73-75 | 410 |
| 92 | Ph | 4-吡啶基 | | 411 |
| 93 | (4-OMe)Ph | Me | 62-64 | 378 |
| 94 | (4-F)Ph | Me | 55-58 | 366 |
| 95 | (4-Cl)Ph | H | | 368,370 |
| 96 | OMe | Me | | 302 |
| 97 | OPh | Me | 156-158 | 364 |
| 98 | SPh | Me | 103-105 | 380 |
| 99 | N-二氢吲哚基 | Me | 128-131 | 389 |
| 100 | $NMe_2$ | Et | | 329 |

实施例 101

{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-(2-苯基-7,8-二氢-5H-吡啶并[4,3-d]嘧啶-6-基)-甲酮



步骤 A：4-氧代-哌啶-1-甲酸叔丁酯。将 4-哌啶酮一水合物盐酸盐(9.22g，60mmol)和二碳酸二叔丁酯(10.9g，50mmol)在 1：1 二氯甲烷/饱和碳酸氢钠水溶液混合物(100mL)中的混合物室温搅拌 15.5 小时。分液并将水层用氯仿萃取(3 次)。将合并的有机萃取液用 1N 磷酸洗涤(3 次)，用硫酸钠干燥，过滤然后蒸发得到 10.0g (100%)白色固体状实施例 101，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$，400MHz) δ 3.70 (t，4H)，2.42 (t，4H)，1.47 (s，9H)。

步骤 B：3-二甲氨基亚甲基-4-氧代-哌啶-1-甲酸叔丁酯。向 4-氧代-哌啶-1-甲酸叔丁酯(按照实施例 101，步骤 A 的方法制备，4.0g，20.0mmol)的二甲基甲酰胺(40mL)溶液中加入叔丁氧基二(二甲氨基)甲烷(4.35mL，22mmol)。将该混合物回流搅拌 15 小时，冷却至室温，用水稀释然后用乙酸乙酯萃取(5 次)。将合并的有机萃取液用水(3 次)和盐水(1 次)洗涤，用硫酸钠干燥，过滤然后蒸发得到 3.64g (72%)棕色油状实施例 101，步骤 B 标题化合物，其具有足够的纯度用于下一步反应。$^1$H NMR ($CDCl_3$，400MHz) δ 7.47 (s，1H)，4.53 (s，2H)，3.58 (t，2H)，3.09 (s，6H)，2.43 (t，2H)，1.46 (s，9H)；MS (APCI) 255 ($MH^+$)。

步骤 C：2-苯基-7,8-二氢-5H-吡啶并[4,3-d]嘧啶-6-甲酸叔丁酯。将 3-二甲氨基亚甲基-4-氧代-哌啶-1-甲酸叔丁酯(按照实施例 101，步骤 B 的方法制备，509mg，2.0mmol)、苄脒盐酸盐水合物(470mg，3.0mmol)和乙醇钠(1M 的乙醇溶液，6.0mL，6.0mmol)在无水乙醇(4mL)中的混合物加热回流约 3 天，冷却至室温然后浓缩。将残余物用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(Biotage Flash 40S™，10→15%乙酸乙酯/己烷)得到 304mg (49%)黄色油状实施例 101，步骤 C 的标题化合物。$^1$H NMR ($CDCl_3$，400MHz) δ 8.52 (s，1H)，8.40-8.38 (c，2H)，7.50-7.44 (c，3H)，4.62 (s，2H)，3.78 (t，2H) 3.02 (t，2H)，1.50 (s，9H)；MS (APCI) 312 ($MH^+$)。

步骤 D：2-苯基-7,8-二氢-5H-吡啶并[4,3-d]嘧啶盐酸盐。向 2-苯基-7,8-二氢-5H-吡啶并[4,3-d]嘧啶-6-甲酸叔丁酯(按照实施例 101，步骤 C 的方法制备，304mg，0.98mmol)的乙酸乙酯(2mL)溶液中加入氯化氢(2.5M 的乙酸乙酯溶液，3.9mL，9.76mmol)。将该混合物室温搅拌 16 小时然后浓缩得到 256mg (>100%)浅黄色固体状实施例 101，步骤 D 的标题化合物。$^1$H NMR ($CD_3OD$，400MHz) δ 8.75 (s，1H)，8.42-8.38 (c，2H)，7.51-7.45 (c，3H)，4.48 (s，2H)，3.68 (t，2H) 3.35-3.25 (被掩盖的，2H)；MS (APCI) 212 ($MH^+$)。

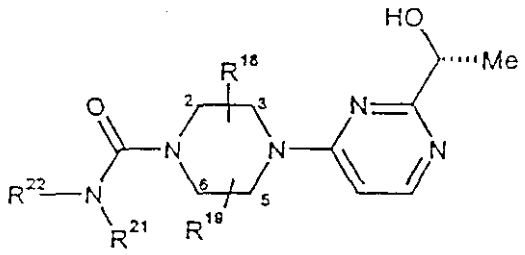
步骤 E：丁酸 1R-[4-(4-氯羰基-3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备，1.36g，4.44mmol)的二氯甲烷(22mL)溶液中于 0℃及氮气氛下依次加入吡啶(0.36mL，4.44mmol)和三光气(883mg，2.97mmol)。将混合物升温至室温搅拌 1.5 小时，然后用饱和碳酸氢钠水溶液终止反应。分液并将水相用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(1→2%甲醇/氯仿)得到 1.59g (97%)棕色油状实施例 101，步骤 E 的标题化合物。$^1$H NMR ($CDCl_3$，400MHz) δ 8.23 (d，1H)，6.39 (d，1H)，5.66 (q，1H)，4.54-4.47 (c，2H)，4.35 (m，1H)，4.25 (m，1H)，3.20 (dt，2H)，2.38 (t，2H)，1.72-1.62 (c，2H)，1.56 (d，3H)，1.31 (d，3H)，1.30 (d，3H)，0.95 (t，3H)；MS (APCI) 369，371 ($MH^+$)。

步骤 F：{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-(2-苯基-7,8-二氢-5H-吡啶并[4,3-d]嘧啶-6-基)-甲酮。将 2-苯基-7,8-二氢-5H-吡啶并[4,3-d]嘧啶盐酸盐(按照实施例 101，步骤 D 的方法制备，160mg，0.65mmol)、丁酸 1R-[4-(4-氯羰基-3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 101，步骤 E 的方法制备，200mg，0.54mmol)和三乙胺(0.19mL，1.36mmol)在四氢呋喃(5mL)中的混合物回流搅拌 3 小时，冷却至室温过夜然后

浓缩。将残余物用 4：1 甲醇/水混合物(5mL)稀释然后加入水合氢氧化锂(114mg，2.71mmol)。将混合物搅拌 2.5 小时，浓缩，然后在饱和碳酸氢钠水溶液和氯仿之间进行分配。分液并将水相用 20%异丙醇/氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(2→5%甲醇/氯仿)得到 183mg (71%)白色泡沫状标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.56 (s, 1H), 8.41-8.39 (c, 2H), 8.20 (d, 1H), 7.50-7.46 (c, 3H), 6.38 (d, 1H), 4.71 (s, 2H), 4.69 (m, 1H), 4.28 (d, 1H), 3.89 (t, 2H) 3.83 (d, 2H), 3.60-3.56 (c, 2H), 3.46-3.39 (c, 2H), 3.09 (t, 2H), 1.50 (d, 3H), 1.18 (d, 6H)；MS (APCI) 212 ($MH^+$)；$[\alpha]_D$ +6.1 (c 1.8, $CHCl_3$)。

## 实施例 102 至 110

实施例 102 至 110 按照与实施例 101 类似的方法从适宜的原料制备。



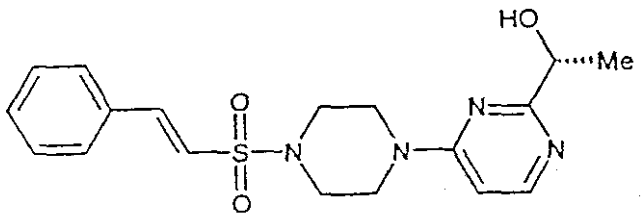

| 实施例 | $R^{22}$ | $R^{21}$ | $R^{18}$ | $R^{19}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|---|
| 102 | 喹啉-2-基 | H | 3R-Me | 5S-Me | 172-174.5 | 407 |
| 103 | 喹啉-3-基 | H | 2R-Me | 6S-Me | | 407 |
| 104 | 喹啉-4-基 | H | 3R-Me | 5S-Me | | 407 |
| 105 | 喹啉-6-基 | H | 3R-Me | 5S-Me | | 407 |
| 106 | 吡啶-3-基-甲基 | 吡啶-3-基-甲基 | 2R-Me | 6S-Me | | 462 |

| 实施例 | $NR^{21}R^{22}$ | $R^{18}$ | $R^{19}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 107 | 2-氨基-7,8-二氢-5H-吡啶并[4,3-d]嘧啶-6-基 | 2R-Me | 6S-Me | 225-228 | 413 |

| | | | | |
|---|---|---|---|---|
| 108 | 2-(1-羟基-1-甲基-乙基)-7,8-二氢-5H-吡啶并[4,3-d]嘧啶-6-基 | 2R-Me | 6S-Me | 456 |
| 109 | 5,7-二氢-二苯并[c,e]吖庚因-6-基 | 2R-Me | 6S-Me | 458 |
| 110 | 4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-基 | 3R-Me | 5S-Me | 499 |

## 实施例 111

## (E)-1R-{4-[4-(2-苯基-乙磺酰基)-哌嗪-1-基]-嘧啶-2-基}-乙醇



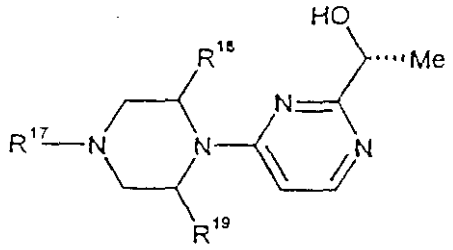

步骤 A: 乙酸(E)-1R-{4-[4-(2-苯基-乙磺酰基)-哌嗪-1-基]-嘧啶-2-基}-乙酯。向乙酸(R)-1-[4-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 2 的方法制备, 0.25g, 1.0mmol)和三乙胺(0.10g, 1.0mmol)的四氢呋喃(5mL)溶液中于室温下加入β-苯乙烯磺酰氯(0.21g, 1.0mmol)并搅拌 1 小时。将混合物用水稀释然后用乙酸乙酯萃取两次。将萃取液用硫酸镁干燥, 过滤然后将滤液浓缩成油, 将其通过快速色谱纯化(9: 1 二氯甲烷: 甲醇)得到油状实施例 111, 步骤 A 的标题化合物, 0.15g (34%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.48 (d, 3H), 2.15 (s, 3H), 3.23 (m, 4H), 3.84 (m, 4H), 5.61 (q, 1H), 6.40 (d, 1H), 6.65 (d, 1H), 7.39-7.52 (m, 6H), 8.21 (d, 1H); MS (TS) 417 ($MH^+$)。

步骤 B: (E)-1R-{4-[4-(2-苯基-乙磺酰基)-哌嗪-1-基]-嘧啶-2-基}-乙醇。向乙酸(E)-1R-{4-[4-(2-苯基-乙磺酰基)-哌嗪-1-基]-

嘧啶-2-基}-乙酯(按照实施例 111，步骤 A 的方法制备，0.14g，0.33mmol)的甲醇(1mL)溶液中于室温下加入 6N 氢氧化钾水溶液(0.25mL)。搅拌 3 小时后，将溶液用乙酸乙酯稀释然后用水洗涤两次。分出有机层，用硫酸镁干燥，过滤然后将滤液浓缩得到白色固体状标题化合物，0.09g (69%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.48 (d, 3H), 3.23 (m, 4H), 3.84 (m, 4H), 4.20 (br s, 1H), 4.71 (q, 1H), 6.40 (d, 1H), 6.65 (d, 1H), 7.39-7.52 (m, 6H), 8.21 (d, 1H)；mp: 68-70℃；MS (TS) 375 ($MH^+$)；$[\alpha]_D$ +20.9 (c 1.0, MeOH)。

## 实施例 112 和 113

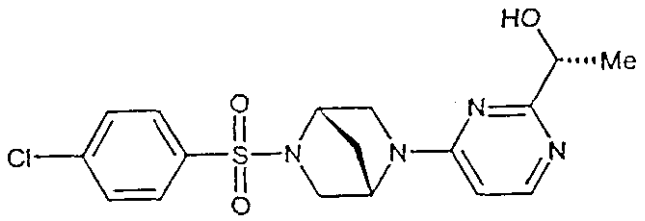
实施例 112 和 113 按照与实施例 111 类似的方法从适宜的原料制备。




| 实施例 | $R^{18}$ | $R^{19}$ | $R^{17}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 112 | (R)-Me | (S)-Me | 异丙基磺酰基 | 152-154 | 343 |
| 113 | (R)-Me | (S)-Me | 1-甲基-1H-咪唑-4-基-磺酰基 | 157-158 | 381 |

## 实施例 114

1R-{4-[5-(4-溴苯磺酰基)-2R,5S-二氮杂-二环[2.2.1]庚-2-基]-嘧啶-2-基}-乙醇



步骤 A：丁酸 1R-[4-(2R,5S-二氮杂-二环[2.2.1]庚-2-基)-嘧啶-2-基]-乙酯。向 2,5-二氮杂-二环[2.2.1]庚烷二氢溴酸盐(7.57g, 88.0mmol; Synthesis, 1990, 10, 925)的二氯甲烷(90mL)悬浮液中加入 1,8-二氮杂二环[5.4.0]十一烷-7-烯(13.7g, 90mmol)然后搅拌至均匀。加入丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备, 10.2g, 45mmol)的二氯甲烷(10mL)溶液然后回流搅拌 14 小时。将混合物过滤并用饱和碳酸氢钠水溶液洗涤。将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到粗产物，将其通过快速色谱纯化(9: 1→5: 1 二氯甲烷:甲醇)得到油状实施例 114, 步骤 A 的标题化合物, 6.75g (51%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.92 (t, 3H), 1.54 (d, 3H), 1.68-1.78 (m, 5H), 2.68 (t, 2H), 3.38 (m, 1H), 3.76 (m, 3H), 4.42 (m, 1H), 5.35 (q, 1H), 6.16 (d, 1H), 8.12 (d, 1H); MS (CI) 291 ($MH^+$)。

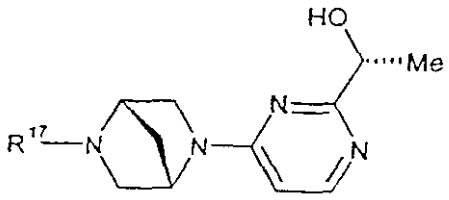
步骤 B：丁酸 1R-4-{5-(4-溴苯磺酰基)-2R,5S-二氮杂-二环[2.2.1]庚-2-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(2R,5S-二氮杂-二环[2.2.1]庚-2-基)-嘧啶-2-基]-乙酯(按照实施例 114, 步骤 A 的方法制备, 0.58g, 2.0mmol)和三乙胺(0.22g, 2.2mmol)的氯仿(10mL)溶液中加入 4-溴苯磺酰氯(0.56g, 2.2mmol)然后室温搅拌 16 小时。将混合物用水洗涤一次，用盐水洗涤一次，用硫酸镁干燥，过滤然后将滤液浓缩得到透明油状实施例 114, 步骤 B 的标题化合物, 0.92g (90%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.92 (t, 3H), 1.54 (d, 3H), 1.68-1.78 (m, 5H), 2.68 (t, 2H), 3.25 (m, 1H), 3.46 (m, 3H), 4.28 (m, 1H), 5.25 (q, 1H), 6.16 (d,

1H), 7.58-7.64 (m, 4H), 8.12 (d, 1H); MS (CI) 510 ($MH^+$)。

步骤 C: 1R-{4-[5-(4-溴苯磺酰基)-2R,5S-二氮杂-二环[2.2.1]庚-2-基]-嘧啶-2-基}-乙醇。向丁酸 1R-{4-[5-(4-溴苯磺酰基)-2R,5S-二氮杂-二环[2.2.1]庚-2-基]-嘧啶-2-基}-乙酯(按照实施例 114, 步骤 B 的方法制备, 0.85g, 1.6mmol)在 2: 1 四氢呋喃:甲醇混合物(10mL)中的溶液中于室温下加入 6N 氢氧化钾水溶液(1mL)。搅拌 6 小时后, 将溶液用二氯甲烷稀释然后用水洗涤两次。将有机层分离, 用硫酸镁干燥, 过滤然后将滤液浓缩成粘稠的油, 将其通过快速色谱纯化(9: 1 二氯甲烷: 甲醇)得到白色泡沫状标题化合物, 0.49g (66%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 1.54 (d, 3H), 1.68 (m, 2H), 1.78 (m, 1H), 3.25 (m, 1H), 3.46 (m, 3H), 4.28 (m, 1H), 4.78 (q, 1H), 6.16 (d, 1H), 7.64 (m, 4H), 8.12 (d, 1H); mp: 83-88℃; MS (CI) 440 ($MH^+$); $[\alpha]_D$ -49.2 (c 1.0, MeOH)。

## 实施例 115 至 120

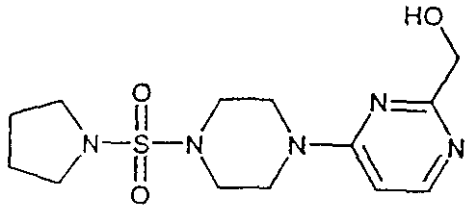
实施例 115 至 120 按照与实施例 114 类似的方法从适宜的原料制备。




| 实施例 | $R^{17}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|
| 115 | 4-氯苯基磺酰基 | 83-88 | 395,397 |
| 116 | 2-噻吩基磺酰基 | 84-86 | 367 |
| 117 | 2-(5-氯噻吩基)-磺酰基 | 62-64 | 401,403 |
| 118 | 4-甲酰胺基(carboxamido 基)苯基-磺酰基 | 148-151 | 404 |
| 119 | 4-(叔丁基苯基)-磺酰基 | 72-75 | 417 |
| 120 | N,N-二甲基氨磺酰基 | 110-111 | 328 |

实施例 121

{4-[4-(吡咯烷-1-磺酰基)-哌嗪-1-基]-嘧啶-2-基}-甲醇

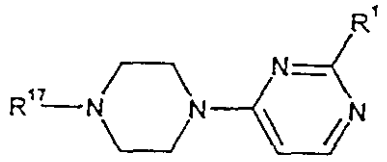


步骤 A：2-甲氧基甲基-4-[4-(吡咯烷-1-磺酰基)-哌嗪-1-基]-嘧啶。向 2-甲氧基甲基-4-哌嗪-1-基-嘧啶(按照制备例 1 的方法制备，2.08g，10mmol)和三乙胺(1.01g，10mmol)的四氢呋喃(20mL)溶液中于 0℃下加入 N-吡咯烷磺酰氯(1.69g，10mmol)然后室温搅拌 3 小时。将混合物用乙酸乙酯稀释然后用水洗涤两次。将有机层分离，用硫酸镁干燥，过滤然后将滤液浓缩成油，将其通过快速色谱纯化(95:5 二氯甲烷：甲醇)得到透明油状实施例 121，步骤 A 的标题化合物，3.24g (93%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.81-1.85 (m，4H)，3.12-3.18 (m，8H)，3.59 (s，3H)，3.81 (m，4H)，4.43 (s，2H)，6.71 (d，1H)，8.18 (d，1H)；MS (TS) 342 ($MH^+$)。

步骤 B：{4-[4-(吡咯烷-1-磺酰基)-哌嗪-1-基]-嘧啶-2-基}-甲醇。向 2-甲氧基甲基-4-[4-(吡咯烷-1-磺酰基)-哌嗪-1-基]-嘧啶(按照实施例 121，步骤 A 的方法制备，3.1g，9.4mmol)的二氯甲烷(47mL)溶液中于 0℃下加入三溴化硼(1M 的二氯甲烷溶液，19mL，18.7mmol)然后室温搅拌 2 小时。将混合物用饱和碳酸氢钠水溶液洗涤两次，将有机层分离，用硫酸镁干燥，过滤然后将滤液浓缩得到油，将其用异丙基醚结晶得到白色固体状标题化合物，2.43g (77%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.82 (m，4H)，3.15 (m，8H)，3.81 (m，4H)，4.35 (d，2H)，4.83 (t，1H)，6.71 (d，1H)，8.18 (d，1H)；mp：128-131℃；MS (CI) 328 ($MH^+$)。

实施例 122 至 125

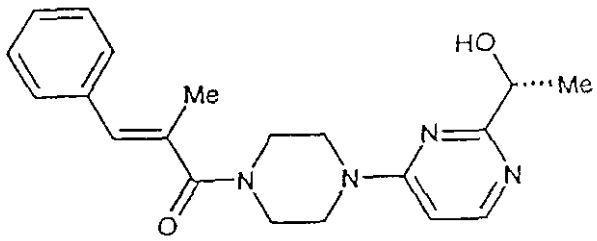
实施例 122 至 125 按照与实施例 121 类似的方法从适宜的原料制备。



| 实施例 | $R^1$ | $R^{17}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|
| 122 | $CH_2OH$ | 2,5-二甲基吡咯烷-1-基磺酰基 | 128-131 | 356 |
| 123 | $CH_2OH$ | 哌啶-1-基磺酰基 | 141-142 | 342 |
| 124 | (R)-CH(Me)OH | 氮杂-二环[3.2.1]辛-8-基磺酰基 | 111-112 | 382 |
| 125 | (R)-CH(Me)OH | 氮杂-二环[3.2.1]辛-3-酮-8-基-磺酰基 | 113-114 | 396 |

实施例 126

(E)-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-哌嗪-1-基}-2-甲基-3-苯基-丙烯酮



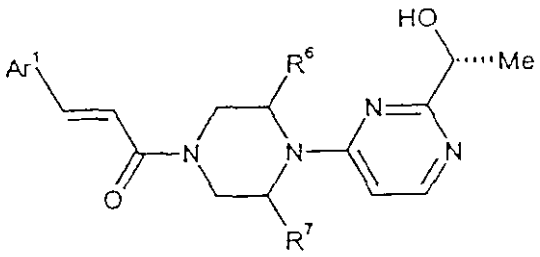
步骤 A: 乙酸(E)-1R-{4-[4-(2-甲基-3-苯基-丙烯酰基)-哌嗪-1-基]-嘧啶-2-基}-乙酯。向乙酸(R)-1-(4-哌嗪-1-基-嘧啶-2-基)-乙酯(按照制备例 2 的方法制备, 0.54g, 2.1mmol)和α-甲基肉桂酸(0.34g, 2.1mmol)的二氯甲烷(10mL)溶液中于室温下依次加入 1-羟基苯并三唑(0.50g, 3.6mmol)和 1-(3-二甲氨基丙基)-3-乙基碳二亚胺盐酸盐(0.45g, 2.4mmol)然后搅拌 48 小时。将混合物用水洗涤一次, 用饱和氯化钠水溶液洗涤一次, 用硫酸镁干燥, 过滤然后将滤

