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(54) Title: ANTI-INFLAMMATORY MEDICAMENTS

(57) Abstract: Novel compounds and methods of using those compounds for the treatment of inflammatory conditions are provided. In a preferred embodiment, modulation of the activation state of p38 kinase protein comprises the step of contacting the kinase protein with the novel compounds.

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ANTI-INFLAMMATORY MEDICAMENTS

BACKGROUND OF THE INVENTION

Related Applications

This application is a continuation-in-part of Application S/N 10/746,460 filed December 24, 2003. This prior application is incorporated by reference herein.

Sequence Listing

The following application contains a sequence listing in computer readable format (CRF). The content the enclosed CRF is hereby incorporated by reference.

Field of the Invention

The present invention relates to novel compounds and methods of using those compounds to treat anti-inflammatory diseases.

Description of the Prior Art

Basic research has recently provided the life sciences community with an unprecedented volume of information on the human genetic code and the proteins that are produced by it. In 2001, the complete sequence of the human genome was reported (Lander, E.S. et al. Initial sequencing and analysis of the human genome. *Nature* (2001) 409:860; Venter, J.C. et al. The sequence of the human genome. *Science* (2001) 291:1304). Increasingly, the global research community is now classifying the 50,000+ proteins that are encoded by this genetic sequence, and more importantly, it is attempting to identify those proteins that are causative of major, under-treated human diseases.

Despite the wealth of information that the human genome and its proteins are providing, particularly in the area of conformational control of protein function, the methodology and strategy by which the pharmaceutical industry sets about to develop small molecule therapeutics has not significantly advanced beyond using native protein active sites for binding to small molecule therapeutic agents. These native active sites are normally used by proteins to perform essential cellular functions by binding to and processing natural substrates or tranducing signals from natural ligands. Because these native pockets are used broadly by many other proteins within protein families, drugs which interact with them are often plagued by lack of selectivity and, as a consequence, insufficient therapeutic windows to achieve maximum efficacy. Side effects and toxicities are revealed in such small molecules, either during preclinical discovery, clinical trials, or later in the marketplace. Side effects and toxicities continue to be a major reason for the high attrition rate seen within the drug development process. For the kinase protein family of proteins, interactions at these native active sites have been recently reviewed:

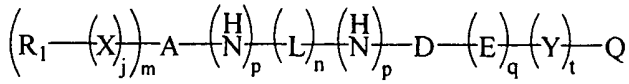
see J. Dumas, Protein Kinase Inhibitors: Emerging Pharmacophores 1997-2001, *Expert Opinion on Therapeutic Patents* (2001) 11: 405-429; J. Dumas, Editor, New challenges in Protein Kinase Inhibition, in *Current Topics in Medicinal Chemistry* (2002) 2: issue 9.

It is known that proteins are flexible, and this flexibility has been reported and utilized with the discovery of the small molecules which bind to alternative, flexible active sites with proteins. For review of this topic, *see* Teague, *Nature Reviews/Drug Discovery*, Vol. 2, pp. 527-541 (2003). *See also*, Wu et al., *Structure*, Vol. 11, pp. 399-410 (2003). However these reports focus on small molecules which bind only to proteins at the protein natural active sites. Peng et al., *Bio. Organic and Medicinal Chemistry Ltrs.*, Vol. 13, pp. 3693-3699 (2003), and Schindler, et al., *Science*, Vol. 289, p. 1938 (2000) describe inhibitors of abl kinase. These inhibitors are identified in WO Publication No. 2002/034727. This class of inhibitors binds to the ATP active site while also binding in a mode that induces movement of the kinase catalytic loop. Pargellis et al., *Nature Structural Biology*, Vol. 9, p. 268 (2002) reported inhibitors p38 alpha-kinase also disclosed in WO Publication No. 00/43384 and Regan et al., *J. Medicinal Chemistry*, Vol. 45, pp. 2994-3008 (2002). This class of inhibitors also interacts with the kinase at the ATP active site involving a concomitant movement of the kinase activation loop.