液浓缩成油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到透明粘稠油状实施例 126，步骤 A 的标题化合物，0.53g (63%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.51 (d, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 3.75 (m, 8H), 5.68 (q, 1H), 6.41 (d, 1H), 6.59 (s, 1H), 7.25-7.43 (m, 5H), 8.23 (d, 1H)；MS (CI) 395 ($MH^+$)；$[\alpha]_D$ +38.6 (c 1.0, MeOH)。

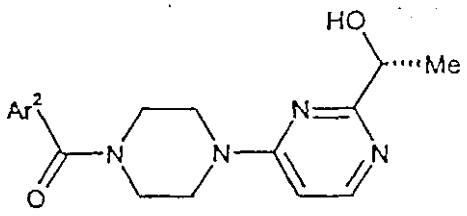
步骤 B：(E)-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-哌嗪-1-基}-2-甲基-3-苯基-丙烯酮。向乙酸(E)-1R-{4-[4-(2-甲基-3-苯基-丙烯酰基)-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 126，步骤 A 的方法制备，0.51g，1.3mmol)的甲醇(5mL)溶液中于室温下加入 6N 氢氧化钾水溶液(1mL)。搅拌 1 小时后，将溶液用乙酸乙酯稀释然后用水洗涤两次。将有机层分离，用硫酸镁干燥，过滤然后将滤液浓缩得到白色固体状标题化合物，0.25g (55%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.51 (d, 3H), 2.14 (s, 3H), 3.75 (m, 8H), 4.22 (br s, 1H), 4.71 (q, 1H), 6.41 (d, 1H), 6.59 (s, 1H), 7.25-7.43 (m, 5H), 8.23 (d, 1H)；mp：119-121℃；MS (CI) 353 ($MH^+$)；$[\alpha]_D$ +16.0 (c 1.0, MeOH)。

## 实施例 127 至 129

实施例 127 至 129 按照与实施例 126 类似的方法从适宜的原料制备。



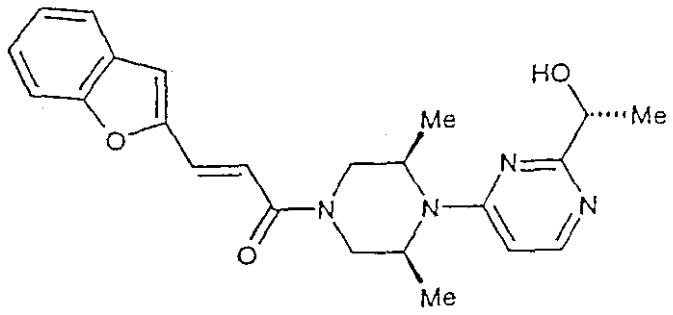

| 实施例 | $Ar^1$ | $R^6$ | $R^7$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 127 | 噻吩-2-基 | H | H | 104-106 | 345 |
| 128 | 噻吩-2-基 | (R)-Me | (S)-Me | 69-73 | 373 |



| 实施例 | $Ar^2$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|
| 129 | 4-(邻-甲苯基氨基甲酰基)-苯基 | 98-103 | 446 |

实施例 130

(E)-3-苯并呋喃-2-基-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-丙烯酮



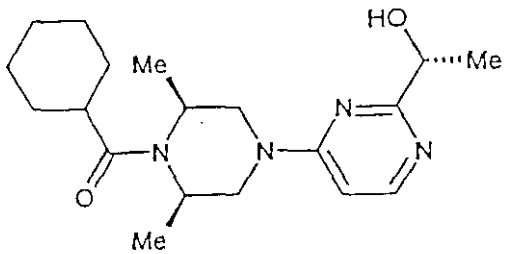
步骤 A: 丁酸(E)-1R-{4-[4-(3-苯并呋喃-2-基-丙烯酰基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备, 0.79g, 2.6mmol)和三乙胺(0.26g, 2.6mmol)的二氯甲烷(90mL)溶液中加入(E)-3-苯并呋喃-2-基-丙烯酰氯(0.54g, 2.6mmol)并室温搅拌 16 小时, 然后回流 2.5 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤, 将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到粗产物, 将其通过快速色谱纯化(9: 1 二氯甲烷: 甲醇)得到粘稠油状实施例 130, 步骤 A 的标题化合物, 0.79g (54%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 0.95 (t, 3H), 1.40 (d, 6H), 1.56 (d, 3H), 1.67 (q, 2H),

2.38 (t, 2H), 3.25 (d, 2H), 4.33 (m, 2H), 4.75 (m, 2H), 5.66 (q, 1H), 5.95 (d, 1H), 6.40 (d, 1H), 7.14-7.37, (m, 5H), 8.06 (d, 1H), 8.22 (d, 1H); MS (CI) 477 ($MH^+$); $[\alpha]_D$ +49.1 (c 1.0, MeOH)。

步骤 B: (E)-3-苯并呋喃-2-基-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-丙烯酮。向丁酸(E)-1R-{4-[4-(3-苯并呋喃-2-基-丙烯酰基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 130, 步骤 A 的方法制备, 0.51g, 1.1mmol)的甲醇(5mL)溶液中于室温下加入 6N 氢氧化钾水溶液(1mL)。搅拌 1 小时后, 将溶液用乙酸乙酯稀释并用水洗涤两次。将有机层分离, 用硫酸镁干燥, 过滤然后将滤液浓缩得到白色固体状标题化合物, 0.49g (75%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 1.40 (d, 6H), 1.56 (d, 3H), 3.25 (d, 2H), 4.33 (m, 2H), 4.75 (m, 2H), 4.68 (q, 1H), 5.95 (d, 1H), 6.40 (d, 1H), 7.14-7.37, (m, 5H), 8.06 (d, 1H), 8.22 (d, 1H); mp: 80-82 ℃; MS (CI) 407 ($MH^+$); $[\alpha]_D$ +17.7 (c 1.0, MeOH)。

## 实施例 131

环己基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮



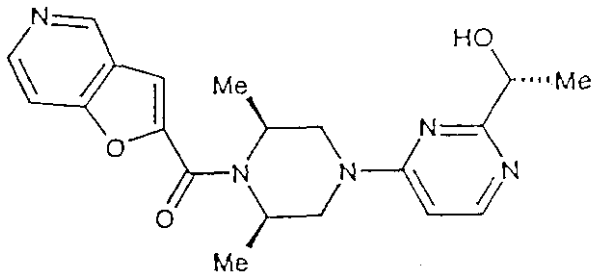

步骤 A: 丁酸 1R-[4-(4-环己烷羰基-3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备, 306mg, 1.0mmol)和三乙胺

(230mg, 1.2mmol)的二氯甲烷(10mL)溶液中于室温下加入环己烷羰酰氯(161mg, 1.1mmol)。1 小时后，将混合物用水洗涤，将二氯甲烷层用硫酸镁干燥然后过滤。将滤液浓缩得到油状实施例 131，步骤 A 的标题化合物，388mg (94%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.94 (t, 3H), 1.2-1.4 (m, 6H), 1.54 (d, 3H), 1.5-1.83 (m, 12H), 2.44 (m, 3H), 3.2-3.3 (m, 2H), 4.4-4.6 (m, 4H), 5.52 (q, 1H), 6.44 (d, 1H), 8.22 (d, 1H); MS (CI) 417 ($MH^+$)。

步骤 B: 环己基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮。向丁酸 1R-[4-(4-环己烷羰基-3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 131，步骤 A 的方法制备，375mg, 9.0mmol)的甲醇(5mL)溶液中加入 6N 氢氧化钾水溶液(0.5mL)然后室温搅拌 4 小时。将反应混合物浓缩，用水稀释然后用二氯甲烷萃取。将萃取液用水洗涤两次，用硫酸镁干燥然后蒸发得到油。将粗产物用乙醚结晶得到白色固体状标题化合物，106 mg (34%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.2-1.4 (m, 6H), 1.55 (d, 3H), 1.6-1.8 (m, 10H), 2.46 (m, 1H), 3.2-3.3 (m, 2H), 4.2-4.6 (m, 4H), 4.78 (q, 1H), 6.43 (d, 1H), 8.22 (d, 1H); mp: 174-175℃; MS (CI) 347 ($MH^+$); $[\alpha]_D$ +18.4 (c 1.0, MeOH)。

## 实施例 132

呋喃并[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮



步骤 A: 7-氯-呋喃并[3,2-c]吡啶-2-甲酸。-78℃及氮气氛下，向正丁基锂(2.5M 的己烷溶液，17mL，g，42.6mmol)的无水乙醚(90mL)溶液中滴加 4-氯-呋喃并[3,2-c]吡啶(5.81g，37.8mmol；J. Heterocycl. Chem. 1975，12，705)的乙醚(85mL)溶液。将混合物于-65℃搅拌 1.5 小时，倒入干冰(100 cc)中，升温至室温然后加入水中。将分出的有机层用水萃取一次，然后将合并的水层用浓盐酸酸化至 pH 得到白色固体状实施例 132，步骤 A 的标题化合物，3.33g (45%)。$^1$H NMR ($CDCl_3$，300MHz) δ 7.69 (s，1H)，7.85 (d，1H)，8.42 (d，1H)；mp：233-235℃(分解)；MS (CI) 153 ($MH^+-CO_2$)。

步骤 B: 7-氯-呋喃并[3,2-c]吡啶-2-甲酰氯。将 7-氯-呋喃并[3,2-c]吡啶-2-甲酸(按照实施例 132，步骤 A 的方法制备，8.94g，45.2mmol)与亚硫酰氯(30mL)和碳酸钠(9.59g，90.5mmol)混合然后在氮气氛下加热回流 16 小时。将冷却的混合物用二氯甲烷稀释然后过滤。将滤液蒸发得到橙色油状实施例 132，步骤 B 的标题化合物，9.19g (94%)。该酰氯不经纯化直接使用。

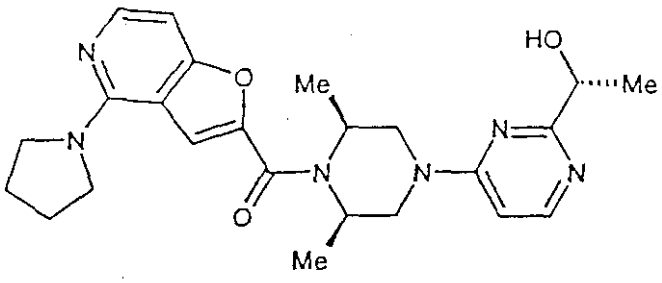
步骤 C: 丁酸 1R-{4-[4-(4-氯-呋喃并[3,2-c]吡啶-2-羰基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备，13.04g，42.5mmol)和三乙胺(8.61g，85.1mmol)的二氯甲烷(90mL)溶液中加入 7-氯-呋喃并[3,2-c]吡啶-2-甲酰氯(按照实施例 132，步骤 B 的方法制备，9.1g，84.0mmol)然后室温搅拌 2 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤，将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到粗产物，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到粘稠油状实施例 132，步骤 C 的标题化合物，18.9g (91%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.95 (t，3H)，1.40 (d，6H)，1.56 (d，3H)，1.67 (m，2H)，2.38 (t，2H)，3.25 (d，2H)，4.33 (m，2H)，4.75 (m，2H)，5.66 (q，1H)，6.40 (d，1H)，7.33 (s，1H)，7.41 (d，1H)，8.23 (d，1H)，8.35 (d，1H)；MS (CI) 487 ($MH^+$)；$[\alpha]_D$ +33.3 (c 1.0，MeOH)。

步骤 D：丁酸 1R-{4-[4-(呋喃并[3,2-c]吡啶-2-羰基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-{4-[4-(4-氯-呋喃并[3,2-c]吡啶-2-羰基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基-乙酯(按照实施例 132，步骤 C 的方法制备，18.6g，38.4mmol)的乙醇(160mL)溶液中加入碳酸钠(4.07g，38.4mmol)和 10%钯碳(6.10g，33 wt%)。将该混合物用 Parr 装置在 50 psi 氢气下氢化 6 小时。滤除催化剂然后将滤液蒸发得到油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到黄色油状实施例 132，步骤 D 的标题化合物，14.2g (82%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.95 (t，3H)，1.40 (d，6H)，1.56 (d，3H)，1.67 (q，2H)，2.38 (t，2H)，3.25 (d，2H)，4.33 (m，2H)，4.75 (m，2H)，5.68 (q，1H)，6.40 (d，1H)，7.37 (s，1H)，7.48 (d，1H)，8.22 (d，1H)，9.04 (s，1H)；MS (CI) 452 ($MH^+$)；$[\alpha]_D$ +36.7 (c 1.0，MeOH)。

步骤 E：呋喃比[3,2-c]吡啶-2-基-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-甲酮。将丁酸 1R-{4-[4-(呋喃并[3,2-c]吡啶-2-羰基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 132，步骤 D 的方法制备，5.48g，12.1mmol)与浓盐酸(15mL)混合然后室温搅拌 6 小时。将混合物倒入冷的 6M 氢氧化钠水溶液中并用乙酸乙酯萃取两次。将有机萃取液用水洗涤一次，用硫酸钠干燥然后蒸发得到泡沫，将其用异丙基醚结晶得到白色固体状标题化合物，3.33g (72%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.43 (d，6H)，1.52 (d，3H)，3.37 (m，2H)，4.38 (m，2H)，4.71 (q，1H)，4.83 (m，2H)，6.43 (d，1H)，7.38 (s，1H)，7.47 (m，1H)，8.22 (m，1H)，8.54 (d，1H)，8.58 (d，1H)，9.04 (s，1H)；mp：142-143 ℃；MS (CI) 382 ($MH^+$)；$[\alpha]_D$ +15.9 (c 1.0，MeOH)。

## 实施例 133

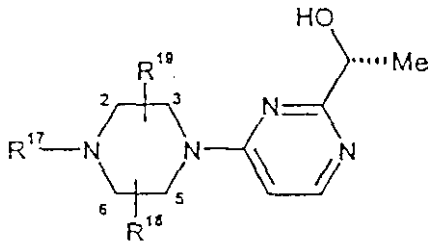
{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-(4-吡咯烷-1-基-呋喃并[3,2-c]吡啶-2-基)-甲酮



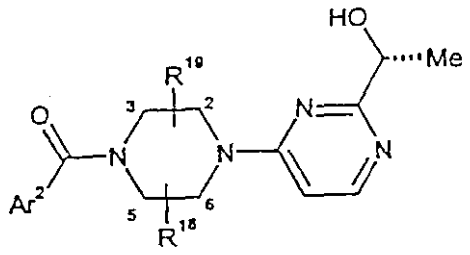
将丁酸 1R-{4-[4-(4-氯-呋喃并[3,2-c]吡啶-2-羰基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 132，步骤 C 的方法制备，0.046g，0.11mmol)的吡咯烷(0.037mL，0.44mmol)溶液加热回流 14 小时然后蒸发得到黄褐色固体状的标题化合物，0.04g (80%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.43 (d，6H)，1.53 (d，3H)，2.08 (m，4H)，3.43 (m，2H)，3.77 (m，4H)，4.43 (m，2H)，4.71 (q，1H)，4.92 (m，2H)，6.43 (d，1H)，6.70 (d，1H)，7.60 (s，1H)，8.08 (d，1H)，8.23 (d，1H)；MS (CI) 451 ($MH^+$)。

实施例 134 至 158

实施例 140 和 142 至 158 按照与实施例 131 类似的方法从适宜的原料制备。实施例 141 按照与实施例 133 类似的方法从适宜的原料制备。



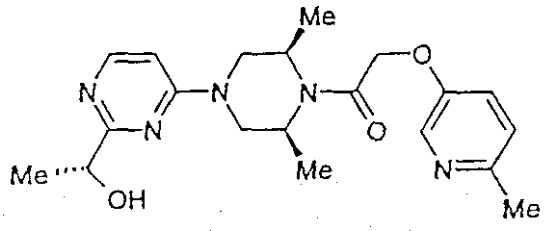
| 实施例 | $R^{17}$ | $R^{18}$ | $R^{19}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 134 | 环丙基羰基 | 2R-Me | 6S-Me | 110-111 | 305 |
| 135 | 环丁基羰基 | 2R-Me | 6S-Me | 134-135 | 319 |
| 136 | 环戊基羰基 | 2R-Me | 6S-Me | 199-200 | 333 |
| 137 | 叔丁基羰基 | 2R-Me | 6S-Me | 168-169 | 321 |



| 实施例 | $Ar^2$ | $R^{18}$ | $R^{19}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 138 | 苯并呋喃-2-基 | 2R-Me | 6S-Me | 124-126 | 381 |
| 139 | 呋喃并[3,2-c]吡啶-2-基 | H | H | 55-65 | 354 |
| 140 | 呋喃并[3,2-c]吡啶-2-基 | 3R-Me | 5S-Me | | 382 |
| 141 | 吗啉-4-基-呋喃并[3,2-c]吡啶-2-基 | 2R-Me | 6S-Me | | 467 |
| 142 | 呋喃并[2,3-c]吡啶-2-基 | 2R-Me | 6S-Me | 129-131 | 382 |
| 143 | 5-氯苯并呋喃-2-基 | H | H | | 387,389 |
| 144 | 5-氯苯并呋喃-2-基 | 3R-Me | 5S-Me | 114-116 | 415,417 |
| 145 | 5,7-二氯苯并呋喃-2-基 | 2R-Me | 6S-Me | 136-137 | 450,452 |
| 146 | 5,7-二氯苯并呋喃-2-基 | 3R-Me | 5S-Me | 152-153 | 450,452 |
| 147 | 5-硝基苯并呋喃-2-基 | 2R-Me | 6S-Me | 153-154 | 426 |
| 148 | 5,7-二甲基苯并呋喃-2-基 | 3R-Me | 5S-Me | 134-136 | 409 |
| 149 | 5-甲氧基苯并呋喃-2-基 | 3R-Me | 5S-Me | 137-138 | 411 |
| 150 | 5-甲氧基苯并呋喃-2-基 | 2R-Me | 6S-Me | 118-119 | 411 |
| 151 | 咪唑并[1,2-a]吡啶-2-基 | H | H | 149-150 | 353 |
| 152 | 咪唑并[1,2-a]吡啶-2-基 | 3R-Me | 5S-Me | 171-173 | 381 |
| 153 | 咪唑并[1,2-a]吡啶-2-基 | 2R-Me | 6S-Me | 147-149 | 381 |
| 154 | 6-氯咪唑并[1,2-b]哒嗪-2-基 | 2R-Me | 6S-Me | 76-84 | 416,418 |
| 155 | 6-甲基咪唑并[1,2-a]吡啶-2-基 | 3R-Me | 5S-Me | 164-165 | 395 |
| 156 | 苯并噁唑-2-基 | 2R-Me | 6S-Me | 126-127 | 382 |
| 157 | 4-氰基苯基 | 2R-Me | 6S-Me | 90-100 | 366 |
| 158 | 6-羟基-哒嗪-3-基 | 2R-Me | 6S-Me | | 359 |

实施例 159

1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-2-(6-甲基-吡啶-3-基氧基)-乙酮



步骤 A：丁酸 1R-[4-(4-氯乙酰基-3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备，9.69g，31.3mmol)和三乙胺(4.74g，46.9mmol)的氯仿(150mL)溶液中于 0℃下滴加氯乙酰氯(3.00mL，37.6mmol)然后在氮气氛下室温搅拌 12 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤，将有机层用硫酸钠干燥，用活性炭处理然后过滤。将滤液浓缩得到油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到油状实施例 159，步骤 A 的标题化合物，8.98g(75%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.96 (d，3H)，1.32 (d，6H)，1.59 (d，3H)，1.71 (m，2H)，2.40 (t，2H)，3.28 (m，2H)，4.28 (s，2H)，4.35 (m，4H)，5.68 (q，1H)，6.41 (d，1H)，8.23 (d，1H)；MS (CI) 383，385 ($MH^+$)。

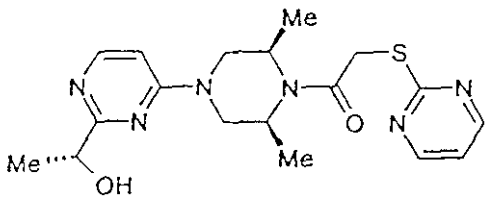
步骤 B：丁酸 1R-(4-{3R,5S-二甲基-4-[(6-甲基-吡啶-3-基氧基)-乙酰基]-哌嗪-1-基}-嘧啶-2-基)-乙酯。向氢化钠(60%的油悬浮液，0.05g，1.3mmol)的四氢呋喃(2mL)悬浮液中于 0℃及氮气氛下加入 6-甲基-3-吡啶醇(0.14g，1.3mmol)的四氢呋喃(3mL)溶液，然后升温至室温搅拌 0.5 小时。然后，加入丁酸 1R-[4-(4-氯乙酰基-3R,5R-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 159，步骤 A 的方法制备，0.40g，1.1mmol)的四氢呋喃(2mL)溶液并回流 1 小时。将混合物用二氯甲烷稀释然后用饱和碳酸氢钠水溶液洗涤，用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(9：

1 二氯甲烷：甲醇)得到油状实施例 159，步骤 B 的标题化合物，0.31g (66%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.96 (d, 3H), 1.32 (d, 6H), 1.59 (d, 3H), 1.71 (m, 2H), 2.40 (t, 2H), 2.46 (s, 3H), 3.28 (m, 2H), 3.78 (s, 2H), 4.35 (m, 4H), 5.68 (q, 1H), 6.41 (d, 1H), 6.83 (m, 1H), 7.14 (m, 1H), 8.08, (d, 1H), 8.23 (d, 1H)；MS (CI) 456 ($MH^+$)。

步骤 C：1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-2-(6-甲基-吡啶-3-基氧基)-乙酮。将丁酸 1R-(4-{3R,5S-二甲基-4-[(6-甲基-吡啶-3-基氧基)-乙酰基]-哌嗪-1-基}-嘧啶-2-基)-乙酯(按照实施例 159，步骤 B 的方法制备，0.30g，0.65mmol)和浓盐酸(3mL)混合然后室温搅拌 6 小时。将混合物用 6N 氢氧化钠水溶液中和至 pH 9 然后用乙酸乙酯萃取两次。将有机萃取液用水洗涤一次，用硫酸钠干燥然后过滤。将滤液浓缩成油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到白色泡沫状标题化合物，0.14g (55%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.38 (d, 6H), 1.55 (d, 3H), 2.46 (s, 3H), 3.28 (m, 2H), 3.76 (s, 2H), 4.35-4.65 (m, 4H), 4.67 (q, 1H), 6.38 (d, 1H), 6.83 (m, 1H), 7.11 (m, 1H), 8.08, (d, 1H), 8.21 (d, 1H)；mp：55-65℃；MS (CI) 330 ($MH^+$)；$[\alpha]_D$ +16.0 (c 1.0, MeOH)。

## 实施例 160

1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-2-(嘧啶-2-基硫基)-乙酮

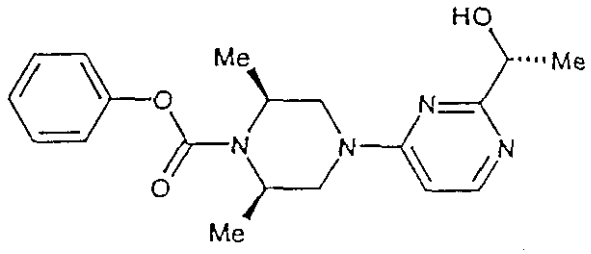



实施例 160 按照与实施例 159 类似的方法从适宜的原料制备。$^1$H

NMR ($CDCl_3$, 300MHz) δ 1.38 (m, 6H), 1.48 (d, 3H), 3.28 (m, 2H), 3.96 (s, 2H), 4.35 (m, 4H), 4.65-4.97 (m, 3H), 6.28 (d, 1H), 6.93 (m, 1H), 7.11 (m, 1H), 8.21 (d, 1H), 8.45 (m, 2H); mp: 60-70℃; MS (CI) 389 ($MH^+$); $[\alpha]_D$ +16.8 (c 1. 0, MeOH)。

## 实施例 161

4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸苯酯



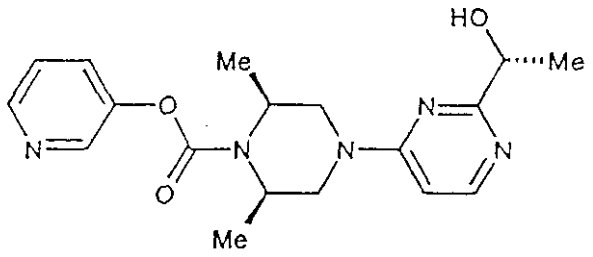

步骤 A: 4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸苯酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯 (按照制备例 3 的方法制备, 0.30g, 0.98mmol)和三乙胺(0.20g, 1.9mmol)的二氯甲烷(5mL)溶液中加入氯甲酸苯酯(0.76g, 4.8mmol)然后在氮气氛下室温搅拌 2 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤, 将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到油, 将其通过快速色谱纯化(9: 1 二氯甲烷: 甲醇)得到油状实施例 161, 步骤 A 的标题化合物, 0.35g (84%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 0.96 (d, 3H), 1.32 (d, 6H), 1.59 (d, 3H), 1.71 (q, 2H), 2.40 (t, 2H), 3.28 (m, 2H), 4.35 (m, 4H), 5.68 (q, 1H), 6.41 (d, 1H), 7.12 (d, 2H), 7.22 (m, 1H), 7.35 (m, 2H), 8.23 (d, 1H); MS (CI) 427 ($MH^+$); $[\alpha]_D$ +39.6 (c 1.0, MeOH)。

步骤 B: 4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-

甲酸苯酯。将 4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸苯酯(按照实施例 161, 步骤 A 的方法制备, 0.31g, 0.70mmol)与浓盐酸(5mL)混合然后室温搅拌 6 小时。将混合物用 6N 氢氧化钠水溶液中和至 pH 9 然后用乙酸乙酯萃取两次。将有机萃取液用水洗涤一次, 用硫酸钠干燥然后过滤。将滤液浓缩成油, 将其通过快速色谱纯化(9: 1 二氯甲烷: 甲醇)得到白色固体状标题化合物, 0.12g (81%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.41 (d, 6H), 1.51 (d, 3H), 3.34 (m, 2H), 4.43 (m, 2H), 4.52 (m, 2H), 4.71 (q, 1H), 6.46 (d, 1H), 7.12 (m, 2H), 7.23 (m, 1H), 7.35 (m, 2H), 8.23 (d, 1H); MS (CI) 357 ($MH^+$); $[\alpha]_D$ +16.9 (c 1.0, MeOH)。

## 实施例 162

4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸吡啶-3-基酯




步骤 A: 4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-羰酰氯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备, 3.61, 11.8mmol)和吡啶(0.93g, 11.8mmol)的二氯甲烷(50mL)溶液中加入三光气(1.17g, 3.9mmol)然后在氮气氛下室温搅拌 16 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤, 将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到油, 将其通过快速色谱纯化(乙酸乙酯)得到黄色油状实施例 162, 步骤 A 的标题化合物, 2.12g, (51%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.90

(t, 3H), 1.31 (d, 6H), 1.56 (d, 3H), 1.68 (m, 2H), 2.38 (t, 2H), 3.21 (m, 2H), 3.88-4.40 (m, 4H), 5.66 (q, 1H), 6.43 (d, 1H), 8.22 (d, 1H); MS (CI) 369, 371 ($MH^+$)。

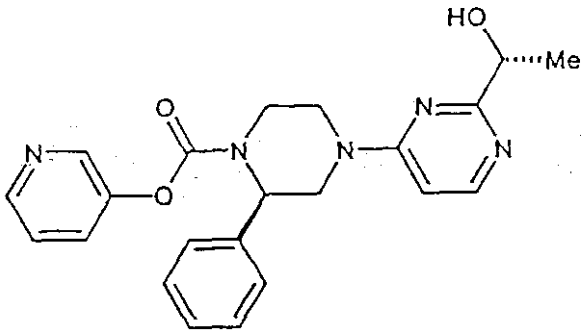
步骤 B: {4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪}-1-甲酸吡啶-3-基酯。向氢化钠(60%油分散液, 0.046g, 1.15mmol)的无水四氢呋喃(8mL)悬浮液中于 0℃下加入 3-羟基吡啶(0.11g, 1.15mmol)。在形成均匀的溶液后, 于 0℃下加入 4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基哌嗪-1-羰酰氯(按照实施例 162, 步骤 A 的方法生产, 0.36g, 0.96mmol)的四氢呋喃(3mL)溶液并将该混合物升温至室温, 然后加热回流 6 小时。将混合物加入水中并用乙酸乙酯萃取两次。将合并的有机层用硫酸钠干燥然后过滤。将滤液浓缩得到油, 将其通过快速色谱纯化(乙酸乙酯)得到半固体状实施例 162, 步骤 B 的标题化合物, 0.31g (78%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 0.90 (t, 3H), 1.35 (m, 6H), 1.61 (d, 3H), 1.69 (m, 2H), 2.41 (t, 2H), 3.30 (m, 2H), 4.11-4.38 (m, 4H), 5.69 (q, 1H), 6.41 (d, 1H), 7.32 (m, 1H), 7.52 (m, 1H), 8.22 (d, 1H), 8.46 (s, 1H), 8.48, (d, 1H); MS (CI) 428 ($MH^+$)。

步骤 C: 4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-甲酸吡啶-3-基酯。将{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪}-1-甲酸吡啶-3-基酯(按照实施例 162, 步骤 B 的方法制备, 0.31g, 0.70mmol)与浓盐酸(5mL)混合然后室温搅拌 6 小时。将混合物用 6N 氢氧化钠水溶液中和至 pH 9 然后用乙酸乙酯萃取两次。将萃取液用水洗涤一次, 用硫酸钠干燥然后过滤。将滤液浓缩成油, 将其通过快速色谱纯化(9: 1 二氯甲烷: 甲醇)得到白色固体状标题化合物, 0.12g (81%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 1.41 (d, 6H), 1.51 (d, 3H), 3.33 (m, 2H), 4.25-4.45 (m, 4H), 4.71 (q, 1H), 6.43 (d, 1H), 7.33 (m, 1H), 7.56 (m, 1H), 8.23 (d, 1H), 8.25 (d, 1H), 8.48 (d, 1H); MS (CI) 358

(MH$^+$)；[α]$_D$ +18.5 (c 1.0, MeOH)。

实施例 163

4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R-苯基-哌嗪-1-甲酸吡啶-3-基酯




步骤 A：丁酸 1R-[4-(3R-苯基-哌嗪-1-基)-嘧啶-2-基]-乙酯。向(R)-2-苯基哌嗪(0.48g, 3.0mmol, Indian J. Chem. Sect. B 1994, 33, 285)和三乙胺(1.21g, 12.0mmol)的四氢呋喃(10mL)溶液中加入丁酸(R)-1-(4-氯嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，0.68g, 3.0mmol)然后室温搅拌 18 小时。将混合物倒入饱和碳酸氢钠水溶液中然后用乙酸乙酯萃取。将合并的有机层用硫酸钠干燥然后过滤。将滤液浓缩得到粗产物，将其通过快速色谱纯化(95：5 二氯甲烷：甲醇)得到粘稠油状实施例 163，步骤 A 的标题化合物，0.70g (67%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.95 (t, 3H), 1.56 (d, 3H), 1.67 (m, 2H), 2.40 (t, 2H), 3.55 (m, 2H), 4.0 (m, 2H), 4.32 (m, 2H), 4.70 (m, 1H), 5.69 (q, 1H), 6.49 (d, 1H), 7.40 (m, 5H), 8.21 (d, 1H)；MS (CI) 355 (MH$^+$)。

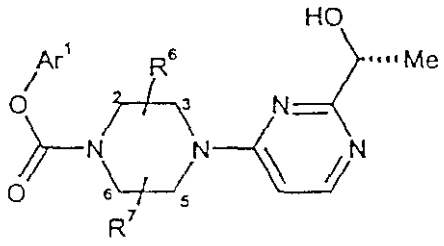
步骤 B：4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R-苯基-哌嗪-1-甲酸吡啶-3-基酯。向丁酸 1R-[4-(3R-苯基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 163，步骤 A 的方法制备，0.22g, 0.6mmol)和三乙胺(0.31g, 3.1mmol)的甲苯(5mL)溶液中加入碳酸二吡啶-3-基酯(0.67g, 3.1mmol)然后加热回流 3 小时。将混合物倒入饱和碳酸氢钠水溶液中，将有机层分离然后将水层用乙酸乙酯萃取。将合并

的有机层用硫酸钠干燥然后过滤。将滤液浓缩得到粗产物，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到黄色油状实施例 163，步骤 B 的标题化合物，0.22g (73%)。MS (CI) 476 ($MH^+$)。

步骤 C：4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R-苯基-哌嗪-1-甲酸吡啶-3-基酯。将 4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R-苯基-哌嗪-1-甲酸吡啶-3-基酯(按照实施例 163，步骤 B 的方法制备，0.21g，0.44mmol)与浓盐酸(2mL)混合然后室温搅拌 6 小时。将混合物用 6N 氢氧化钠水溶液中和至 pH 9 然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用硫酸钠干燥然后过滤。将滤液浓缩成油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到白色固体状标题化合物，0.13g (73%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 1.55 (d, 3H), 3.55 (m, 2H), 4.0 (m, 2H), 4.32 (m, 2H), 4.71 (m, 1H), 4.75 (q, 1H), 6.40 (d, 1H), 7.18-7.41 (m, 7H), 8.24 (d, 1H), 8.35 (br s, 1H), 8.45 (d, 1H)；MS (CI) 406 ($MH^+$)。

## 实施例 164 至 173

实施例 164 至 173 按照与实施例 163 类似的方法从适宜的原料制备。

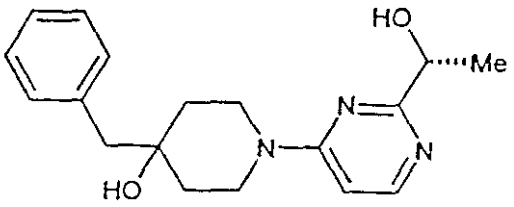



| 实施例 | $R^7$ | $R^6$ | $Ar^1$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 164 | 3R-Me | 5S-Me | 苯基 | | 357 |
| 165 | 3R-Me | 5S-Me | 2-甲基-吡啶-3-基 | 65-75 | 372 |
| 166 | H | H | 吡啶-3-基 | 107-110 | 330 |
| 167 | 3R-Me | 5S-Me | 2-氯-吡啶-3-基 | 60-70 | 392,394 |
| 168 | 3R-Me | 5S-Me | 5-氯-吡啶-3-基 | 65-69 | 392,394 |

| | | | | | |
|---|---|---|---|---|---|
| 169 | 3R-Me | 5S-Me | 异喹啉-5-基 | 60-70 | 407 |
| 170 | 3R-Me | 5S-Me | 4-氯-吡啶-3-基 | 60-70 | 392, 394 |
| 171 | 3R-Me | 5S-Me | 6-甲基-吡啶-3-基 | 60-70 | 372 |
| 172 | 2RS-$CH_2OMe$ | H | 吡啶-3-基 | | 388 |
| 173 | 2RS-$CO_2Et$ | H | 吡啶-3-基 | | 402 |

## 实施例 174

(R)-4-苄基-1-[2-(1-羟基-乙基)-嘧啶-4-基]-哌啶-4-醇



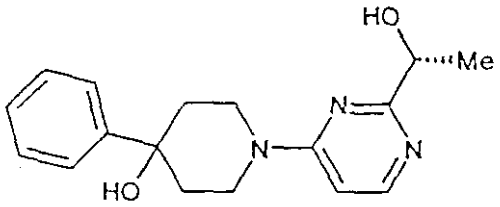

步骤 A: 丁酸(R)-1-[4-(4-苄基-4-羟基-哌啶-1-基)-嘧啶-2-基]-乙酯。向 4-苄基-4-羟基哌啶(0.95g, 5.0mmol)和三乙胺(0.51g, 5.0mmol)的二氯甲烷(10mL)溶液中加入丁酸(R)-1-(4-甲磺酰氧基-嘧啶-2-基)-乙酯(按照制备例 8 的方法制备, 1.23g, 4.0mmol)然后室温搅拌 18 小时。将混合物用水洗涤一次, 用饱和氯化钠水溶液洗涤一次, 将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油, 将其通过快速色谱纯化(95: 5 二氯甲烷: 甲醇)得到粘稠油状实施例 174, 步骤 A 的标题化合物, 0.99g (52%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 0.95 (t, 3H), 1.53 (d, 3H), 1.65-1.78 (m, 4H), 1.88 (m, 2H), 2.08 (m, 2H), 2.48 (t, 2H), 3.45 (m, 2H), 4.42 (br s, 1H), 5.68 (q, 1H), 6.41 (d, 1H), 7.30-7.48 (m, 5H), 8.18 (d, 1H); MS (CI) 384 ($MH^+$)。

步骤 B: (R)-4-苄基-1-[2-(1-羟基-乙基)-嘧啶-4-基]-哌啶-4-醇。向丁酸(R)-1-[4-(4-苄基-4-羟基-哌啶-1-基)-嘧啶-2-基]-乙酯(按照实施例 174, 步骤 A 的方法制备, 0.20g, 0.52mmol)的甲醇

(5mL)溶液中加入 1N 氢氧化钠水溶液(1mL)然后室温搅拌 4 小时。将混合物用二氯甲烷稀释然后用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到泡沫状标题化合物，0.12g (68%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.49 (d, 3H), 1.74 (br s, 2H), 1.82 (m, 2H), 2.08 (m, 2H), 3.42 (m, 2H), 4.42 (br s, 1H), 4.71 (q, 1H), 6.43 (d, 1H), 7.33-7.48 (m, 5H), 8.21 (d, 1H); MS (CI) 314 ($MH^+$)。

## 实施例 175

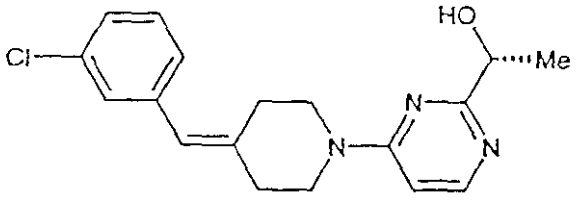
(R)-4-苯基-1-[2-(1-羟基-乙基)-嘧啶-4-基]-哌啶-4-醇




实施例 175 按照与实施例 174 类似的方法从适宜的原料制备。mp: 114℃; MS (CI) 300 ($MH^+$)。

## 实施例 176

(R)-1-{4-[4-(3-氯亚苄基)-哌啶-1-基]-嘧啶-2-基}-乙醇




步骤 A: 1-[4-(3-氯亚苄基)-哌啶-1-基]-1-甲酸叔丁酯。向 4-氯苄基三苯基氯化鏻(4.23g, 10.0mmol)的四氢呋喃(40mL)悬浮液中于 0

℃及氮气氛下加入正丁基锂的己烷溶液(2.5M 的己烷溶液，4.4mL，11.0mmol)然后搅拌 0.5 小时。于 10-15℃下加入 4-氧代-哌啶-1-甲酸叔丁酯(按照实施例 101，步骤 A 的方法制备，1.99g，10.0mmol)的四氢呋喃(10mL)溶液然后升温至室温。将混合物蒸发得到油，将其通过快速色谱纯化(9：1 己烷:乙酸乙酯)得到油状实施例 176，步骤 A 的标题化合物，2.63g (85%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.39 (s，9H)，2.48 (m，2H)，2.57 (m，2H)，3.68-3.82 (m，4H)，6.36 (s，1H)，7.08 (m，1H)，7.12-7.28 (m，3H)；MS (CI) 308 ($MH^+$)。

步骤 B：4-(3-氯-亚苄基)-哌啶盐酸盐。向[1-[4-(3-氯亚苄基)-哌啶-1-基]-1-甲酸叔丁酯(按照实施例 176，步骤 A 的方法制备，2.5g，8.1mmol)的二氯甲烷(20mL)溶液中于室温下加入氯化氢(4M 的二氧六环溶液，4.0mL，16.0mmol)然后搅拌 4 小时。将混合物蒸发至干，悬浮在乙醚中然后过滤得到白色固体状实施例 176，步骤 B 的标题化合物，1.63g (82%)。$^1$H NMR ($CDCl_3/D_2O$，300MHz) δ 2.48 (m，2H)，2.57 (m，2H)，3.63 (m，2H)，3.77 (m，2H)，6.36 (s，1H)，7.10 (m，1H)，7.12-7.28 (m，3H)；mp：147-151℃。

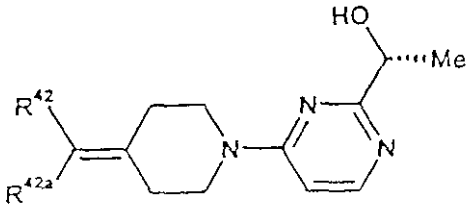
步骤 C：丁酸(R)-1-{4-[4-(3-氯-亚苄基)-哌啶-1-基]-嘧啶-2-基}-乙酯。向 4-(3-氯亚苄基)-哌啶盐酸盐(按照实施例 176，步骤 B 的方法制备，0.46g，2.0mmol)和三乙胺(0.61g，6.0mmol)的二氯甲烷(10mL)溶液中加入乙酸(R)-1-(4-氯嘧啶-2-基)-乙酯(按照制备例 5 的方法制备，0.54g，2.2mmol)然后室温搅拌 12 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤，将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到粗产物，将其通过快速色谱纯化(95：5 二氯甲烷：甲醇)得到粘稠油状实施例 176，步骤 C 的标题化合物，0.64g (80%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.95 (d，6H)，1.51 (d，3H)，1.68 (m，2H) 2.35 (m，2H)，2.47-2.64 (m，4H)，3.67-3.75 (m，4H)，5.68 (q，1H)，6.36 (s，1H)，6.40 (d，1H)，6.98 (m，1H)，7.12-7.28 (m，3H)，8.18 (m，1H)；MS (CI)

400 ($MH^+$)。

步骤 D: (R)-1-{4-[4-(3-氯亚苄基)-哌啶-1-基]-嘧啶-2-基}-乙醇。向丁酸(R)-1-{4-[4-(3-氯-亚苄基)-哌啶-1-基]-嘧啶-2-基}-乙酯(按照实施例 176, 步骤 C 的方法制备, 0.62g, 1.55mmol)的甲醇(8mL)溶液中加入 1N 氢氧化钠水溶液(1mL)然后室温搅拌 4 小时。将混合物用氯仿稀释然后用水洗涤一次, 用饱和氯化钠水溶液洗涤一次, 将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到粗产物, 将其通过快速色谱纯化(95: 5 二氯甲烷: 甲醇)得到白色固体状标题化合物, 0.31g (61%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 1.51 (d, 3H), 2.46 (m, 2H), 2.56 (m, 2H), 3.07 (m, 2H), 3.77 (m, 2H), 4.35 (d, 1H), 4.69 (q, 1H), 6.36 (s, 1H), 6.40 (d, 1H), 7.07 (m, 1H), 7.12-7.28 (m, 3H), 8.18 (m, 1H); mp: 45-55 ℃; MS (CI) 330 ($MH^+$); $[\alpha]_D$ +16.8 (c 1.0, MeOH)。

## 实施例 177 至 181

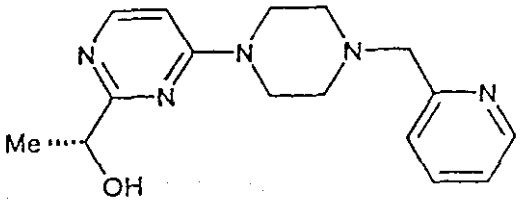
实施例 177 至 181 按照与实施例 176 类似的方法从适宜的原料制备。




| 实施例 | $R^{42}$ | $R^{42a}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|
| 177 | 4-氯苯基 | H | | 330, 332 |
| 178 | (E)-2-苯基-乙烯-1-基 | H | | 322 |
| 179 | 苯甲酰基 | H | 44-59 | 324 |
| 180 | 苯基 | 苯基 | 108-109 | 372 |
| 181 | 苯基 | 吡啶-2-基 | 98-101 | 373 |

## 实施例 182

## (R)-1-[4-(4-吡啶-2-基甲基-哌嗪-1-基)-嘧啶-2-基]-乙醇



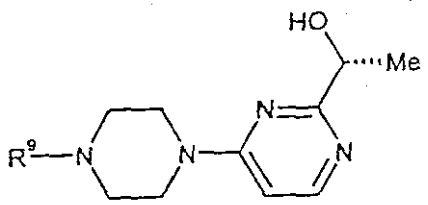
步骤 A：乙酸(R)-1-[4-(4-吡啶-2-基甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。向乙酸(R)-1-[4-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 2 的方法制备，1.55g，6.2mmol)和三乙胺(0.86mL，6.2mmol)的四氢呋喃(20mL)溶液中于室温下加入 2-吡啶甲基氯化物盐酸盐(1.01g，6.2mmol)然后搅拌 1 小时。将混合物用水稀释然后用乙酸乙酯萃取两次。将合并的萃取液用硫酸镁干燥，过滤然后将滤液浓缩成油，将其通过快速色谱纯化(95：5 二氯甲烷：甲醇)得到实施例 182，步骤 A 的标题化合物，0.98g (46%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.58 (d, 3H), 2.15 (s, 3H) 2.62 (t, 4H), 3.72 (t, 4H), 3.75 (s, 2H), 5.67 (q, 1H), 6.35 (d, 1H), 7.22 (m, 1H), 7.46 (d, 1H), 7.73 (m, 1H), 8.21 (d, 1H), 8.62 (d, 1H)；MS (CI) 342 ($MH^+$)。

步骤 B：(R)-1-[4-(4-吡啶-2-基甲基-哌嗪-1-基)-嘧啶-2-基]-乙醇。向乙酸(R)-1-[4-(4-吡啶-2-基甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照实施例 182，步骤 A 的方法制备，0.14g，0.33mmol)的二氧六环(6mL)溶液中于室温下加入 6N 氢氧化钾水溶液(0.5mL)。搅拌 3 小时后，将溶液用乙酸乙酯稀释然后用水洗涤两次。将有机层分离，用硫酸镁干燥，过滤然后将滤液浓缩得到白色固体状标题化合物，0.09g (69%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.52 (d, 3H), 2.38-2.59 (m, 4H), 3.72-3.77 (m, 6H), 4.69 (q, 1H), 6.37 (d, 1H), 7.22 (d, 1H), 7.41 (d, 1H), 7.69 (m, 1H), 8.21 (d,