More recently, it has been disclosed that kinases utilize activation loops and kinase domain regulatory pockets to control their state of catalytic activity. This has been recently reviewed (see, e.g., M. Huse and J. Kuriyan, *Cell* (2002) 109:275).

SUMMARY OF THE INVENTION

The present invention is broadly concerned with new compounds for use in treating anti-inflammatory conditions and methods of treating such conditions. In more detail, the inventive compounds have the formula



(IA)

wherein:

R^1 is selected from the group consisting of aryls (preferably C_6-C_{18}, and more preferably C_6-C_{12}) and heteroaryls;

each X and Y is individually selected from the group consisting of -O-, -S-, -NR_6-, -NR_6SO_2-, -NR_6CO-, alkynyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkenyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylenes (preferably C_1-C_{18}, and more preferably C_1-C_{12}), -$O(CH_2)_h$-, and -$NR_6(CH_2)_h$-, where each h is individually selected from the group consisting of 1, 2, 3, or 4, and where for each of alkylenes (preferably C_1-C_{18}, and more preferably C_1-C_{12}), -$O(CH_2)_h$-, and -$NR_6(CH_2)_h$-, one of the methylene groups present therein may be optionally double-bonded to a side-chain oxo group except that where -$O(CH_2)_h$- the introduction of the side-chain oxo group does not form an ester moiety;

A is selected from the group consisting of aromatic (preferably C_6-C_{18}, and more preferably C_6-C_{12}), monocycloheterocyclic, and bicycloheterocyclic rings;

D is phenyl or a five- or six-membered heterocyclic ring selected from the group consisting of pyrazolyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, thienyl, pyridyl, and pyrimidyl;

E is selected from the group consisting of phenyl, pyridinyl, and pyrimidinyl;

L is selected from the group consisting of -C(O)- and -$S(O)_2$-;

j is 0 or 1;

m is 0 or 1;

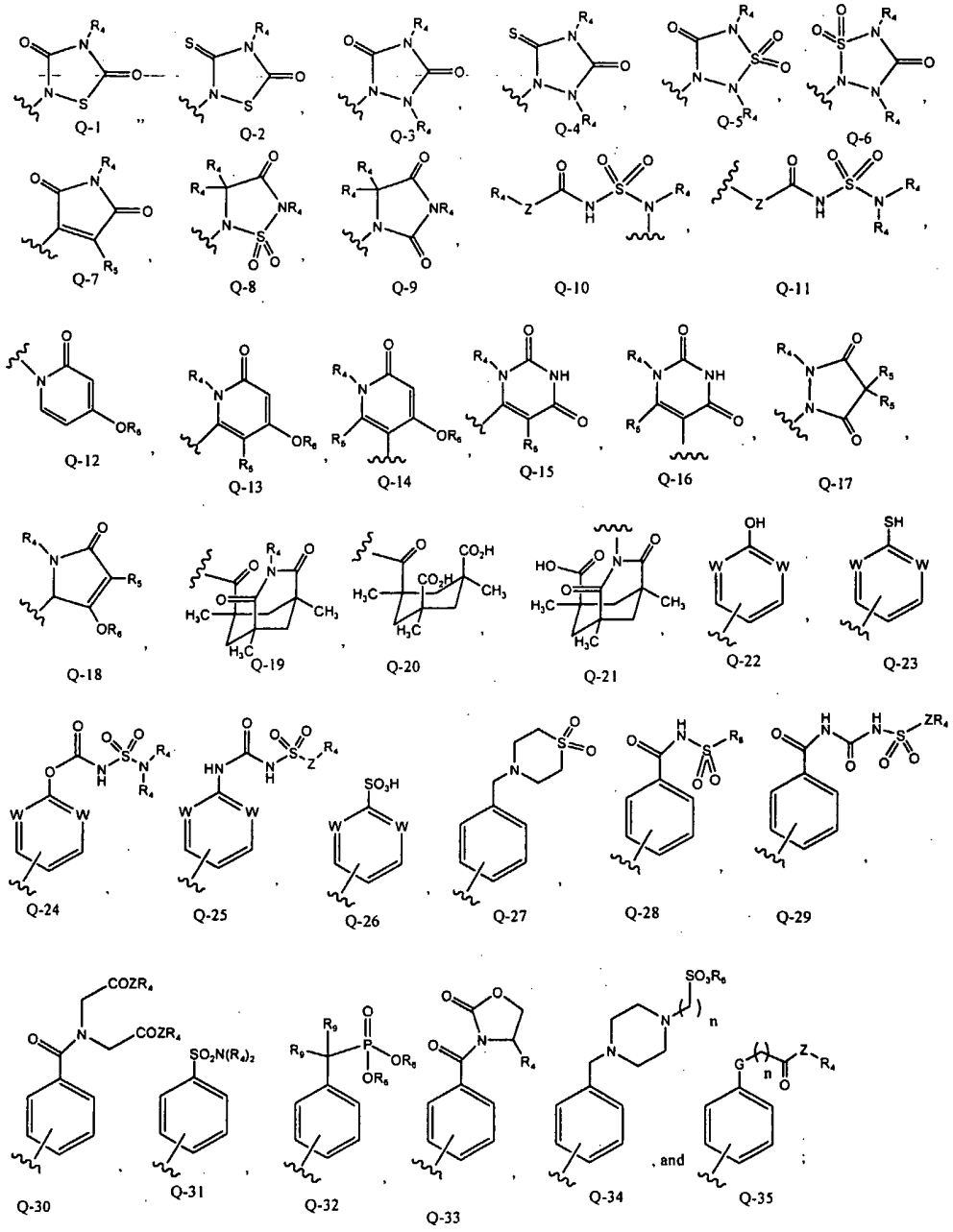
n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