1H) 8.58, (d, 1H); mp: 68-70℃; MS (CI) 300 ($MH^+$); $[\alpha]_D$ +16.2 (c 1.0, MeOH)。

实施例 183 至 187

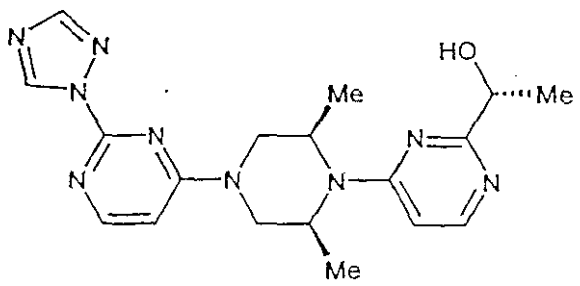
实施例 183 至 187 按照与实施例 182 类似的方法从适宜的原料制备。



| 实施例 | $R^9$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|
| 183 | 苯基甲基 | | 299 |
| 184 | 异喹啉-2-基-甲基 | | 350 |
| 185 | 苯并噻吩-2-基-甲基 | | 355 |
| 186 | 苯并噻唑-2-基-甲基 | | 356 |
| 187 | 苯并呋喃-2-基-甲基 | | 339 |

实施例 188

1R-{4-[2R,6S-二甲基-4-(2-[1,2,4]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇



步骤 A: 4-(3R,5S-二甲基-哌嗪-1-基)-2-甲磺酰基-嘧啶。向顺-

2,6-二甲基哌嗪(10.7g, 94.1mmol)和三乙胺(9.52g, 94.1mmol)的氯仿(300mL)溶液中于室温下加入 4-氯-2-甲磺酰基嘧啶(15.1g, 78.4mmol; Heterocycles 1985, 23, 611)然后搅拌 1 小时。将混合物用饱和碳酸氢钠水溶液洗涤并将分离的有机层用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到橙色固体，将其在乙醚中形成浆液然后过滤得到白色固体状实施例 188，步骤 A 的标题化合物，15.4g (73%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 1.01 (m, 6H), 2.35-2.78 (m, 4H), 2.85 (s, 3H), 3.32 (m, 2H), 6.81 (d, 1H), 8.2 (d, 1H); mp: 182-183℃; MS (CI) 301 ($MH^+$)。

步骤 B: 4-(3R,5S-二甲基-哌嗪-1-基)-2-[1,2,4]三唑-1-基-嘧啶。向氢化钠(60%油分散液，0.37g，9.4mmol)的二甲基甲酰胺(5mL)浆液中于 0℃及氮气氛下加入 1,2,4-三唑(0.67g，9.4mmol)的二甲基甲酰胺(4mL)溶液。10 分钟后，滴加 4-(3R,5S-二甲基-哌嗪-1-基)-2-甲磺酰基-嘧啶(按照实施例 188，步骤 A 的方法制备，2.54g，9.4mmol)在温热的二甲基甲酰胺(5mL)中的溶液然后室温搅拌 2 小时，然后加热至 100℃ 0.5 小时。将混合物加入饱和碳酸氢钠水溶液中然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(9: 1 二氯甲烷: 甲醇)得到油状实施例 188，步骤 B 的标题化合物，0.50g (62%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 1.01 (m, 6H), 2.35-2.88 (m, 5H), 3.32 (m, 1H), 6.81 (d, 1H), 8.16-8.23 (m, 2H), 9.25 (d, 1H); MS (CI) 260 ($MH^+$)。

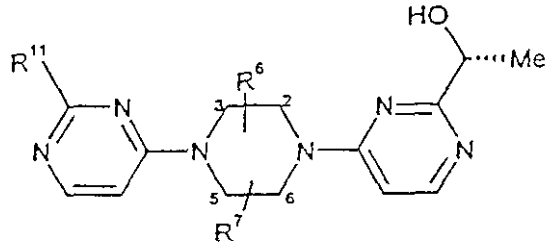
步骤 C: 丁酸 1R-{4-[2R,6S-二甲基-4-(2-[1,2,3]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙酯。向 4-(3R,5S-二甲基-哌嗪-1-基)-2-[1,2,4]三唑-1-基-嘧啶(按照实施例 188，步骤 B 的方法制备，0.46g，1.8mmol)的乙腈(3mL)溶液中加入丁酸(R)-1-(4-甲磺酰氧基-嘧啶-2-基)-乙酯(按照制备例 8 的方法制备，0.57g，

2.0mmol)然后在氮气氛下加热回流 6 小时。将混合物加入饱和碳酸氢钠水溶液中然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到油状实施例 188，步骤 C 的标题化合物，0.22g (54%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 0.95 (t, 3H), 1.51 (m, 6H), 1.54 (d, 3H), 1.63 (m, 2H), 2.38 (t, 2H), 3.38 (m, 2H), 4.33-4.64 (m, 4H), 5.68 (q, 1H), 6.28 (d, 1H), 6.58 (d, 1H), 8.10 (s, 1H), 8.26-8.32 (m, 2H), 9.10 (d, 1H)；MS (CI) 452 ($MH^+$)；$[\alpha]_D$ +50.0 (c 1.0, MeOH)。

步骤 D：1R-{4-[2R,6S-二甲基-4-(2-[1,2,4]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇。将丁酸 1R-{4-[2R,6S-二甲基-4-(2-[1,2,3]三唑-1-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 188，步骤 C 的方法制备，0.18g，0.40mmol)与浓盐酸(2mL)混合然后室温搅拌 4 小时。将混合物加入饱和碳酸氢钠水溶液中然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到白色固体状标题化合物，0.13g (87%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 1.31 (d, 6H), 1.51 (d, 3H), 3.42 (m, 2H), 4.42-4.73 (m, 5H), 6.41 (d, 1H), 6.56 (d, 1H), 8.12 (s, 1H), 8.24 (d, 1H), 8.30 (d, 1H), 9.10 (s, 1H)；MS (CI) 382 ($MH^+$)；$[\alpha]_D$ +18.6 (c 1.0, MeOH)。

## 实施例 189 至 195

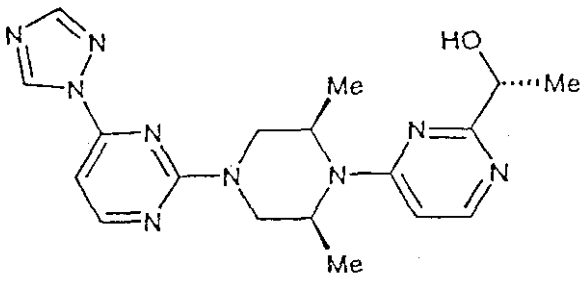
实施例 189 至 195 按照与实施例 188 类似的方法从适宜的原料制备。



| 实施例 | $R^{11}$ | $R^7$ | $R^6$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 189 | 2-羟基苯基 | 2R-Me | 6S-Me | 60-70 | 407 |
| 190 | 咪唑-1-基 | 2R-Me | 6S-Me | 60-70 | 381 |
| 191 | [1,2,3]三唑-1-基 | 2R-Me | 6S-Me | 70-80 | 382 |
| 192 | 吡咯-1-基 | 2R-Me | 6S-Me | 70-80 | 380 |
| 193 | 4-甲基咪唑-1-基 | 2R-Me | 6S-Me | 70-80 | 395 |
| 194 | 2-甲基咪唑-1-基 | 2R-Me | 6S-Me | 70-80 | 395 |
| 195 | 2,4-二甲基咪唑-1-基 | 2R-Me | 6S-Me | 70-80 | 409 |

实施例 196

1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶 2-基}-乙醇



步骤 A: 2-甲硫基-4-[1,2,4]三唑-1-基-嘧啶。向氢化钠(60%油分散液, 24.2g, 605mmol)的二甲基甲酰胺(800mL)浆液中于 0℃及氮气氛下加入 1,2,4-三唑(0.67g, 9.4mmol)的二甲基甲酰胺(4.0mL)溶液。10 分钟后, 于 10℃下滴加 4-氯-2-甲硫基嘧啶(97.2g, 605mmol)的二甲基甲酰胺(200mL)溶液然后室温搅拌 14 小时。将混

合物加入水中，滤出固体沉淀然后真空干燥得到白色固体状实施例196，步骤A的标题化合物，113g (94%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 2.82 (s, 3H), 6.82 (d, 1H), 8.18 (d, 1H), 8.19 (s, 1H), 9.35 (s, 1H)；mp: 125-126℃；MS (CI) 194 ($MH^+$)。

步骤B: 2-甲磺酰基-4-[1,2,4]三唑-1-基-嘧啶。向机械搅拌中的3-氯过氧苯甲酸(75%, 127g, 551mmol)的氯仿(625mL)溶液中加入2-甲硫基-4-[1,2,4]三唑-1-基-嘧啶(按照实施例196，步骤A的方法制备，50.7g, 262mmol)的氯仿(625mL)溶液然后室温搅拌16小时。将混合物过滤并将滤液用饱和碳酸钠水溶液洗涤6次。将有机层用硫酸钠干燥，过滤然后浓缩得到白色固体状实施例196，步骤B的标题化合物，37.8g (64%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 3.62 (s, 3H), 6.82 (d, 1H), 8.19 (s, 1H), 8.24 (d, 1H), 9.35 (s, 1H)；mp: 135-136℃；MS (CI) 226 ($MH^+$)。

步骤C: 2-(3R,5S-二甲基-哌嗪-1-基)-4-[1,2,4]三唑-1-基-嘧啶。将2-甲磺酰基-4-[1,2,4]三唑-1-基-嘧啶(按照实施例196，步骤B的方法制备，32.5g, 144mmol)与顺-2,6-二甲基哌嗪(34.5g, 302mmol)混合然后于135℃加热1小时，冷却，溶于2N盐酸水溶液并用乙酸乙酯洗涤一次。将酸性含水层用6N氢氧化钠水溶液于0℃下碱化至pH 9然后用乙酸乙酯萃取4次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其用己烷结晶得到白色固体状实施例196，步骤C的标题化合物，31.8g (71%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 0.99 (d, 6H), 2.38 (m, 4H), 3.30 (s, 2H), 6.82 (d, 1H), 8.18 (d, 1H), 8.19 (s, 1H), 9.35 (s, 1H)；mp: 143-145℃；MS (CI) 260 ($MH^+$)。

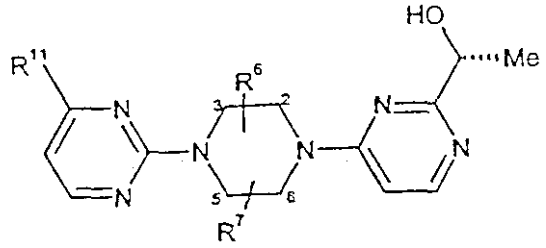
步骤D: 丁酸 1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙酯。向2-(3R,5S-二甲基-哌嗪-1-基)-4-[1,2,4]三唑-1-基-嘧啶(按照实施例196，步骤C的方法制备，8.33g, 32.1mmol)的乙腈(30mL)溶液中加入丁酸(R)-1-

(4-三氟甲磺酰氧基-嘧啶-2-基)-乙酯(按照制备例 9 的方法制备，5.50g，16.1mmol)然后在氮气氛下加热回流 3 小时。将冷却的混合物过滤并将固体用乙酸乙酯洗涤两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(99：1 二氯甲烷：甲醇)得到油状实施例 196，步骤 D 的标题化合物，3.61g (50%)。$^1$H NMR ($CDCl_3$，400MHz) δ 0.91 (d，6H)，1.26 (t，3H)，1.59 (d，3H)，1.69 (q，2H)，2.40 (m，2H)，3.40 (d，2H)，4.60 (m，4H)，5.70 (q，1H)，6.39 (d，1H)，6.58 (d，1H)，8.12 (s，1H)，8.25 (d，1H)，8.31 (d，1H)，8.35 (s，1H)；MS (CI) 452 ($MH^+$)。

步骤 E：1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇。将丁酸 1R-{4-[2R,6S-二甲基-4-(4-[1,2,4]三唑-1-基-嘧啶-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 196，步骤 D 的方法制备，3.60g，8.0mmol)与浓盐酸(10mL)混合然后室温搅拌 4 小时。将混合物加入饱和碳酸氢钠水溶液中然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(99：1 二氯甲烷：甲醇)得到白色固体状标题化合物，2.35g (77%)。$^1$H NMR ($CDCl_3$，400MHz) δ 1.31 (d，6H)，1.51 (d，3H)，3.34 (m，2H)，4.42 (m，2H)，4.68-4.82 (m，3H)，6.42 (d，1H)，7.11 (d，1H)，8.11 (s，1H)，8.23 (d，1H)，8.49 (d，1H)，9.12 (s，1H)；mp：181-182℃；MS (CI) 382 ($MH^+$)。

## 实施例 197 至 200

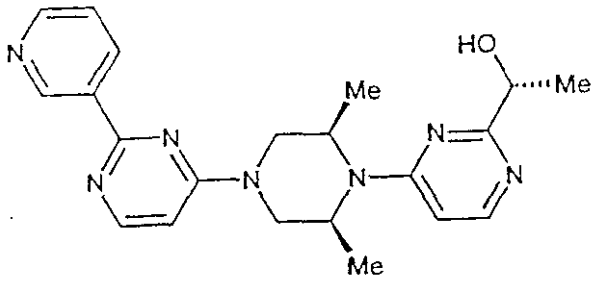
实施例 197 至 200 按照与实施例 196 类似的方法从适宜的原料制备。



| 实施例 | $R^{11}$ | $R^7$ | $R^6$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 197 | 咪唑-1-基 | 2R-Me | 6S-Me | 60-70 | 381 |
| 198 | 吗啉-4-基 | 2R-Me | 6S-Me | 70-80 | 400 |
| 199 | 吡咯烷-1-基 | 2R-Me | 6S-Me | 70-80 | 384 |
| 200 | 4-甲基哌嗪-1-基 | 3R-Me | 5S-Me | 168-170 | 413 |

实施例 201

1R-{4-[2R,6S-二甲基-4-(2-吡啶-3-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇



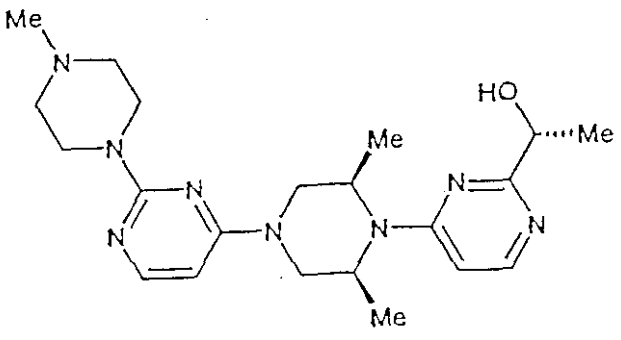
步骤 A: 2-吡啶-3-基-嘧啶-4-基三氟甲磺酸酯。向 2-吡啶-3-基-3H-嘧啶-4-酮(150mg, 0.87mmol; J. Med. Chem. 1990, 33, 1230)和三乙胺(0.13mL, 0.95mmol)的二氯甲烷(3mL)溶液中于 0℃及氮气氛下滴加三氟甲磺酸酐(0.22mL, 0.91mmol)的二氯甲烷(2mL)溶液。将混合物于 0℃搅拌 30 分钟，然后用二氯甲烷稀释并用水洗涤一次，然后将水层用二氯甲烷萃取两次。将有机萃取液合并，依次用饱和碳酸钠水溶液和饱和氯化钠水溶液洗涤，用硫酸钠干燥然后过滤。将滤液蒸发得到橙色油状实施例 201，步骤 A 的标题化合物，

0.22g (95%)，其不经纯化直接使用。

步骤 B：1R-{4-[2R,6S-二甲基-4-(2-吡啶-3-基-嘧啶-4-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇。将 2-吡啶-3-基-嘧啶-4-基三氟甲磺酸酯(按照实施例 201，步骤 A 的方法制备，0.15g，0.5mmol)的四氢呋喃(3mL)溶液于 0℃下滴加到丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4 的方法制备，0.15g，0.45mmol)的四氢呋喃(2mL)溶液中并于室温下搅拌 1 小时。将混合物加入饱和碳酸氢钠水溶液中并用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其溶于浓盐酸(3mL)然后室温搅拌 4 小时。将混合物加入饱和碳酸氢钠水溶液中然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到白色泡沫状标题化合物，0.091g (48%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 1.31 (d, 6H), 1.51 (d, 3H), 3.34 (m, 2H), 4.42-4.70 (m, 4H), 4.71 (q, 1H), 6.40 (d, 1H), 6.56 (d, 1H), 7.37 (m, 1H), 8.22 (d, 1H), 8.36 (d, 1H), 8.62-8.68 (m, 2H), 9.53 (m, 1H)；mp：61-70℃；MS (CI) 392 ($MH^+$)。

## 实施例 202

1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇



步骤 A：丁酸 1R-{4-[4-(2-甲磺酰基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向 4-(3R,5S-二甲基-哌嗪-1-基)-2-甲磺酰基-嘧啶(按照实施例 188，步骤 A 的方法制备，7.70g，14.3mmol)的乙腈(30mL)溶液中加入丁酸 1R-(4-三氟甲磺酰氧基-嘧啶-2-基)-乙酯(按照制备例 9 的方法制备，5.50g，16.1mmol)然后在氮气氛下加热回流 3 小时。将冷却的混合物过滤并将固体用乙酸乙酯洗涤两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(98：2 二氯甲烷：甲醇)得到油状实施例 202，步骤 A 的标题化合物，4.01g (62%)。$^1$H NMR ($CDCl_3$，400MHz) δ 0.93 (t，3H)，1.21 (d，6H)，1.55 (d，3H)，1.64 (q，2H)，2.36 (t，2H)，3.25 (s，3H)，3.37 (m，2H)，4.5-4.7 (m，4H)，5.65 (q，1H)，6.33 (d，1H)，6.68 (d，1H)，8.22 (d，1H)，8.28 (d，1H)；MS (CI) 463 ($MH^+$)。

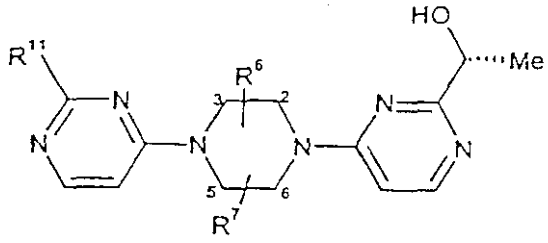
步骤 B：1R-{4-[4-(2-甲磺酰基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。将丁酸 1R-{4-[4-(2-甲磺酰基-嘧啶-4-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 202，步骤 A 的方法制备，0.42g，0.9mmol)与浓盐酸(3mL)混合然后室温搅拌 4 小时。将混合物加入饱和碳酸氢钠水溶液中然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(99：1 二氯甲烷：甲醇)得到白色泡沫状实施例 202，步骤 B 的标题化合物，0.25g (71%)。$^1$H NMR ($CDCl_3$，400MHz) δ 1.26 (d，6H)，1.50 (d，3H)，3.25 (s，3H)，3.41 (m，2H)，4.5-4.7 (m，5H)，6.37 (d，1H)，6.71 (d，1H)，8.24 (d，1H)，8.30 (d，1H)；MS (CI) 393 ($MH^+$)。

步骤 C：1R-(4-{2R,6S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇。将 1R-{4-[4-(2-甲磺酰基-嘧啶-4-基)-2,6-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇(按照实施例

202，步骤 B 的方法制备，0.25g，6.4mmol)与 N-甲基哌嗪(2.0mL)混合然后在氮气氛下于 80℃加热 1 小时。将混合物加入水中然后用乙酸乙酯萃取两次。将合并的萃取液用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其通过快速色谱纯化(96：4 氯仿：甲醇)得到白色泡沫状标题化合物，0.11g (41%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 1.31 (d, 6H), 1.51 (d, 3H), 2.47 (s, 3H), 2.63 (m, 4H), 3.23 (m, 2H), 3.94 (m, 4H), 4.33 (m, 2H), 4.57 (m, 2H), 4.71 (q, 1H), 5.96 (d, 1H), 6.46 (d, 1H), 7.98 (d, 1H), 8.23 (d, 1H)；mp：60-70℃；MS (CI) 413 ($MH^+$)。

实施例 203 至 207

实施例 203 至 207 按照与实施例 202 类似的方法从适宜的原料制备。

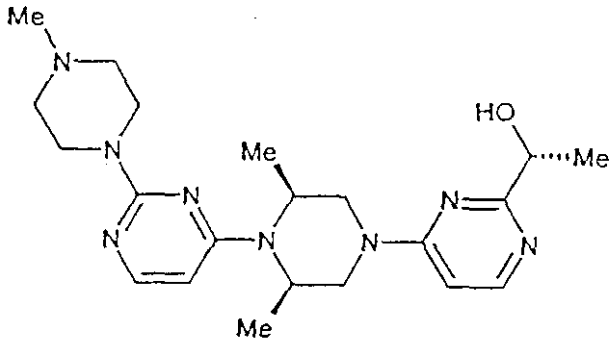



| 实施例 | $R^{11}$ | $R^7$ | $R^6$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 203 | 吗啉-4-基 | 2R-Me | 6S-Me | 70-80 | 400 |
| 204 | 吡咯烷-1-基 | 2R-Me | 6S-Me | 70-80 | 384 |
| 205 | 2,6-二甲基吗啉-4-基 | 2R-Me | 6S-Me | | 428 |
| 206 | 3,5-二甲基哌啶-1-基 | 2R-Me | 6S-Me | | 426 |
| 207 | 5-甲基-呋喃-2-基 | 2R-Me | 6S-Me | 123-128 | 395 |

实施例 208

1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌

嗪-1-基}-嘧啶-2-基)-乙醇



步骤 A：4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-2-甲磺酰基-嘧啶。向顺-1-苄基-3,5-二甲基哌嗪(24.9g，122mmol，Org. Prep. Proceed. Int. 1976，8，19)的二甲基乙酰胺(60mL)溶液中加入4-氯-2-甲磺酰基嘧啶(11.8g，61.3mmol)并于120℃搅拌16小时。将混合物在水和乙酸乙酯之间进行分配并将水层用乙酸乙酯萃取两次。将合并的有机层用1%硫酸铜水溶液洗涤3次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到橙色固体，将其在异丙基醚(100mL)中形成浆液然后过滤得到橙色固体状实施例208，步骤A的标题化合物，16.5g (75%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.35 (d，6H)，2.25 (m，2H)，2.76 (m，2H)，3.23 (s，3H)，3.53 (s，2H)，4.35-4.65 (m，2H)，6.51 (d，1H)，7.26 (m，2H)，7.34 (m，3H)，8.24 (d，1H)；MS (CI) 361 ($MH^+$)。

步骤 B：4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-2-(4-甲基哌嗪-1-基)-嘧啶。将4-(4-苄基-2R,6S-二甲基哌嗪-1-基)-2-甲磺酰基嘧啶(按照实施例208，步骤A的方法制备，11.5g，31.9mmol)与N-甲基哌嗪(15mL，128mmol)混合然后于120℃加热2小时。将混合物用乙酸乙酯稀释然后用水洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到橙色固体状实施例208，步骤B的标题化合物，14.7g (84%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.30 (d，6H)，2.21 (m，2H)，2.33 (s，3H)，2.46 (m，4H)，2.72 (d，2H)，3.53 (s，2H)，3.78 (m，4H)，4.31

(m, 2H), 5.79 (d, 1H), 7.24 (m, 2H), 7.31 (m, 3H), 7.90 (d, 1H); MS (CI) 381 ($MH^+$)。

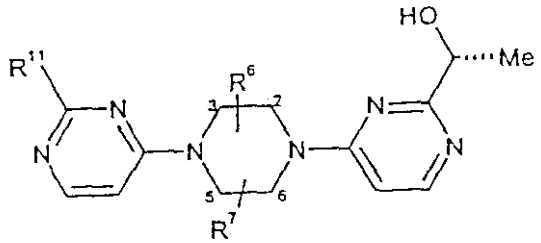
步骤 C: 4-(2R,6S-二甲基-哌嗪-1-基)-2-(4-甲基哌嗪-1-基)-嘧啶。向 4-(4-苄基-2R,6S-二甲基哌嗪-1-基)-2-(4-甲基-哌嗪-1-基)-嘧啶(按照实施例 208, 步骤 B 的方法制备, 9.8g, 25.8mmol)的甲醇(200mL)和盐酸(1N 的乙醚溶液, 38.7mL, 38.7mmol)溶液中加入甲酸铵(16.3g, 25.8mmol)。室温搅拌 5 分钟后, 加入 10%钯碳(1.96g, 20 wt%, 预先用异丙醇湿润)并将混合物加热回流 2 小时。将冷却的反应液过滤并将滤液浓缩得到固体, 将其用乙酸乙酯稀释并用水洗涤两次, 用饱和氯化钠水溶液洗涤一次, 将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到透明油状实施例 208, 步骤 C 的标题化合物, 6.01g (81%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 1.25 (s, 6H), 2.31 (s, 3H), 2.24-2.44 (m, 4H), 2.90 (m, 4H), 3.76 (m, 4H), 4.25 (m, 2H), 5.79 (d, 1H), 7.90 (d, 1H); MS (CI) 291 ($MH^+$)。

步骤 D: 丁酸 1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙酯。向 4-(2R,6S-二甲基-哌嗪-1-基)-2-(4-甲基-哌嗪-1-基)-嘧啶(按照实施例 208, 步骤 C 的方法制备, 9.0g, 31.1mmol)和三乙胺(6.5g, 46.5mmol)的二甲基甲酰胺(90mL)溶液中加入丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备, 7.78g, 34.1mmol)然后在氮气氛下加热回流 3 小时。将冷却的混合物过滤并将固体用乙酸乙酯洗涤两次。将合并的萃取液用水洗涤一次, 用饱和氯化钠水溶液洗涤一次, 将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油, 将其通过快速色谱纯化(95:5 氯仿: 甲醇)得到油状实施例 208, 步骤 D 的标题化合物, 11.4g (76%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 0.95 (t, 3H), 1.18 (d, 6H), 1.54 (d, 3H), 2.23-2.35 (m, 7H), 2.51 (m, 4H), 3.21 (m, 2H), 3.81 (m, 4H), 4.32 (m, 2H), 4.52 (m, 2H), 5.65 (q, 1H), 5.82 (d, 1H), 6.38 (d, 1H), 7.39 (d, 1H), 8.18 (d, 1H); MS (CI) 483 ($MH^+$)。

步骤 E：1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙醇。将丁酸 1R-(4-{3R,5S-二甲基-4-[2-(4-甲基-哌嗪-1-基)-嘧啶-4-基]-哌嗪-1-基}-嘧啶-2-基)-乙酯(按照实施例 208，步骤 D 的方法制备，11.3g，23.5mmol)与浓盐酸(60mL)混合然后室温搅拌 4 小时。将混合物加入饱和碳酸氢钠水溶液中然后用 10%异丙醇/氯仿萃取 5 次。将合并的萃取液用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液蒸发得到油，将其用异丙醇结晶得到白色固体状标题化合物，7.34g (76%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.21 (d，6H)，1.51 (d，3H)，2.34 (s，3H)，2.45 (m，4H)，3.24 (m，4H)，3.76 (m，2H)，4.30-4.53 (m，4H)，4.68 (q，1H)，5.82 (d，1H)，6.42 (d，1H)，7.94 (d，1H)，8.21 (d，1H)；mp. 181-182℃；MS (CI) 413 ($MH^+$)。

## 实施例 209 至 211

实施例 209 至 211 按照与实施例 208 类似的方法从适宜的原料制备。

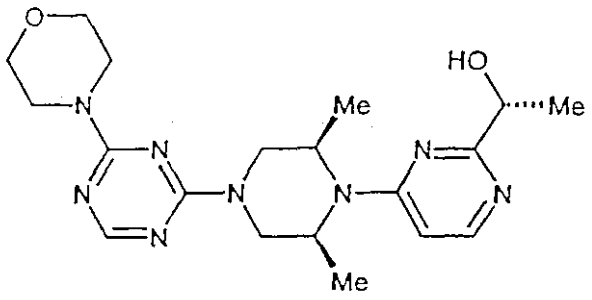



| 实施例 | $R^{11}$ | $R^7$ | $R^6$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 209 | 2,6-二甲基吗啉-4-基 | 3R-Me | 5S-Me | | 428 |
| 210 | 4-乙基哌嗪-1-基 | 3R-Me | 5S-Me | 144-146 | 427 |
| 211 | 4-异丙基哌嗪-1-基 | 3R-Me | 5S-Me | 137-139 | 441 |

## 实施例 212

1R-{4-[2R,6S-二甲基-4-(4-吗啉-4-基-[1,3,5]三嗪-2-基)-哌

嗪-1-基]-嘧啶-2-基}-乙醇



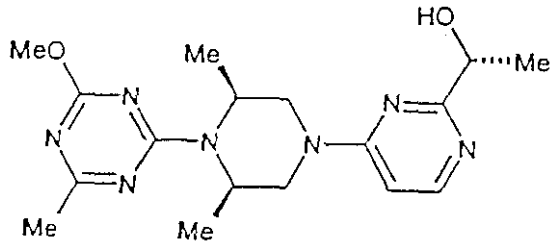
步骤 A：丁酸 1R-{4-[4-(4-氯-6-吗啉代-[1,3,5]三嗪-2-基)-2R,6S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4 的方法制备，0.31g，1.0mmol)和碳酸氢钠(0.17g，2.0mmol)的二甲基甲酰胺(3mL)溶液中加入 2,4-二氯-6-吗啉代-[1,3,5]三嗪(0.24g，1.0mmol；Chem. Pharm. Bull. 1997，45，291)然后室温搅拌 2 小时。将混合物用乙酸乙酯稀释并用水洗涤两次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到油，将其通过快速色谱纯化(99：1 氯仿：甲醇)得到白色固体状实施例 212，步骤 A 的标题化合物，0.19g (37%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.93 (t，3H)，1.23 (d，6H)，1.53 (d，3H)，1.66 (m，2H)，2.37 (t，2H)，3.16 (m，2H)，3.72-3.78 (m，10H)，4.12-4.78 (m，2H)，5.65 (q，1H)，6.34 (d，1H)，8.19 (m，2H)；MS (CI) 505，507 ($MH^+$)。

步骤 B：1R-{4-[2R,6S-二甲基-4-(4-吗啉-4-基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇。向丁酸 1R-{4-[4-(4-氯-6-吗啉代-[1,3,5]三嗪-2-基)-2R,6S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 212，步骤 A 的方法制备，0.15g，0.35mmol)的乙醇(10mL)溶液中加入 10%钯碳(0.75g，500wt%)然后用 Parr 装置在 45-50 psi 下氢化 12 小时。滤除催化剂并将滤液浓缩成油，将其加入浓盐酸(2mL)中然后室温搅拌 6 小时。将混合物用氯仿稀释然后用水洗涤两次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥

然后过滤。将滤液浓缩得到白色固体状标题化合物，0.47g (40%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.23 (d, 6H), 1.53 (d, 3H), 3.16 (m, 2H), 3.72-3.78 (m, 10H), 4.12-4.78 (m, 3H), 6.34 (d, 1H), 8.19 (m, 2H); mp: 78-82℃; MS (CI) 401 ($MH^+$); $[\alpha]_D$ +15.1 (c 1.0, MeOH)。

## 实施例 213

### 1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙醇

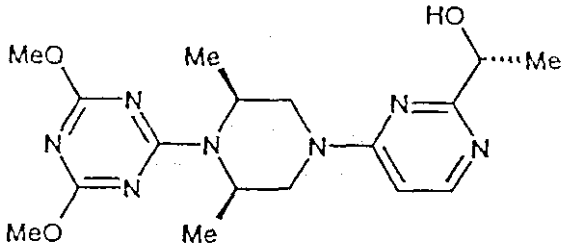



步骤 A: 丁酸 1R-{4-[4-(4-氯-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备，1.47g，6.43mmol)和碳酸氢钠(2.25g，26.8mmol)的二甲基甲酰胺(10mL)溶液中加入 2,4-二氯-6-甲基-[1,3,5]三嗪(0.88g，5.3mmol; Monatsh. Chem. 1970, 101, 724)然后室温搅拌 2 小时。将混合物用乙酸乙酯(150mL)稀释然后用水洗涤两次，用 10%硫酸铜水溶液洗涤一次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到黄褐色固体状实施例 213，步骤 A 的标题化合物，2.12g (91%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.93 (t, 3H), 1.23 (m, 6H), 1.54 (d, 2H), 1.66 (m, 2H), 2.31 (s, 3H), 2.37 (m, 2H), 2.41 (s, 1H), 3.19 (m, 2H), 4.22-4.55 (m, 2H), 4.91 (m, 2H), 5.65 (q, 1H), 6.40 (d, 1H), 8.20 (d, 1H); MS (CI) 434, 436 ($MH^+$)。

步骤 B：1R-{4-[4-(4-甲氧基-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙醇。通过将金属钠(0.4g, 17.3mmol)溶于甲醇(40mL)中制备新鲜的甲醇钠的甲醇溶液。向该混合物中加入丁酸 1R-{4-[4-(4-氯-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 213，步骤 A 的方法制备，1.5g，3.46mmol)并将其室温搅拌 16 小时。将反应混合物蒸发得到油，用氯仿稀释然后用水洗涤两次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到透明的油，将其用异丙基醚结晶得到白色固体状标题化合物，0.85g (72%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.23 (d, 6H), 1.48 (d, 3H), 2.36 (s, 3H), 3.20-3.26 (m, 2H), 3.90 (s, 3H), 4.18-4.43 (m, 2H), 4.63 (m, 2H), 4.68 (q, 1H), 4.85 (d, 1H), 6.42 (d, 1H), 8.18 (d, 1H)；mp：161-162℃；MS (CI) 360 ($MH^+$)；$[\alpha]_D$ +16.8 (c 1.0, MeOH)。

## 实施例 214

1R-{4-[4-(4,6-二甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



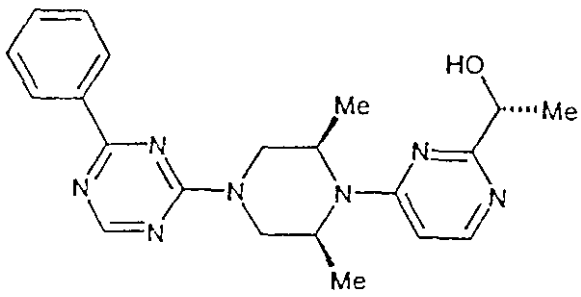

步骤 A：丁酸 1R-{4-[4-(4,6-二氯-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备，3.25g, 10.5mmol)和碳酸氢钠(1.01g，19.2mmol)的二甲基甲酰胺(8mL)溶液中加入氰尿酰氯(1.76g，9.6mmol)然后室温搅拌 2 小时。将混合

物用乙酸乙酯稀释然后用水洗涤两次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到白色半固体状实施例 214，步骤 A 的标题化合物，1.42g (68%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.93 (t, 3H), 1.23 (m, 6H), 1.54 (d, 3H), 1.66 (m, 2H), 2.37 (m, 2H), 3.19 (m, 2H), 4.42-4.55 (m, 2H), 4.91 (m, 2H), 5.65 (q, 1H), 6.40 (d, 1H), 8.20 (d, 1H); MS (CI) 446, 448 ($MH^+$)。

步骤 B: 1R-{4-[4-[4-(4,6-二甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。通过将金属钠(0.18g, 8.0mmol)溶于甲醇(16mL)中制备新鲜的甲醇钠的甲醇溶液。向该混合物中于 0℃下加入丁酸 1R-{4-[4-(4,6-二氯-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 214，步骤 A 的方法制备，0.91g, 2.0mmol)，然后升温至室温 1 小时。将混合物蒸发得到油，用氯仿稀释然后用水洗涤一次，用饱和氯化钠水溶液洗涤一次，用硫酸钠干燥然后过滤。将滤液浓缩得到透明的油，将其用异丙基醚结晶得到白色固体状标题化合物，0.54g (72%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.23 (d, 6H), 1.50 (d, 3H), 3.20 (m, 2H), 3.95 (s, 6H), 4.32 (m, 1H), 4.67-4.86 (m, 4H), 6.34 (d, 1H), 8.22 (d, 1H); mp: 187-188℃; MS (CI) 376 ($MH^+$)。

## 实施例 215

1R-{2R,6S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙醇



步骤 A: 丁酸 1R-{4-[4-(4-氯-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4 的方法制备, 2.35g, 7.67mmol)和碳酸氢钠(1.29g, 15.3mmol)的二甲基甲酰胺(25mL)溶液中于 0℃下分批加入 2,4-二氯-6-苯基[1,3,5]三嗪(1.73g, 7.67mmol; HeLv. Chim. Acta 1950, 33, 1365)。将反应混合物升温至室温然后在氮气氛下搅拌 4 小时, 倒入水中然后过滤得到浅黄褐色固体状实施例 215, 步骤 A 的标题化合物, 1.99g (51%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 0.94 (t, 3H), 1.25 (d, 6H), 1.57 (d, 3H), 1.68 (m, 2H), 2.40 (t, 2H), 3.27 (d, 2H), 4.65 (m, 2H), 4.82 (d, 1H), 5.00 (d, 1H), 5.68 (q, 1H), 6.34 (d, 1H), 7.46 (m, 3H), 8.21 (d, 1H), 8.40 (d, 2H); MS (CI) 496, 498 ($MH^+$)。

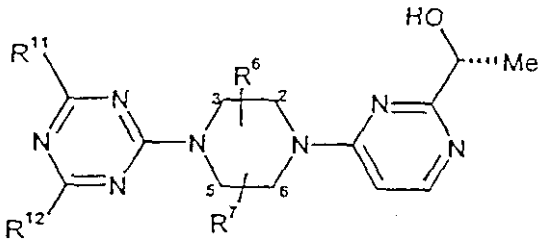
步骤 B: 丁酸 1R-{4-[4-(6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-{4-[4-(4-氯-6-苯基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 215, 步骤 A 的方法制备, 4.81g, 9.7mmol)的甲醇(50mL)溶液中加入 10%钯碳(940mg, 20wt%)、甲酸铵(5.98g, 97mmol)和盐酸(2M 的乙醚溶液, 7.1mL, 14.2mmol)然后然后回流 1.5 小时。将混合物冷却然后过滤。将滤液浓缩然后在氯仿和饱和碳酸氢钠水溶液之间进行分配。将有机层分离, 用硫酸钠干燥, 过滤然后将滤液蒸发得到油, 将其通过快速色谱纯化(99: 1 氯仿: 甲醇)得到透明油状实施例 215, 步骤 B 的标题化合物, 2.69g (59%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 0.95 (t, 3H), 1.25 (d, 6H), 1.57 (d, 3H), 1.68 (m, 2H), 2.40 (t, 2H), 3.27 (d, 2H), 4.65 (m, 2H), 4.82 (d, 1H), 5.00 (d, 1H), 5.68 (q, 1H), 6.34 (d, 1H), 7.46 (m, 3H), 8.21 (d, 1H), 8.40 (d, 2H), 8.66 (s, 1H); MS (CI) 462 ($MH^+$)。

步骤 C: 1R-{2R,6S-二甲基-4-(4-苯基-[1,3,5]三嗪-2-基)-哌嗪-

1-基]-嘧啶-2-基}-乙醇。将浓盐酸(10mL)加入到丁酸 1R-{4-[4-(6-苯基[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 215, 步骤 B 的方法制备, 2.69g, 5.8mmol)中然后室温搅拌 5 小时。将反应混合物冷却至 0℃, 用氯仿稀释, 然后缓慢加入 6M 氢氧化钠水溶液直至呈碱性(pH 9)。分液并将水层用氯仿萃取两次。将合并的有机萃取液用饱和氯化钠水溶液洗涤一次, 用硫酸钠干燥, 过滤然后将滤液浓缩得到油, 将其通过快速色谱纯化(97: 3 氯仿: 甲醇)得到白色泡沫, 将其用异丙基醚结晶得到白色固体状标题化合物, 1.55g (68%)。$^1$H NMR ($CDCl_3$, 400MHz) δ 1.28 (d, 6H), 1.54 (d, 3H), 3.31 (d, 2H), 4.63 (m, 2H), 4.77 (q, 1H), 4.85 (d, 1H), 5.50 (d, 1H), 6.42 (d, 1H), 7.50 (m, 3H), 8.25 (d, 1H), 8.41 (d, 2H), 8.68 (s, 1H); mp: 133-134℃; MS (CI) 392 ($MH^+$); $[\alpha]_D$ +18.7 (c 1.07, MeOH)。

## 实施例 216 至 235

实施例 216 至 235 按照与实施例 215 类似的方法从适宜的原料制备。

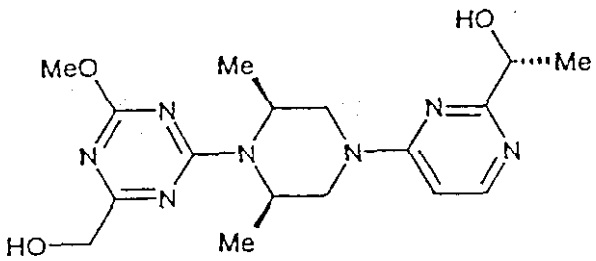



| 实施例 | $R^{11}$ | $R^{12}$ | $R^6$ | $R^7$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|---|
| 216 | Cl | 吗啉 4-基 | 2R-Me | 6S-Me | 138-141 | 435, 437 |
| 217 | H | 吗啉-4-基 | 3R-Me | 5S-Me | 152 | 401 |
| 218 | OMe | 吗啉-4-基 | 2R-Me | 6S-Me | 176-178 | 431 |
| 219 | Me | 4-甲基-哌嗪-1-基 | 3R-Me | 5S-Me | | 428 |
| 220 | Me | H | 2R-Me | 6S-Me | 91-94 | 330 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 221 | OMe | OMe | 2R-Me | 6S-Me | 128-129 | 376 |
| 222 | OEt | Me | 3R-Me | 5S-Me | 141-142 | 374 |
| 223 | OiPr | Me | 3R-Me | 5S-Me | 87-91 | 388 |
| 224 | 苯基 | H | 3R-Me | 5S-Me | 154-155 | 392 |
| 225 | 苯基 | OMe | 3R-Me | 5S-Me | | 422 |
| 226 | 苯基 | OMe | 2R-Me | 6S-Me | 135-138 | 422 |
| 227 | iPr | H | 2R-Me | 6S-Me | 122-124 | 358 |
| 228 | iPr | OMe | 3R-Me | 5S-Me | 75-80 | 388 |
| 229 | 苯基 | H | H | H | 115-117 | 364 |
| 230 | OMe | Me | H | H | 173-175 | 332 |
| 231 | 邻-甲苯基 | H | 3R-Me | 5S-Me | 123-125 | 406 |
| 232 | 邻-甲苯基 | OMe | 3R-Me | 5S-Me | 143-145 | 436 |
| 233 | 环丙基 | H | 3R-Me | 5S-Me | 134-135 | 356 |
| 234 | 环丙基 | H | 2R-Me | 6S-Me | 133-134 | 356 |
| 235 | OMe | $CH_2OMe$ | 3R-Me | 5S-Me | 104-105 | 390 |

## 实施例 236

1R-{4-[4-(4-羟甲基-6-甲氧基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



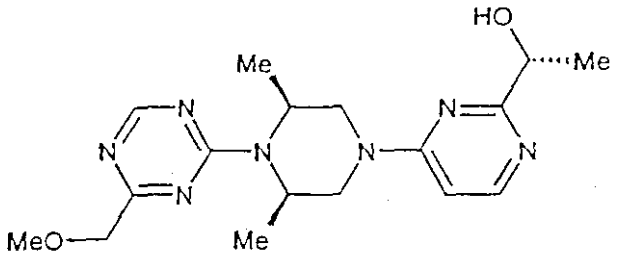

步骤 A: 丁酸 1R-{4-[4-(4-氯-6-重氮甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备, 3.06g, 10.0mmol)和碳酸氢钠(1.68g, 20.0mmol)的二甲基

甲酰胺(10mL)溶液中加入 2,4-二氯-6-重氮甲基-[1,3,5]三嗪(1.90g, 10.0mmol; J. Am. Chem. Soc. 1957, 79, 944)然后室温搅拌 2 小时。将混合物用乙酸乙酯稀释，用水洗涤两次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液浓缩然后通过快速色谱纯化(乙酸乙酯)得到泡沫状实施例 236，步骤 A 的标题化合物，1.84g (41%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 0.94 (t, 3H), 1.23 (m, 6H), 1.55 (d, 3H), 1.66 (m, 2H), 2.38 (m, 2H), 3.19 (m, 2H), 4.22-4.45 (m, 2H), 4.86 (m, 2H), 5.10 (s, 1H), 5.65 (q, 1H), 6.40 (d, 1H), 8.20 (d, 1H); mp: 106-108℃; MS (CI) 461, 463 ($MH^+$)。

步骤 B: 1R-{4-[4-(4-羟甲基-6-甲氧基-[1,3.5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。将丁酸 1R-{4-[4-(4-氯-6-重氮甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 236，步骤 A 的方法制备，1.5g, 3.2mmol)溶于乙酸乙酯(20mL)然后在室温下缓慢加入 10%硫酸水溶液(5mL)，搅拌 5 分钟然后用 6N 氢氧化钠水溶液碱化至 pH 9。将分离的乙酸乙酯层用盐水洗涤一次，用硫酸镁干燥然后浓缩得到半固体。向通过将金属钠(0.92g, 4.0mmol)溶于甲醇(6mL)制得的新鲜的甲醇钠溶液中加入粗品固体(0.89g, 2.0mmol)。将该混合物室温搅拌 4 小时然后蒸发至干。将残余物通过快速色谱纯化(95: 5 二氯甲烷: 甲醇)得到白色固体状标题化合物，0.084g (13%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.23 (d, 6H), 1.49 (d, 3H), 3.14-3.21 (m, 2H), 3.96 (m, 2H), 3.90 (s, 3H), 4.18-4.38 (m, 2H), 4.69 (q, 1H), 4.97 (m, 2H), 6.44 (d, 1H), 8.20 (d, 1H); mp: 170-171℃; MS (CI) 376 ($MH^+$); $[\alpha]_D$ +16.6 (c 1.0, MeOH)。