t is 0 or 1;

Q is selected from the group consisting of


Q-1
Q-2
Q-3
Q-4
Q-5
Q-6
Q-7
Q-8
Q-9
Q-10
Q-11
Q-12
Q-13
Q-14
Q-15
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Q-32
Q-33
Q-34
, and
Q-35

each R_4 group is individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aminoalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkoxyalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aryls (preferably C_6-C_{18}, and more preferably C_6-C_{12}), aralkyls (preferably C_6-C_{18}, and more preferably C_6-C_{12} and preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclyls, and heterocyclylalkyls except when the R_4 substituent places a heteroatom on an *alpha*-carbon directly attached to a ring nitrogen on Q;

when two R_4 groups are bonded with the same atom, the two R_4 groups optionally form an alicyclic or heterocyclic 4-7 membered ring;

each R_5 is individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aryls (preferably C_6-C_{18}, and more preferably C_6-C_{12}), heterocyclyls, alkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arylaminos (preferably C_6-C_{18}, and more preferably C_6-C_{12}), cycloalkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclylaminos, hydroxys, alkoxys (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aryloxys (preferably C_6-C_{18}, and more preferably C_6-C_{12}), alkylthios (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arylthios (preferably C_6-C_{18}, and more preferably C_6-C_{12}), cyanos, halogens, perfluoroalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylcarbonyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), and nitros;

each R_6 is individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), allyls, and β-trimethylsilylethyl;

each R_8 is individually selected from the group consisting of alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), phenyl, naphthyl, aralkyls (wherein the aryl is preferably C_6-C_{18}, and more preferably C_6-C_{12}, and wherein alkyl is preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclyls, and heterocyclylalkyls (wherein the alkyl is preferably C_1-C_{18}, and more preferably C_1-C_{12});

each R_9 group is individually selected from the group consisting of -H, -F, and alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), wherein when two R_9 groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring;

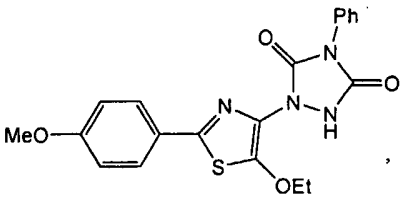
G is alkylene (preferably C_1-C_8, and more preferably C_1-C_4), $N(R_6)$, O;

each Z is individually selected from the group consisting of -O- and $-N(R_4)-$; and

each ring of formula (IA) optionally includes one or more of R_7, where R_7 is a noninterfering substituent individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aryls (preferably C_6-C_{18}, and more preferably C_6-C_{12}), heterocyclyls, alkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arylaminos (preferably C_6-C_{18}, and more preferably C_6-C_{12}), cycloalkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclylaminos, hydroxys, alkoxys (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aryloxys (preferably C_6-C_{18}, and more preferably C_6-C_{12}), alkylthios (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arthylthios, cyanos, halogens, nitrilos, nitros, alkylsulfinyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylsulfonyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aminosulfonyls, and perfluoroalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}).