## 实施例 237

1R-{4-[4-(4-甲氧基甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇



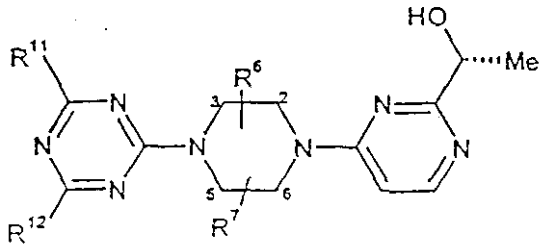
步骤 A：丁酸 1R-{4-[4-(4-氯-6-甲氧基甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。将丁酸 1R-{4-[4-(4-氯-6-重氮甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 236，步骤 A 的方法制备，1.5g，3.2mmol)溶于甲醇(10mL)然后加入 10%硫酸水溶液(3mL)。将混合物室温搅拌 1 小时然后用乙酸乙酯稀释。将分出的乙酸乙酯层用饱和氯化钠水溶液洗涤一次，用硫酸镁干燥然后浓缩成油，将其通过快速色谱纯化(99：1 二氯甲烷：甲醇)得到油状实施例 237，步骤 A 的标题化合物，1.02 (60%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.95 (t，3H)，1.26 (d，6H)，1.58 (d，3H)，1.67 (q，2H)，2.41 (t，2H)，3.24 (m，2H)，3.51 (s，3H)，4.18-4.38 (m，4H)，4.69 (q，1H)，4.92 (m，2H)，6.47 (d，1H)，8.24 (d，1H)；MS (CI) 464，466 ($MH^+$)。

步骤 B：1R-{4-[4-(4-甲氧基甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。向丁酸 1R-{4-[4-(4-氯-6-甲氧基甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 237，步骤 A 的方法制备，0.43g，0.92mmol)的甲醇(8mL)和盐酸(2M 的乙醚溶液，0.7mL，1.37mmol)溶液中加入甲酸铵(0.58g，9.2mmol)和 10%钯碳(0.085g，20wt%)然后加热回流 3 小时。蒸除溶剂，加入浓盐酸(2mL)然后室温搅拌 16 小时，用 6N 氢氧化钠水溶液碱化至 pH 9 然后用乙酸乙酯稀释。将分出的乙酸乙酯层用饱和氯化钠水溶液洗涤一次，用硫酸镁干燥然后浓缩成油，将其通过快速色谱纯化(9：1 二氯甲烷：甲醇)得到白色固体状标题化

合物，0.12g (36%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.25 (d, 6H), 1.49 (d, 3H), 3.24 (m, 2H), 3.51 (s, 3H), 4.18-4.38 (m, 4H), 4.72 (q, 1H), 4.97 (m, 2H), 6.47 (d, 1H), 8.22 (d, 1H), 8.57 (s, 1H)；MS (CI) 360 ($MH^+$)。

## 实施例 238 至 240

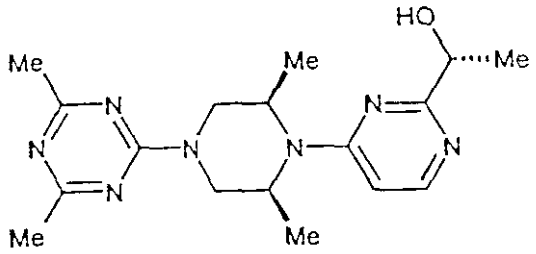
实施例 238 至 240 按照与实施例 237 类似的方法从适宜的原料制备。




| 实施例 | $R^{11}$ | $R^{12}$ | $R^7$ | $R^6$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|---|
| 238 | $CH_2OH$ | H | 3R-Me | 5S-Me | 173-175 | 346 |
| 239 | OMe | $CH_2OMe$ | 3R-Me | 5S-Me | 143-145 | 390 |
| 240 | $CH_2OH$ | 苯基 | 2R-Me | 6S-Me | 173-175 | 422 |

## 实施例 241

1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙醇



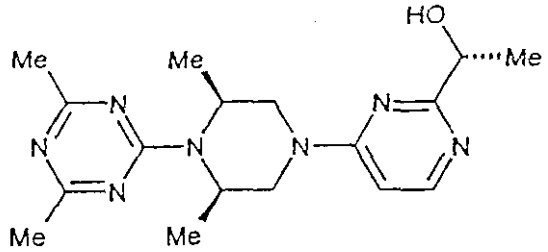

步骤 A：丁酸 1R-{4-[4-(4-甲基-6-三氯甲基-[1,3,5]三嗪-2-基)-

2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯二苯甲酰基-L-酒石酸盐(按照制备例 15 的方法制备，1.33g，2.0mmol)和碳酸氢钠(0.34g，4.0mmol)的二甲基甲酰胺(5mL)溶液中加入 2-甲基-4,6-二-三氯甲基-[1,3,5]三嗪(1.00g，3.0mmol；Bull. Chem. Soc., Jpn. 1969，42，2924)然后室温搅拌 14 小时。将混合物用乙酸乙酯稀释然后用水洗涤两次，将有机层用硫酸镁干燥然后浓缩。将粗品油通过快速色谱纯化(95：5 二氯甲烷：甲醇)得到泡沫状实施例 241，步骤 A 的标题化合物，0.71g (69%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.95 (t，3H)，1.22 (m，6H)，1.56 (d，3H)，1.66 (m，2H)，2.37 (m，2H)，2.55 (s，1H)，3.27 (m，2H)，4.48-4.78 (m，2H)，4.84 (m，2H)，5.67 (q，1H)，6.32 (d，1H)，8.22 (d，1H)；MS (CI) 517，519 ($MH^+$)。

步骤 B：1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙醇。将丁酸 1R-{4-[4-(4-甲基-6-三氯甲基-[1,3,5]三嗪-2-基)-2R,6S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 241，步骤 A 的方法制备，0.65g，1.2mmol)和 10%钯碳(0.2g)在三乙胺(1mL)和甲醇(20mL)中的悬浮液用 Parr 装置于 40 psi 氢化 0.5 小时。滤除催化剂并将滤液浓缩得到固体，将其溶于浓盐酸(2mL)然后搅拌 6 小时。将该混合物用水稀释，用 6N 氢氧化钠水溶液碱化至 pH 9 然后用二氯甲烷萃取。将萃取液用水洗涤两次，用饱和氯化钠水溶液洗涤一次，将有机层用硫酸钠干燥然后过滤。将滤液浓缩得到透明的油，将其用异丙基醚结晶得到白色固体状标题化合物，0.25g (58%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.21 (d，6H)，1.49 (d，3H)，2.40 (s，6H)，3.16 (m，2H)，4.45-4.68 (m，2H)，4.71 (q，1H)，4.84 (m，2H)，6.42 (d，1H)，8.20 (d，1H)；mp：172-173 ℃；MS (CI) 344 ($MH^+$)；$[\alpha]_D$ +17.2 (c 1.0，MeOH)。

实施例 242

1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇




步骤 A: 4-甲基-6-三氯甲基-[1,3,5]三嗪-2-基甲磺酸酯。向 2-羟基-4-甲基-6-三氯甲基-[1,3,5]三嗪(1.14g, 5.0mmol; J. Amer. Chem. Soc. 1956, 78, 2447)和三乙胺(0.51g, 5.5mmol)的二氯甲烷溶液中于 0℃下加入甲磺酰氯(0.57g, 5.0mmol), 搅拌 1 小时然后加入饱和碳酸氢钠水溶液中。将分出的有机层用饱和氯化钠水溶液洗涤一次, 用硫酸镁干燥然后过滤。将滤液蒸发得到橙色油状实施例 242, 步骤 A 的标题化合物, 0.98g (65%), 其不经纯化直接使用。MS (CI) 291, 293 ($MH^+$)。

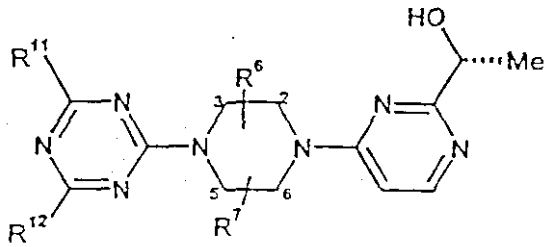
步骤 B: 丁酸 1R-{4-[3R,5S-二甲基-4-(4-甲基-6-三氯甲基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙酯。向丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 3 的方法制备, 0.62g, 2.0mmol)和碳酸氢钠(0.34g, 4.0mmol)的二甲基甲酰胺(5mL)溶液中加入 4-甲基-6-三氯甲基-[1,3,5]三嗪-2-基甲磺酸酯(按照实施例 242, 步骤 A 的方法制备, 1.00g, 3.0mmol)然后室温搅拌 14 小时。将混合物用乙酸乙酯稀释然后用水洗涤两次, 将有机层用硫酸镁干燥然后浓缩。将粗品油通过快速色谱纯化(乙酸乙酯)得到透明油状实施例 242, 步骤 B 的标题化合物, 0.41mg (96%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 0.95 (t, 3H), 1.22 (m, 6H), 1.56 (d, 3H), 1.66 (m, 2H), 2.37 (m, 2H), 2.55 (s, 3H), 3.27 (m, 2H), 4.48-4.78 (m, 2H), 4.84 (m, 2H), 5.67 (q, 1H),

6.32 (d, 1H), 8.22 (d, 1H); MS (CI) 517, 519 ($MH^+$)。

步骤 C: 1R-{4-[4-(4,6-二甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基-哌嗪-1-基]-嘧啶-2-基}-乙醇。将丁酸 1R-{4-[3R,5S-二甲基-4-(4-甲基-6-三氯甲基-[1,3,5]三嗪-2-基)-哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 242, 步骤 B 的方法制备, 0.65g, 1.2.mmol)和 10%钯碳(0.2g, 30wt%)在三乙胺(1mL)和甲醇(20mL)中的悬浮液用 Parr 装置在 40 psi 下氢化 0.5 小时。滤除催化剂并将滤液浓缩得到固体, 将其溶于浓盐酸(3mL)并搅拌 6 小时。将该混合物用水稀释, 用 6N 氢氧化钠水溶液碱化至 pH 9 然后用二氯甲烷萃取。将萃取液用水洗涤两次, 用饱和氯化钠水溶液洗涤一次, 将有机层用硫酸钠干燥然后浓缩得到透明的油, 将其用异丙基醚结晶得到白色固体状标题化合物, 0.25g (23%)。$^1H$ NMR ($CDCl_3$, 300MHz) δ 1.21 (d, 6H), 1.49 (d, 3H), 2.40 (s, 6H), 3.16 (m, 2H), 4.45-4.68 (m, 2H), 4.71 (q, 1H), 6.42 (d, 1H), 8.20 (d, 1H); MS (CI) 344 ($MH^+$); mp: 157-159℃; $[\alpha]_D$ +17.2 (c 1.0, MeOH)。

## 实施例 243 至 246

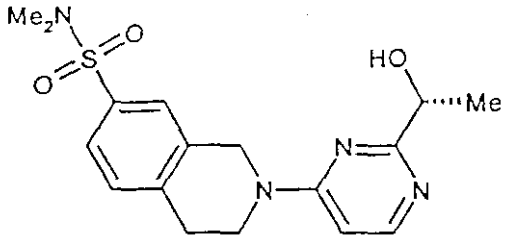
实施例 243 至 246 按照与实施例 242 类似的方法从适宜的原料制备。




| 实施例 | $R^{11}$ | $R^{12}$ | $R^7$ | $R^6$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|---|
| 243 | Me | 苯基 | 2R-Me | 6S-Me | | 406 |
| 244 | Me | 苯基 | 3R-Me | 5S-Me | 132-134 | 406 |
| 245 | Me | 四氢呋喃-2-基 | 2R-Me | 6S-Me | | 428 |
| 246 | Me | 邻-甲苯基 | 2R-Me | 6S-Me | 148-150 | 436 |

实施例 247

(R)-2-[2-(1-羟基-乙基)-嘧啶-4-基]-1,2,3,4-四氢-异喹啉-7-磺酸二甲基酰胺



步骤 A：2-三氟乙酰基-1,2,3,4-四氢-异喹啉-7-磺酸二甲基酰胺。将 2-三氟乙酰基-1,2,3,4-四氢-异喹啉-7-磺酰氯(400mg, 1.22mmol, J. Med. Chem. 1980, 23, 837)、二甲基胺盐酸盐(150mg, 1.83mmol)和三乙胺(0.50mL, 3.66mmol)在二氧六环(10mL)中的混合物回流搅拌 30 分钟，冷却至室温，浓缩然后通过快速柱色谱纯化(10→50%乙酸乙酯/己烷)得到 337mg (82%)黄色油状实施例 247，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$, 300MHz, 9：5 旋转异构体的混合物) δ 7.67-7.52 (c, 2H), 7.36 (t, 1H), 4.87 (s, 1.3H), 4.81 (s, 0.7H), 3.96-3.86 (c, 2H), 3.08-3.02 (c, 2H), 2.72 (s, 6H)；MS (TS) 337 ($MH^+$)。

步骤 B：1,2,3,4-四氢-异喹啉-7-磺酸二甲基酰胺。将 2-三氟乙酰基-1,2,3,4-四氢-异喹啉-7-磺酸二甲基酰胺(按照实施例 247，步骤 A 的方法制备，337mg, 1.0mmol)和碳酸钾(207mg, 1.5mmol)在 3：1 甲醇/水混合物(10mL)中的混合物室温搅拌 1 小时然后浓缩。将剩余的含水残余物用 10%异丙醇/氯仿萃取(7)并将合并的有机萃取液用硫酸钠干燥，过滤然后蒸发得到 214mg (89%)白色固体状实施例 247，步骤 B 的标题化合物。$^1$H NMR ($CD_3OD$, 300MHz) δ 7.52 (d, 1H), 7.48 (s, 1H), 7.36 (d, 1H), 4.90 (s, 2H), 3.11 (t, 2H), 2.91 (t, 2H), 2.65 (s, 6H)；MS (CI/$NH_3$) 241 ($MH^+$)。

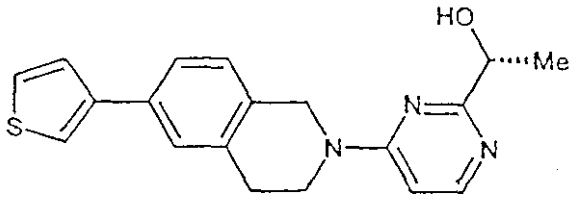
步骤 C：乙酸(R)-1-[4-(7-二甲基氨磺酰基-3,4-二氢-1H-异喹啉-

2-基)-嘧啶-2-基]-乙酯。向 1,2,3,4-四氢-异喹啉-7-磺酸二甲基酰胺(按照实施例 247，步骤 B 的方法制备，210mg，0.88mmol)的异丙醇(5mL)溶液中依次加入乙酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 5 的方法制备，175mg，0.88mmol)和三乙胺(0.24mL，1.75mmol)。将该混合物室温搅拌 1.75 小时然后加热回流 1.5 小时，冷却至室温，蒸发然后通过快速柱色谱纯化(1%甲醇/氯仿)得到 327mg (92%)白色固体状实施例 247，步骤 C 的标题化合物。$^1$H NMR ($CDCl_3$，250MHz) δ 8.28 (d，1H)，7.68-7.58 (c，2H)，7.47 (d，1H)，6.44 (d，1H)，5.72 (q，1H)，4.86 (s，2H)，3.92 (t，2H)，3.05 (t，2H)，2.73 (s，6H)，2.19 (s，3H)，1.62 (d，3H)；MS (TS) 431 ($MH^+$)。

步骤 D：(R)-2-[2-(1-羟基-乙基)-嘧啶-4-基]-1,2,3,4-四氢-异喹啉-7-磺酸二甲基酰胺。向乙酸(R)-1-[4-(7-二甲基氨磺酰基-3,4-二氢-1H-异喹啉-2-基)-嘧啶-2-基]-乙酯(按照实施例 247，步骤 C 的方法制备，326mg，0.81mmol)在 4：1 甲醇/水混合物(8mL)中的溶液中加入水合氢氧化锂(170mg，4.0mmol)。将该混合物室温搅拌 50 分钟，浓缩，重新悬浮在水中然后用 10%异丙醇/氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发，然后通过快速柱色谱纯化(1%甲醇/氯仿)得到白色泡沫，将其用乙醚/甲醇重结晶进行进一步纯化得到 90mg (31%)白色固体状标题化合物。mp：120.5-122℃；$^1$H NMR ($CDCl_3$，300MHz) δ 8.24 (d，1H)，7.62-7.59 (c，2H)，7.35 (d，1H)，6.44 (d，1H)，4.83 (s，2H)，4.73 (q，1H)，4.34 (br s，1H)，3.93-3.85 (c，2H)，3.03 (t，2H)，2.71 (s，6H)，1.52 (d，3H)；MS (TS) 363 ($MH^+$)。

## 实施例 248

1-[4-(6-噻吩-3-基-3,4-二氢-1H-异喹啉-2-基)-嘧啶-2-基]-乙醇




步骤 A：6-噻吩-3-基-3,4-二氢-1H-异喹啉-2-甲酸叔丁酯。将二(苄腈)氯化钯(II) (30mg, 0.079mmol)和 1,4-二(二苯基膦基)丁烷(33.6mg, 0.079mmol)在甲苯(3mL)中的混合物室温搅拌 20 分钟。向该混合物中加入 6-三氟甲磺酰氧基-3,4-二氢-1H-异喹啉-2-甲酸叔丁酯(300mg, 0.79mmol, Synth. Commun. 1995, 25, 3255)、噻吩-3-硼酸(131mg, 1.02mmol)、1M 碳酸钠水溶液(1.57mL, 1.57mmol)和乙醇(2mL)。将该深色的混合物在氮气氛下搅拌加热回流过夜，冷却至室温，用饱和碳酸氢钠水溶液稀释然后用乙酸乙酯萃取(4 次)。将合并的有机萃取液用硫酸钠干燥，用硅藻土过滤，蒸发然后通过快速柱色谱纯化(己烷→5%乙酸乙酯/己烷)得到 252mg (100%)浅黄色蜡状固体状实施例 248，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$, 250MHz) δ 7.47-7.38 (c, 5H), 7.14 (d, 1H), 4.60 (s, 2H), 3.72-3.64 (c, 2H), 2.95-2.82 (c, 2H), 1.52 (s, 9H); MS (TS) 316 ($MH^+$)。

步骤 B：6-噻吩-3-基-3,4-二氢-1H-异喹啉盐酸盐。将 6-噻吩-3-基-3,4-二氢-1H-异喹啉-2-甲酸叔丁酯(按照实施例 248，步骤 A 的方法制备，250mg, 0.79mmol)和盐酸(4M 的二氧六环溶液，6mL, 23.8mmol)的混合物室温搅拌 1 小时然后浓缩得到 170mg (86%)黄色固体状实施例 248，步骤 B 的标题化合物，其不经纯化直接用于随后的步骤。$^1$H NMR ($CD_3OD$, 250MHz) δ 7.66 (m, 1H), 7.61-7.53 (c, 2H), 7.51-7.42 (c, 2H), 7.23 (d, 2H), 4.38 (s, 2H), 3.52 (t, 2H), 3.16 (t, 2H); MS (TS) 216 ($MH^+$)。

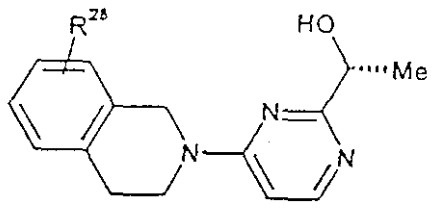
步骤 C：乙酸(R)-1-[4-(6-噻吩-3-基-3,4-二氢-1H-异喹啉-2-

基)-嘧啶-2-基]-乙酯。向 6-噻吩-3-基-3,4-二氢-1H-异喹啉盐酸盐(按照实施例 248, 步骤 B 的方法制备, 170mg, 0.68mmol)的异丙醇(6mL)溶液中依次加入乙酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 5 的方法制备, 136mg, 0.68mmol)和三乙胺(0.28mL, 2.04mmol)。将该混合物回流搅拌 7 小时, 冷却至室温过夜, 蒸发然后通过快速柱色谱纯化(0.5→1%甲醇/氯仿)得到 253mg (98%)黄色固体状实施例 248, 步骤 C 的标题化合物。$^1$H NMR ($CDCl_3$, 250MHz) δ 8.26 (d, 1H), 7.52-7.36 (c, 6H), 6.43 (d, 1H), 5.73 (q, 1H), 4.76 (s, 2H), 3.96-3.82 (c, 2H), 3.02 (t, 2H), 2.21 (s, 3H), 1.63 (d, 3H); MS (TS) 380 ($MH^+$)。

步骤 D: 1-[4-(6-噻吩-3-基-3,4-二氢-1H-异喹啉-2-基)-嘧啶-2-基]-乙醇。向乙酸(R)-1-[4-(6-噻吩-3-基-3,4-二氢-1H-异喹啉-2-基)-嘧啶-2-基]-乙酯(按照实施例 248, 步骤 C 的方法制备, 253mg, 0.67mmol)在 3: 1: 1 甲醇/四氢呋喃/水的混合物(5mL)中的溶液中加入水合氢氧化锂(84mg, 2.0mmol)。将该混合物室温搅拌 1 小时, 浓缩, 重新悬浮在水中然后用氯仿萃取(4 次)。将合并的有机萃取液用硫酸钠干燥, 过滤, 蒸发, 然后通过快速柱色谱纯化(2%甲醇/氯仿)得到黄色固体, 将其用乙醚/甲醇重结晶进行进一步纯化得到 163mg (72%)白色固体状标题化合物。mp: 125.5-127.5℃; $^1$H NMR ($CDCl_3$, 300MHz) δ 8.22 (d, 1H), 7.47-7.35 (c, 5H), 7.22 (d, 1H), 6.42 (d, 1H), 4.78-4.72 (c, 2H), 4.46 (br s, 1H), 3.93-3.84 (c, 2H), 2.99 (t, 2H), 1.54 (d, 3H); MS (APCI) 338 ($MH^+$)。

## 实施例 249 至 252

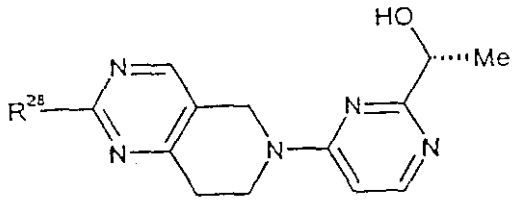
实施例 249 至 252 按照与实施例 248 类似的方法从适宜的原料制备。



| 实施例 | $R^{28}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|
| 249 | 6-噻吩-2-基 | 104-105 | 338 |
| 250 | 6-嘧啶-5-基 | | 334 |
| 251 | 7-嘧啶-5-基 | 135-137 | 334 |
| 252 | 6-羟基 | | 272 |

实施例 253 至 258

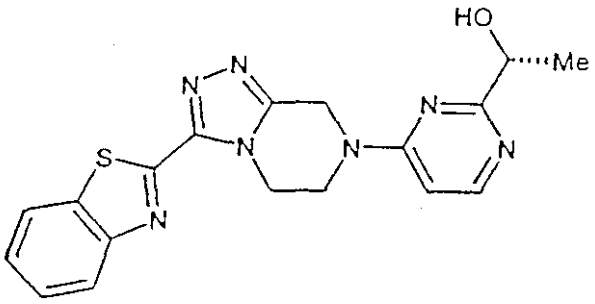
实施例 253 至 258 按照与实施例 86 类似的方法从适宜的原料制备。



| 实施例 | $R^{28}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|
| 253 | H | 79-82 | 258 |
| 254 | Me | | 272 |
| 255 | $CF_3$ | 130-132 | 326 |
| 256 | $NH_2$ | 208-210 | 273 |
| 257 | Ph | 128-131 | 334 |
| 258 | 吡啶-4-基 | 144-148 | 335 |

实施例 259

(R)-1-[4-(3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡嗪-7-基)-嘧啶-2-基]-乙醇




步骤 A: 5-乙氧基-3,6-二氢-2H-吡嗪-1-甲酸苄酯。向 3-氧代-哌嗪-1-甲酸苄酯(2.0g, 8.54mmol, Maybridge)的二氯甲烷(18mL)溶液中于室温下加入三乙基氧鎓四氟硼酸盐(4.1g, 21.3mmol)。将该混合物搅拌 3 天,然后依次加入冰屑和饱和碳酸氢钠水溶液直至达到中性 pH 值终止反应。分出有机层并将水层用氯仿萃取(3 次)。将合并的有机萃取液用盐水洗涤(1 次),用硫酸钠干燥然后浓缩得到 2.11g (95%)浅黄色油状实施例 259, 步骤 A 的标题化合物,其具有足够的纯度用于下一步骤。$^1$H NMR ($CDCl_3$, 300MHz) δ 7.43-6.97 (c, 5H), 5.17 (s, 2H), 4.10 (q, 2H), 3.98 (s, 2H), 3.60-3.40 (c, 4H), 1.27 (t, 3H); MS (APCI) 263 ($MH^+$)。

步骤 B: 3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡嗪-7-甲酸苄酯。将 5-乙氧基-3,6-二氢-2H-吡嗪-1-甲酸苄酯(按照实施例 259, 步骤 A 的方法制备, 490mg, 1.87mmol)和苯并噻唑-2-甲酸酰肼(360mg, 1.87mmol; J. Org. Chem. 1958, 23, 1344)在正丁醇(2mL)中的混合物回流搅拌过夜,冷却至室温,浓缩然后通过快速柱色谱纯化(1%甲醇/氯仿)得到 580mg 黄色固体状实施例 259, 步骤 B 的标题化合物(含有等摩尔量的苯并噻唑-2-甲酸酰肼杂质,其可在随后的步骤中除去)。

步骤 C: 3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡嗪。向 3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡

嗪-7-甲酸苄酯(按照实施例 259，步骤 B 的方法制备，580mg，含有苯并噻唑-2-甲酸酰肼杂质)的二氯甲烷(10mL)溶液中于 0℃下加入三溴化硼的溶液(1M 的二氯甲烷溶液，4.45mL，4.45mmol)。将该混合物升温至室温过夜，加入水终止反应然后浓缩。将残余的水层用乙醚洗涤(6 次)，用饱和碳酸氢钠水溶液中和然后用 10%异丙醇/氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(1→10%甲醇/氯仿)得到 175mg (36%，两步)白色固体状实施例 259，步骤 C 的标题化合物。$^1$H NMR ($CDCl_3$，300MHz) δ 8.05 (d，1H)，7.96 (d，1H)，7.57-7.41 (c，2H)，4.62 (t，2H)，4.36 (s，2H)，3.35 (t，2H)；MS (APCI) 258 ($MH^+$)。

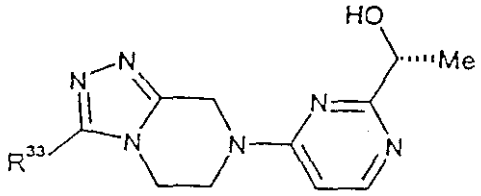
步骤 D：丁酸(R)-1-[4-(3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡嗪-7-基)-嘧啶-2-基]-乙酯。将 3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡嗪(按照实施例 259，步骤 C 的方法制备，170mg，0.66mmol)、丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，150mg，0.66mmol)和三乙胺(0.28mL，1.98mmol)在正丁醇(2.2mL)中的混合物加热回流过夜，冷却至室温，蒸发然后通过快速柱色谱纯化(1%甲醇/氯仿)得到 224mg (76%)无色固体状实施例 259，步骤 D 的标题化合物。$^1$H NMR ($CDCl_3$，300MHz) δ 8.37 (d，1H)，8.08 (d，1H)，7.97 (d，1H)，7.57-7.43 (c，2H)，6.53 (d，1H)，5.71 (q，1H)，5.09 (s，2H)，4.82 (t，2H)，4.33-4.26 (c，2H)，2.42 (t，2H)，1.78-1.64 (c，2H)，1.61 (d，3H)，0.99 (t，3H)；MS (APCI) 450 ($MH^+$)。

步骤 E：(R)-1-[4-(3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡嗪-7-基)-嘧啶-2-基]-乙醇。向丁酸(R)-1-[4-(3-苯并噻唑-2-基-5,6-二氢-8H-[1,2,4]三唑并[4,3-a]吡嗪-7-基)-嘧啶-2-基]-乙酯(按照实施例 259，步骤 D 的方法制备，220mg，0.49mmol)在 3：1：1 四氢呋喃/甲醇/水的混合物(5mL)中的溶液中加入水合氢氧化锂(62mg，1.47mmol)。将该混合物室温搅拌 3 小时，浓缩然后用氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发，然后通过快速柱色谱纯

化(5%甲醇/氯仿)得到 192mg (100%)无色固体状标题化合物。mp: 216.5-218.5℃; $^1$H NMR ($CDCl_3$, 300MHz) δ 8.37 (d, 1H), 8.06 (d, 1H), 7.97 (d, 1H), 7.56-7.45 (c, 2H), 6.56 (d, 1H), 5.11 (s, 2H), 4.83 (t, 2H), 4.77 (m, 1H), 4.35-4.25 (c, 2H), 4.16 (s, 1H), 1.54 (d, 3H); MS (APCI) 380 ($MH^+$), $[\alpha]_D$ +14.2 (c 1.0, $CHCl_3$)。

## 实施例 260 至 263

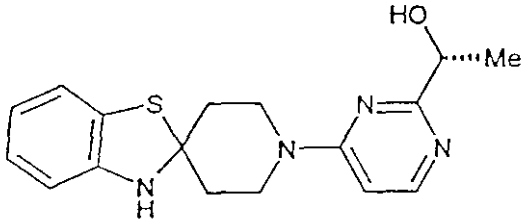
实施例 260 至 263 按照与实施例 259 类似的方法从适宜的原料制备。




| 实施例 | $R^{33}$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|
| 260 | 苯基 | 161-164 | 323 |
| 261 | 喹喔啉基-6-基 | 212-215 | 375 |
| 262 | 苯并噻吩-2-基 | 224-226 | 379 |
| 263 | 联苯-4-基 | 123-125 | 399 |

## 实施例 264

(R)-1-[4-(螺[苯并噻唑啉-2,4'-哌啶])-嘧啶-2-基]-乙醇



步骤 A：螺[苯并噻唑啉-2,4'-哌啶]盐酸盐。向 1'-苄基螺[苯并噻唑啉-2,4'-哌啶] (500mg, 1.69mmol; Indian J. Chem. 1976, 14B, 984)的丙酮(5mL)溶液中于 0℃下加入氯甲酸 1-氯乙酯(0.37mL, 3.38mmol)。将该混合物于 0℃搅拌 2 小时，升温至室温然后浓缩。将残余物通过快速柱色谱纯化(10→25%乙酸乙酯/己烷)得到中间体氨基甲酸酯，将其在甲醇(2mL)中回流 30 分钟。将反应混合物蒸发得到 128mg (31%)白色固体状实施例 264，步骤 A 的标题化合物。$^1$H NMR ($CD_3OD$, 400MHz) δ 6.98 (dd, 1H), 6.88 (t, 1H), 6.68-6.64 (c, 2H), 3.48-3.34 (c, 2H), 3.25-3.11 (c, 2H), 2.39-2.20 (c, 4H); MS (APCI) 207 ($MH^+$)。

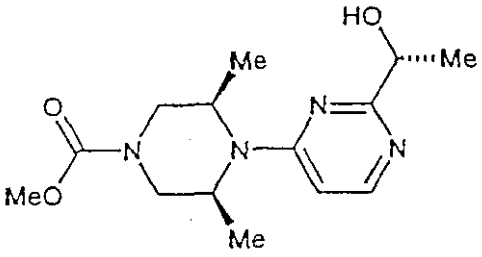
步骤 B：丁酸(R)-1-[4-(螺[苯并噻唑啉-2,4'-哌啶])-嘧啶-2-基]-乙酯。向螺[苯并噻唑啉-2,4'-哌啶]盐酸盐(按照实施例 264，步骤 A 的方法制备，147mg, 0.60mmol)的异丙醇(4mL)溶液中依次加入丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，140mg, 0.60mmol)和三乙胺(0.25mL, 1.8mmol)。将该混合物回流搅拌 2 小时，浓缩，然后通过快速柱色谱纯化(1%→2%甲醇/氯仿)得到 210mg (88%)黄色油状实施例 264，步骤 B 的标题化合物。$^1$H NMR ($CDCl_3$, 300MHz) δ 8.20 (d, 1H), 7.09 (dd, 1H), 6.95 (t, 1H), 6.78 (t, 1H), 6.68 (d, 1H), 6.40 (d, 1H), 5.68 (q, 1H), 4.32-4.18 (c, 2H), 4.02 (s, 1H), 3.38-3.25 (c, 2H), 2.39 (t, 2H), 2.36-2.25 (c, 2H), 1.99-1.83 (c, 2H), 1.75-1.64 (c, 2H), 1.57 (d, 3H), 0.96 (t, 3H); MS (APCI) 399 ($MH^+$)。

步骤 C：(R)-1-[4-(螺[苯并噻唑啉-2,4'-哌啶])-嘧啶-2-基]-乙醇。将丁酸(R)-1-[4-(螺[苯并噻唑啉-2,4'-哌啶])-嘧啶-2-基]-乙酯(按照实施例 264，步骤 B 的方法制备，204mg, 0.51mmol)和水合氢氧化锂(65mg, 1.53mmol)在 2: 2: 1 四氢呋喃/甲醇/水(5mL)中的混合物室温搅拌 1 小时。蒸除有机溶剂并将残余物用 10%异丙醇/氯仿萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然

后通过快速柱色谱纯化(2%甲醇/氯仿，2 次)得到红色泡沫，将其重结晶(乙酸乙酯)得到 42mg (25%)黄色固体状标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.18 (d, 1H), 7.07 (d, 1H), 6.93 (td, 1H), 6.78 (td, 1H), 6.69 (d, 1H), 6.42 (d, 1H), 4.69 (m, 1H), 4.35-4.16 (c, 3H), 4.02 (s, 1H), 3.41-3.28 (c, 2H), 2.37-2.24 (c, 2H), 1.99-1.85 (c, 2H), 1.49 (d, 3H); MS (APCI) 329 ($MH^+$); $[\alpha]_D$ +17.3 (c 1.0, MeOH)。

实施例 265

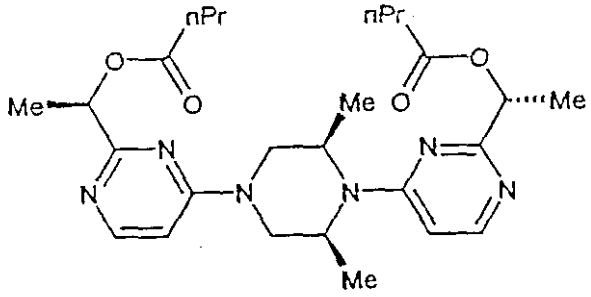
4-[2-(1R-羟基-乙基)-嘧啶-4-基]-3R,5S-二甲基-哌嗪-1-甲酸甲酯




向丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4 的方法制备，70mg，23μmol)的四氢呋喃(2mL)溶液中于室温及氮气氛下依次加入三乙胺(63μL，46μmol)和氯甲酸甲酯(21μL，27μmol)。将该混合物搅拌 1 小时然后浓缩。将残余物溶于 3：1：1 甲醇/四氢呋喃/水的混合物(2mL)中并加入水合氢氧化锂(29mg，69μmol)。将该混合物搅拌 1 小时，浓缩，重新悬浮在水中，然后用 10%异丙醇/氯仿萃取(4 次)。将合并的有机萃取液用饱和碳酸氢钠水溶液洗涤(1 次)，用硫酸钠干燥，过滤然后蒸发得到 50mg (74%，2 步)无色油状标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.21 (d, 1H), 6.33 (d, 1H), 4.70 (m, 1H), 4.63-3.92 (c, 5H), 3.76 (s, 3H), 3.20-3.02 (c, 2H), 1.50 (d, 3H), 1.25 (d, 6H); MS (APCI) 295 ($MH^+$); $[\alpha]_D$ +19. 0 (c 0.9, MeOH)。

## 实施例 266

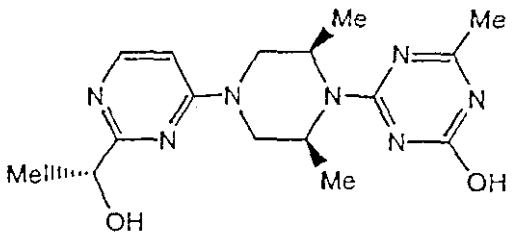
丁酸 1R-(4-{4-[2-(1R-丁酰氧基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-嘧啶-2-基)-乙酯



向丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4 的方法制备，200mg，0.65mmol)的异丙醇(2mL)溶液中于室温下依次加入三乙胺(0.18mL，1.31mmol)和丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，150mg，0.65mmol)。将该混合物加热回流 18 小时，冷却至室温，浓缩，然后通过快速柱色谱纯化(1%甲醇/氯仿)得到 321mg (99%)黄色油状标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.22 (d, 2H), 6.43 (d, 1H), 6.32 (d, 1H), 5.68 (q, 2H), 4.72-4.24 (c, 4H), 3.30-3.12 (c, 2H), 2.39 (t, 4H), 1.77-1.63 (c, 4H), 1.57 (d, 6H), 1.28-1.17 (c, 6H), 0.96 (t, 6H); MS (APCI) 499 ($MH^+$)。

## 实施例 267

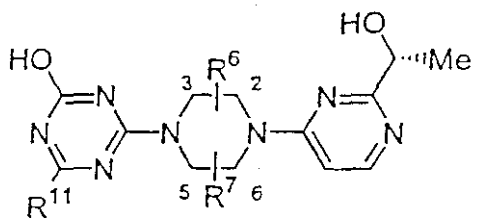
4-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-2R,6S-二甲基-哌嗪-1-基}-6-甲基-[1,3,5]三嗪-2-醇



将丁酸 1R-{4-[4-(4-氯-6-甲基-[1,3,5]三嗪-2-基)-3R,5S-二甲基哌嗪-1-基]-嘧啶-2-基}-乙酯(按照实施例 213, 步骤 A 的方法制备, 0.30g, 0.70mmol)加入浓盐酸(3mL)中然后加热回流 12 小时。将混合物用固体碳酸氢钠中和至 pH 7 然后用氯仿萃取。将有机萃取液用硫酸钠干燥然后过滤。将滤液浓缩成油, 将其通过快速色谱纯化(92: 8 氯仿: 甲醇)得到白色固体状标题化合物, 0.15g (64%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.21 (d, 6H), 1.49 (d, 3H), 2.36 (s, 3H), 3.21-3.27 (m, 2H), 4.22-4.43 (m, 2H), 4.63 (m, 2H), 4.69 (q, 1H), 6.42 (d, 1H), 8.18 (d, 1H); mp: 247-248℃; MS (CI) 346 ($MH^+$)。

## 实施例 268 至 275

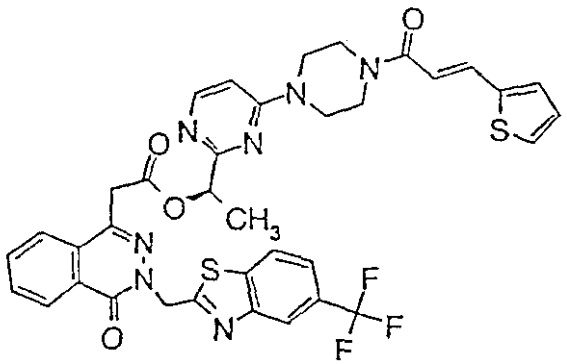
实施例 268 至 275 按照与实施例 267 类似的方法从适宜的原料制备。




| 实施例 | $R^{11}$ | $R^6$ | $R^7$ | mp(℃) | MS($MH^+$) |
|---|---|---|---|---|---|
| 268 | H | 3R-Me | 5S-Me | >250 | 332 |
| 269 | 异丙基 | 3R-Me | 5S-Me | >250 | 374 |
| 270 | 环己基 | 3R-Me | 5S-Me | >250 | 414 |
| 271 | 苯基 | 3R-Me | 5S-Me | >250 | 408 |
| 272 | 环丙基 | 3R-Me | 5S-Me | >250 | 372 |
| 273 | 甲基 | 2R-Me | 6S-Me | >250 | 346 |
| 274 | 环丙基 | 2R-Me | 6S-Me | >250 | 372 |
| 275 | 苯基 | 2R-Me | 6S-Me | >250 | 408 |

## 实施例 276

(E)-[4-氧代-3-(5-三氟甲基-苯并噻唑-2-基甲基)-3,4-二氢-酞嗪-1-基]-乙酸 1R-{4-[4-(3-噻吩-2-基-丙烯酰基)-哌嗪-1-基]-嘧啶-2-基}-乙酯

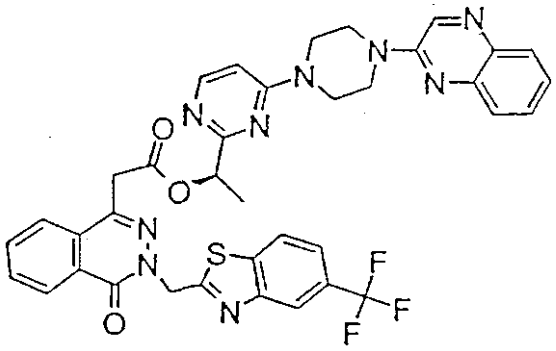


向[4-氧代-3-(5-三氟甲基-苯并噻唑-2-基甲基)-3,4-二氢-酞嗪-1-基]-乙酸(0.59g, 1.41mmol)的二氯甲烷(30mL)和 4-二甲氨基吡啶(0.18g, 1.41mmol)溶液中于室温下依次加入 1-(3-二甲氨基丙基)-3-乙基碳二亚胺盐酸盐(0.54g, 2.82mmol)和(E)-1-{4-[2-(1R-羟基-乙基)-嘧啶-4-基]-哌嗪-1-基}-3-噻吩-2-基-丙烯酮(按照实施例 127 的方法制备, 0.49g, 1.41mmol)然后搅拌 20 小时。将混合物用饱和碳酸氢钠水溶液洗涤一次, 用饱和氯化钠水溶液洗涤一次, 用硫酸镁干燥然后过滤。将滤液浓缩成油, 将其通过快速色谱纯化(乙酸乙酯)得到白色泡沫状标题化合物, 0.65g (62%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.51 (d, 3H), 3.41-3.77 (m, 8H), 4.28 (m, 2H), 5.18 (q, 1H), 5.79 (d, 1H), 6.35 (d, 1H), 6.68 (d, 1H), 7.05, (m, 1H), 7.32 (d, 1H), 7.68 (m, 1H), 7.71-7.90 (m, 5H), 8.18 (d, 1H), 8.27 (d, 1H), 8.46 (m, 1H); mp: 105-109℃; MS (CI) 746 ($MH^+$); $[\alpha]_D$ +49.2 (c 1.0, MeOH)。

## 实施例 277

(E)-[4-氧代-3-(5-三氟甲基-苯并噻唑-2-基甲基)-3,4-二氢-酞

嗪-1-基]-乙酸 1R-[4-(4-喹喔啉-2-基-哌嗪-1-基)-嘧啶-2-基]-乙酯



实施例 277 按照与实施例 276 类似的方法从适宜的原料制备。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.53 (d, 3H), 3.38-3.87 (m, 8H), 4.28 (m, 2H), 5.18 (q, 1H), 6.35 (d, 1H), 7.68 (m, 1H), 7.68-7.94 (m, 8H), 8.18 (d, 1H), 8.21-8.37 (m, 2H), 8.46 (m, 1H); mp: 108-112℃; MS (CI) 738 ($MH^+$)。

制备例 1

2-甲氧基甲基 4-哌嗪-1-基-嘧啶。

步骤 A: 2-甲氧基甲基-嘧啶-4-基-甲磺酸酯。向冰冷的 2-甲氧基甲基-3H-嘧啶-4-酮 (35.0g, 250mmol; US 5,215,990) 和三乙胺 (25.6g, 250mmol) 的二氯甲烷 (250mL) 溶液中滴加甲磺酰氯 (28.6g, 250mmol)。将该混合物在 1 小时内缓慢升温至室温, 然后依次用饱和碳酸氢钠水溶液和水洗涤。将有机层用硫酸镁干燥, 过滤然后蒸发得到黄褐色固体状制备例 1, 步骤 A 的标题化合物, 49.2g (90%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 3.55 (s, 3H), 3.82 (s, 3H), 4.42 (s, 2H), 6.36 (d, 1H), 8.12 (d, 1H); mp: 39-40℃; MS (TS) 219 ($MH^+$)。

步骤 B: 2-甲氧基甲基-4-哌嗪-1-基-嘧啶。向 2-甲氧基甲基-嘧啶-4-基-甲磺酸酯 (按照制备例 1, 步骤 A 的方法制备, 43.6g, 200mmol) 的四氢呋喃 (400mL) 溶液中加入哌嗪 (34.4g, 400mmol)。

将该混合物加热回流 0.5 小时，冷却至室温然后过滤。将滤液浓缩然后减压干燥得到半固体状标题化合物，36.6g (85%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 2.45 (br s, 1H), 2.88 (m, 4H), 3.45 (s, 3H), 3.72 (m, 4H), 4.46 (s, 2H), 6.38 (d, 1H), 8.22 (d, 1H); MS (TS) 209 ($MH^+$)。

制备例 2

乙酸(R)-1-(4-哌嗪-1-基-嘧啶-2-基)-乙酯。将乙酸(R)-1-(4-甲磺酰氧基-嘧啶-2-基)-乙酯(按照制备例 6 的方法制备，24.1g, 92mmol)和哌嗪(16.0g, 184mmol)在四氢呋喃(200mL)中的混合物加热回流 1 小时。将该混合物冷却，过滤，浓缩然后通过快速柱色谱纯化(9: 1 二氯甲烷/甲醇)得到 24.4g (88%)油状标题化合物。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.56 (d, 3H), 2.25 (s, 3H), 2.83 (m, 4H), 3.63 (m, 4H), 5.54 (q, 1H), 6.38 (d, 1H), 8.24 (d, 1H); MS (CI) 251 ($MH^+$)。

制备例 3

丁酸 1R-[4-(3R,5S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。将丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，18.5g, 80.9mmol)和顺-2,6-二甲基哌嗪(18.6g, 162mmol)在四氢呋喃(400mL)中的混合物室温搅拌过夜，用乙醚稀释，用饱和碳酸氢钠水溶液(1 次)和水(3 次)洗涤。将合并的含水萃取液用 10%异丙醇/氯仿反萃取(6 次)。将合并的有机萃取液用硫酸钠干燥，过滤，蒸发然后通过快速柱色谱纯化(1→5%甲醇/氯仿)得到 20.9g (84%)蜡状黄色固体状标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.14 (d, 1H), 6.31 (d, 1H), 5.65 (q, 1H), 4.53-4.16 (c, 2H), 2.89-2.78 (c, 2H), 2.47-2.33 (c, 2H), 2.38 (t, 2H), 1.73-1.60 (c, 2H), 1.55 (d, 3H), 1.11 (d, 6H), 0.94 (t, 3H); MS (APCI) 307 ($MH^+$)。

## 制备例 4

丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯

步骤 A：丁酸 1-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。将丁酸(R)-1-(4-三氟甲磺酰氧基-嘧啶-2-基)-乙酯(按照制备例 9 的方法制备，84.8g，248mmol)和顺-1-苄基-3,5-二甲基-哌嗪(101g，496mmol，Org. Prep. Proceed. Int. 1976，8，19)在乙腈(310mL)中的混合物回流搅拌 15 小时，浓缩然后通过快速柱色谱纯化(15%乙酸乙酯/己烷)得到 52g (53%)橙色油状制备例 4，步骤 A 的标题化合物。$^1$H NMR ($CDCl_3$，400MHz) δ 8.15 (d，1H)，7.39-7.24 (c，5H)，6.25 (d，1H)，5.66 (q，1H)，4.45 (m，1h)，4.24 (m，1H)，3.52 (s，2H)，2.73 (d，2H)，2.37 (t，2H)，2.22 (d，2H)，1.70-1.60 (c，2H)，1.55 (d，3H)，1.30 (d，3H)，1.27 (d，3H)，0.93 (t，3H)；MS (APCI) 398 ($MH^+$)。

步骤 B：丁酸 1R-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯和丁酸 1S-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。将丁酸 1-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4，步骤 A 的方法制备，131g，79%ee)通过手性 HPLC 在如下条件下纯化(柱：15cm 内径 x 25cm Prochrom 柱，用来自 Chiral Technologies Inc.，730 Springdale Dr.，Exton，PennsyLvania，19341 的 Chiracel AD 填充；流动相：90:10 正庚烷/异丙醇；流速：约 1L/分钟；上样量：4.2g/轮)得到制备例 4，步骤 B 的标题化合物(109g，>98%ee)和(12.6g，93%ee)，均为黄色油状。上述化合物的 $^1$H NMR 和 MS 数据与制备例 4，步骤 A 的物质相符。

步骤 C：丁酸 1R-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯盐酸盐。向丁酸 1R-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯(按照制备例 4，步骤 B 的方法制备，109g，

275mmol)的甲醇(500mL)溶液中加入氯化氢(5M 的甲醇溶液, 56mL, 278mmol)。将该混合物室温搅拌 5 分钟然后浓缩得到 118g (99%)浅黄色泡沫状制备例 4, 步骤 C 的标题化合物。

步骤 D: 丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯。向丁酸 1R-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯盐酸盐(按照制备例 4, 步骤 C 的方法制备, 54.2g, 125mmol)的甲醇(200mL)溶液中依次加入甲酸铵(79g, 1.25mol)和 10%钯碳(13.5g, 25wt%)在甲醇(200mL)中的浆液。将该混合物回流搅拌 1 小时然后用硅藻土过滤。将滤液浓缩, 用饱和碳酸氢钠水溶液稀释然后用氯仿萃取(2 次)。将合并的有机萃取液用硫酸钠干燥, 过滤然后蒸发得到 40.8g 黄色油状标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.16 (d, 1h), 6.26 (d, 1H), 5.66 (q, 1H), 4.39 (m, 1H), 4.22 (m, 1H), 2.93 (app s, 4H), 2.38 (t, 2H), 1.71-1.62 (c, 2H), 1.56 (d, 3H), 1.27 (d, 3H), 1.24 (d, 3H), 0.94 (t, 3H); MS (APCI) 307 ($MH^+$)。

## 制备例 5

乙酸(R)-1-(4-氯-嘧啶-2-基)-乙酯。将(R)-2-(1-乙酰氧基-乙基)-3H-嘧啶-4-酮(按照制备例 13 的方法制备, 3.00g, 16.5mmol)在室温下加入到三氯氧磷(10mL)中然后搅拌 3 小时。真空蒸除过量的三氯氧磷并将得到的油在氯仿和饱和碳酸钠水溶液之间进行分配。分液并将有机层用水洗涤两次, 用饱和氯化钠水溶液洗涤一次, 用硫酸镁干燥然后过滤。将滤液蒸发得到橙色油状标题化合物, 2.88g (87%)。$^1$H NMR ($CDCl_3$, 300MHz) δ 1.56 (d, 3H), 2.18 (s, 3H), 5.68 (q, 1H), 6.32 (d, 1H), 8.21 (d, 1H); MS (CI) 201, 203 ($MH^+$); $[\alpha]_D$ +27.6 (c 1.0, MeOH)。

## 制备例 6

乙酸(R)-1-(4-甲磺酰氧基-嘧啶-2-基)-乙酯。向冰冷的(R)-2-(1-

乙酰氧基-乙基)-3H-嘧啶-4-酮(按照制备例 13 的方法制备，2.58g，14.2mmol)和三乙胺(1.43g，14.2mmol)的二氯甲烷(20mL)溶液中滴加甲磺酰氯(1.63g，14.2mmol)然后搅拌 1 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤，用硫酸镁干燥然后过滤。将滤液蒸发得到油状标题化合物，3.15g (85%)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.56 (d，3H)，2.18 (s，3H)，3.82 (s，3H)，5.56 (q，1H)，6.38 (d，1H)，8.24 (d，1H)；MS (CI) 261 ($MH^+$)；$[\alpha]_D$ +53.8 (c 1.1，MeOH)。

制备例 7

丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯。将(R)-2-(1-丁酰氧基-乙基)-3H-嘧啶-4-酮(按照制备例 14 的方法制备，3.00g，16.5mmol)于室温下加入到三氯氧磷(10mL)中然后搅拌 3 小时。真空蒸除过量的三氯氧磷并将得到的油在二氯甲烷和饱和碳酸钠水溶液之间进行分配。分液并将有机层用水洗涤一次，用饱和氯化钠水溶液洗涤一次，用硫酸镁干燥然后过滤。将滤液蒸发得到橙色油状标题化合物，3.19g (85%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.98 (t，3H)，1.54 (d，3H)，1.67 (m，2H)，2.48 (t，2H)，5.68 (q，1H)，6.36 (d，1H)，8.21 (d，1H)；$[\alpha]_D$ +27.6 (c 1.0，MeOH)。

制备例 8

丁酸(R)-1-(4-甲磺酰氧基-嘧啶-2-基)-乙酯。向冰冷的(R)-2-(1-丁酰氧基-乙基)-3H-嘧啶-4-酮(按照制备例 14 的方法制备，17.8g，97.8mmol)和三乙胺(9.9g，97.8mmol)的二氯甲烷(100mL)溶液中滴加甲磺酰氯(11.21g，97.8mmol)然后搅拌 1 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤，用硫酸镁干燥然后过滤。将滤液蒸发得到油状标题化合物，24.1g (94%)。$^1$H NMR ($CDCl_3$，300MHz) δ 0.99 (t，3H)，1.54 (d，3H)，1.68 (m，2H)，2.48 (t，2H)，3.81 (s，3H)，5.54 (q，1H)，6.38 (d，1H)，8.24 (d，1H)；

MS (CI) 261 ($MH^+$); $[\alpha]_D$+28.8 (c 1.0, MeOH)。

制备例 9

丁酸(R)-1-(4-三氟甲磺酰氧基-嘧啶-2-基)-乙酯。

方法 1：向(R)-2-(1-丁酰氧基-乙基)-3H-嘧啶-4-酮(按照制备例 14 的方法制备，52g，248mmol)和三乙胺(36.2mL，260mmol)的二氯甲烷(830mL)溶液中于 0℃以及在氮气氛中搅拌下通过加液漏斗在 30 分钟内滴加三氟甲磺酸酐(44mL，260mmol)的二氯甲烷(70mL)溶液，保持内部温度为 4-8℃。将该混合物于 4℃继续搅拌 15 分钟，然后用水终止反应。搅拌 10 分钟后，分液并将水层用二氯甲烷萃取(3 次)。将合并的有机萃取液用硫酸钠干燥，过滤然后浓缩得到 47.2g (约 100%)深色油状标题化合物，将其立即用于下一步骤。$^1H$ NMR ($CDCl_3$, 400MHz) δ 8.83 (d, 1H), 7.03 (d, 1H), 5.82 (q, 1H), 2.41-2.32 (c, 2H), 1.72-1.60 (c, 2H), 1.62 (d, 3H), 0.95 (t, 3H)；MS (APCI) 343 ($MH^+$)。

方法 2：向(R)-2-(1-丁酰氧基-乙基)-3H-嘧啶-4-酮(按照制备例 14 的方法制备，4.20g，20.0mmol)和三乙胺(2.02g，20.0mmol)的二氯甲烷(20mL)溶液中滴加三氟甲磺酰氯(3.37g，20.0mmol)，保持内部温度在-20℃以下，然后搅拌 0.5 小时。将混合物依次用饱和碳酸氢钠水溶液和水洗涤，用硫酸钠干燥然后过滤。将滤液蒸发得到深色油状标题化合物，6.42g (94%)，将其立即用于下一步骤。$^1H$ NMR 和 MS 数据与制备例 9，方法 1 的数据一致。

制备例 10

(R)-1-(4-氯-嘧啶-2-基)-乙醇。向丁酸(R)-1-(4-氯-嘧啶-2-基)-乙酯(按照制备例 7 的方法制备，250mg，1.1mmol)的二氧六环(0.9mL)溶液中加入浓盐酸(0.9mL)。将该混合物室温搅拌 5 小时，用饱和碳酸氢钠水溶液终止反应，然后加入固体碳酸氢钠直至不再有气体溢出。加入二氯甲烷然后分液。将水相用二氯甲烷萃取(3 次)并

将合并的有机萃取液用硫酸钠干燥，过滤然后蒸发得到 125mg (71%)浅黄色油状标题化合物。$^1$H NMR ($CDCl_3$, 400MHz) δ 8.59 (d, 1H), 7.25 (d, 1H), 4.92 (q, 1H), 3.81 (br s, 1H), 1.56 (d, 3H); MS (APCI) 159, 161 ($MH^+$)。

制备例 11

(R)-(+)-2-(1-羟基-乙基)-3H-嘧啶-4-酮盐酸盐

步骤 A: (R)-(+)-2-羟基-丙脒盐酸盐。向一个 22 升的、装有回流冷凝器、机械搅拌器、温度计和氮气入口的三颈圆底烧瓶中加入四氢呋喃(7.3L)、(R)-(+)-2-羟基-丙酰胺(731g, 8.2mol)和三乙基氧鎓四氟硼酸盐(95%, 1.97kg, 9.8mol)。将得到的黄色溶液室温搅拌 2 小时，此时的 NMR 样品显示了原料的消耗和所需的亚胺酸酯的存在。将溶液真空浓缩得到黄色油，将其加入甲醇(2L)中。将该溶液冷却至 15℃然后向溶液中通入无水氨气泡 5 小时。将形成的悬浮液搅拌 2 小时，浓缩得到粘稠的混合物，将其用乙酸乙酯稀释然后用硅藻土过滤。将滤液冷却至 10℃，向溶液中通入无水氯化氢气泡 2 小时，升温至室温然后过滤得到 418g (41%)制备例 11，步骤 A 的标题化合物。mp: 134-138℃; $^1$H NMR (DMSO-$d_6$, 300MHz) δ 1.33 (t, 3H), 4.42 (q, 1H), 6.25-6.88 (br s, 1H), 8.72-9.25 (br s, 3H)。

步骤 B: (R)-(+)-2-(1-羟基-乙基)-3H-嘧啶-4-酮盐酸盐。向一个 22 升的、装有回流冷凝器、机械搅拌器、温度计和氮气入口的三颈圆底烧瓶中加入甲醇(8L)、氢氧化钾(946g, 14.7mol)、R-(+)-2-羟基-丙脒(按照制备例 11，步骤 A 的方法制备，1848g, 14.7mol)和 3-羟基-丙烯酸乙酯的钠盐(按照制备例 12，步骤 C 的方法制备，2030g, 14.7mol)。将形成的浆液室温搅拌 3 小时。加入浓盐酸(1.32L)将 pH 从 12.5 调至 7。滤出固体并用异丙醇洗涤。将滤液浓缩得到油，用异丙醇(4L)稀释，冷却至 10℃然后向溶液中通入无水氯化氢气泡 4 小时。将形成的悬浮液过滤并将固体干燥得到 2242g

(87%)标题化合物。mp: 180-184℃(分解); $^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.46 (d, 3H), 4.84 (q, 1H), 6.52 (d, 1H), 8.00 (d, 1H)。

## 制备例 12

2-(1-羟基-乙基)-3H-嘧啶-4-酮

步骤 A: 2-羟基-丙亚氨酸乙酯盐酸盐。将乳腈(378g, 5.32mol)的乙醚(1.46L)和乙醇(0.34L)溶液用氯化氢气体于 0-5℃饱和 0.5 小时然后于 5℃放置 60 小时。滤出形成的沉淀并用乙醚洗涤两次得到固体状制备例 12, 步骤 A 的标题化合物, 815g (99%)。mp: 165-168℃; $^1$H NMR ($CD_3OD$, 250MHz) δ 1.45-1.53 (c, 6H), (c, 3H)。

步骤 B: 2-羟基-丙脒盐酸盐。将 2-羟基-丙亚氨酸乙酯盐酸盐(按照制备例 12, 步骤 A 的方法制备, 751g, 4.87mol)的乙醇(3.75L)悬浮液于 0℃下用氨气饱和 1 小时, 保持内温<5℃, 然后室温搅拌 18 小时。滤出固体然后于 40℃真空干燥得到第一批产品。将滤液浓缩至一半体积, 然后过滤收集第二批产品并真空干燥。将第一批和第二批产品合并得到黄色固体状制备例 12, 步骤 B 的标题化合物, 608g (99%)。mp: 134-138℃; $^1$H NMR (DMSO-$d_6$, 400MHz) δ 1.30 (d, 3H), 4.38 (q, 1H), 6.23 (br s, 1H), 7.35 (br s, 1H), 8.78 (br s, 3H)。

步骤 C: 3-羟基-丙烯酸乙酯钠盐。向氢化钠(60%油分散液, 269g, 16.7mol)的异丙基醚(12L)悬浮液中缓慢加入乙酸乙酯(1280g, 14.2mol), 加入的速率为使内温保持在 45℃。将该混合物继续搅拌 0.5 小时, 然后于 42℃下滴加甲酸乙酯(2232g, 30.1mol)并于室温下搅拌 18 h。将混合物过滤并将固体用乙醚洗涤两次, 用己烷洗涤一次然后干燥得到白色固体状制备例 12, 步骤 C 的标题化合物, 1930g (99%)。$^1$H NMR (DMSO-$d_6$, 300MHz) δ 1.03 (t, 3H), 3.86 (q, 2H), 4.08 (d, 1H), 8.03 (d, 1H)。

步骤 D: 2-(1-羟基-乙基)-3H-嘧啶 4-酮。向 3-羟基-丙烯酸乙酯钠

盐(按照制备例 12，步骤 C 的方法制备，1301g，9.42mol)的水(1.3L)溶液中于室温下加入 2-羟基丙脒盐酸盐(按照制备例 12，步骤 B 的方法制备，610g，4.9mol)的水(1.3L)溶液并搅拌 48 小时。用乙酸将溶液调至 pH 7.0 然后用氯仿连续萃取 48 小时。将萃取液用硫酸钠干燥然后过滤。将滤液浓缩得到固体，将其在乙醚中形成浆液，过滤然后干燥得到固体状标题化合物，232g (38%)。mp：121-124℃；$^1$H NMR (DMSO-$d_6$，400MHz) δ 1.30 (d，3H)，4.46 (q，1H)，5.62 (br s，1H)，6.13 (d，1H)，7.80 (d，1H)。

制备例 13

(R)-2-(1-乙酰氧基-乙基)-3H-嘧啶-4-酮。向乙酸乙烯酯(4.3g，50mmol)的二氧六环(63mL)溶液中加入 2-(1-羟基-乙基)-3H-嘧啶-4-酮(按照制备例 12 的方法制备，2.1g，15.1mmol)，然后将混合物加热至 50℃。向形成的溶液中加入脂酶 P30 (0.21g，10wt%)然后继续加热 24 小时。将反应混合物过滤并将滤液蒸发得到粘稠的糖浆状液体残余物。将残余物通过快速柱色谱纯化(95：5 二氯甲烷：甲醇)得到无色液体状标题化合物，0.97g (92%理论值)。$^1$H NMR ($CDCl_3$，300MHz) δ 1.61 (d，3H)，2.20 (s，3H)，5.65 (q，1H)，6.35 (d，1H)，7.97 (d，1H)，11.94 (s，1H)；$[\alpha]_D$ +39.9 (c 1.0，MeOH)。

制备例 14

(R)-2-(1-丁酰氧基-乙基)-3H-嘧啶-4-酮

方法 1：向丁酸乙烯酯(17.7g，310mmol)的二氧六环(650mL)溶液中加入 2-(1-羟基-乙基)-3H-嘧啶-4-酮(按照制备例 12 的方法制备，21.8g，155mmol)，然后将混合物加热至 50℃。向形成的溶液中加入脂酶 P30 (4.35g，20 wt%)然后继续加热 24 小时。将反应混合物过滤并将滤液蒸发得到粘稠的糖浆状液体残余物，将其在二氯甲烷和水之间进行分配。分液并将有机层用硫酸钠干燥，过滤然后蒸发得到无

色液体状标题化合物，9.35g（86%理论值）。$^1$H NMR（$CDCl_3$，300MHz）0.95（t，3H），1.65（m，5H），2.40（m，2H），5.65（q，1H），6.45（d，1H），8.00（d，1H）；$[\alpha]_D$ +29.5（c 1.0，MeOH）。

方法 2：向冷的（5℃）（R）-（+）-2-（1-羟基-乙基）-3H-嘧啶-4-酮盐酸盐（按照制备例 11 的方法制备，750g，4.3mol）的二氯甲烷（8L）溶液中依次加入三乙胺（1216mL，8.7mol）和 4-二甲氨基吡啶（25.9g，0.21mol）。然后在 5 小时内缓慢加入丁酸酐（730mL，4.4mol）的二氯甲烷（730mL）溶液，保持温度低于 3℃。将混合物用半饱和的盐水（4L）洗涤两次，然后用饱和碳酸氢钠水溶液（4L）洗涤一次，用硫酸钠干燥，过滤然后真空浓缩得到 869g（96%）油状标题化合物。该化合物的 $^1$H NMR 和 MS 数据与制备例 14，方法 1 的数据一致。

## 制备例 15

丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯二苯甲酰基-L-酒石酸盐

步骤 A：丁酸 1R-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯二二苯甲酰基-L-酒石酸盐。向（R）-2-（1-丁酰氧基-乙基）-3H-嘧啶-4-酮（按照制备例 14 的方法制备，254g，1.25mol）和三乙胺（176mL，1.3mol）的二氯甲烷（2.3L）溶液中于 5℃下在 3 小时内缓慢加入三氟甲磺酸酐（211mL，1.25mol）的二氯甲烷（355mL）溶液。然后加入冷水（1.4L）终止反应并分液。将有机层用饱和碳酸氢钠水溶液（1.5L）洗涤一次，用饱和氯化钠水溶液洗涤一次（1L），然后真空蒸除溶剂。将得到的油溶于二甲基乙酰胺（890mL），然后于 80℃下在 1 小时内缓慢加入到顺-1-苄基-3,5-二甲基-哌嗪（735g，3.6mol）的二甲基乙酰胺（1.3L）溶液中。于 80℃加热 3.5 小时，此时经气相色谱判断反应已经完成。冷却至室温后，加入水（2.5L）和异丙基醚（2.5L），分液，将有机层用水洗涤一次（2L）。然后将异丙基醚层与硫酸铜（126g）的水（3L）溶液充分混合，用一层硅藻土过滤，将滤饼用异丙基

醚(1L)洗涤。倾析掉滤液的含水层，将剩余的有机层用水(2L)洗涤然后用二苯甲酰基-L-酒石酸(619g，2.4mol)的异丙基醚(5.3L)溶液处理。将形成的粘稠浆液搅拌 16 小时然后滤出固体，用异丙基醚(2L)洗涤然后于 50℃真空干燥得到 854g (71%)白色固体状制备例 15，步骤 A 的标题化合物。$^1$H NMR (DMSO-$d_6$，400MHz) δ 0.89 (t，3H)，1.23 (d，3H)，1.25 (d，3H)，1.48 (d，3H)，1.54 (dd，2H)，2.20 (dd，2H)，2.31 (dt，2H)，2.77 (d，2H)，3.57 (s，1H)，4.45 (m，1H)，4.24 (m，1H)，5.51 (q，1H)，6.60 (d，1H)，7.30 (m，1H)，7.39 (m，4H)，7.64 (m，7H)，7.77 (m，4H)，8.05 (c，7H)，8.17 (d，1H)。

步骤 B：丁酸 1R-[4-(2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯二苯甲酰基-L-酒石酸盐。向丁酸 1R-[4-(4-苄基-2R,6S-二甲基-哌嗪-1-基)-嘧啶-2-基]-乙酯二二苯甲酰基-L-酒石酸盐(按照制备例 15，步骤 A 的方法制备，50g，0.045mol)和 5%钯碳(含水 50%，10g，20 wt%)在甲醇(400mL)中的混合物中于氮气氛下加入环己烯(4.6mL，0.045mol)。将该混合物加热回流 6 小时，此时经 TLC 判断反应已经完成。冷却至 40℃后，将混合物用硅藻土过滤并用甲醇(100mL)洗涤。通过常压蒸馏将甲醇逐渐用异丙醇替换，直至达到 80-82℃的恒定沸点，然后将形成的白色浆液冷却至室温并搅拌 4 小时。滤出固体，用异丙醇(100mL)洗涤然后于 50℃真空干燥得到 25.7g (86%)白色固体状标题化合物。$^1$H NMR (DMSO-$d_6$，400MHz) δ 0.90 (t，3H)，1.15 (d，3H)，1.21 (d，3H)，1.47 (d，3H)，1.55 (q，2H)，2.3 (m，2H)，3.04 (m，2H)，3.2 (m，2H)，4.4 (br s，1H)，4.6 (br s，1H)，5.5 (q，1H)，5.74 (s，2H)，6.6 (d，1H)，7.5 (t，4H)，7.6 (m，2H)，8.0 (m，4H)，8.2 (d，1H)。