In one preferred embodiment, the compound has the structure of formula (I) except that:

when Q is Q-3 or Q-4, then the compound of formula (I) is not



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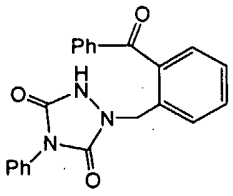
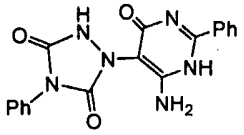


, or



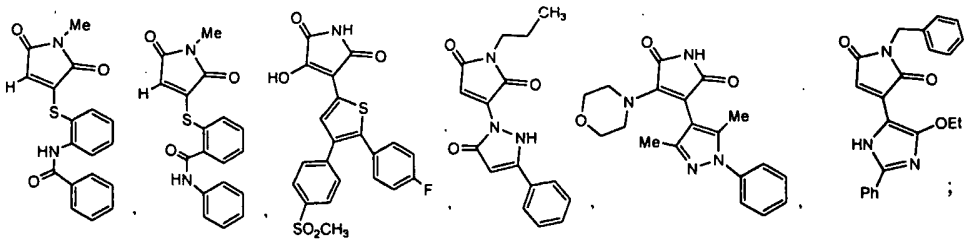
;

when Q is Q-7, q is 0, and R_5 and D are phenyl, then A is not phenyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, or imidazolyl;

when Q is Q-7, R_5 is -OH, Y is -O-, -S-, or -CO-, m is 0, n is 0, p is 0, and A is phenyl, pyridyl, or thiazolyl, then D is not thienyl, thiazolyl, or phenyl;

when Q is Q-7, R_5 is -OH, m is 0, n is 0, p is 0, t is 0, and A is phenyl, pyridyl, or thiazolyl, then D is not thienyl, thiazolyl, or phenyl;

when Q is Q-7, then the compound of formula (I) is not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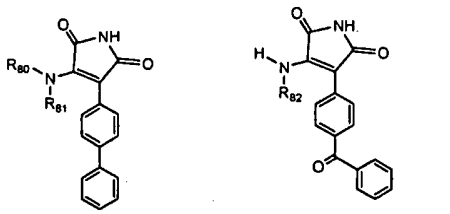
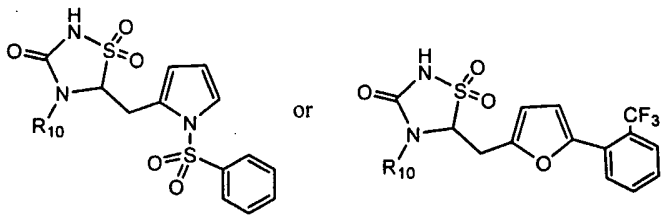


R80 is H, Me
R81 is substituted phenyl

R82 is substituted phenyl

when Q is Q-8, then Y is not $-CH_2O-$;

when Q is Q-8, the compound of formula (I) is not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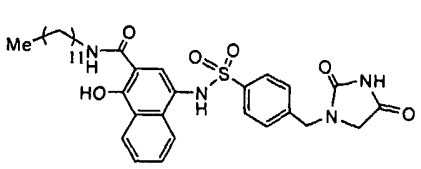
R_{10} = alkyl, aryl, arylalkoxyalkyl, or arylalkyls

when Q is Q-9, then the compound of formula (I) is not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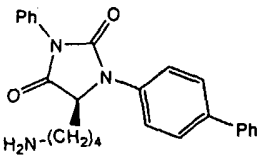
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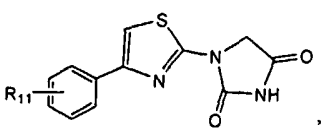
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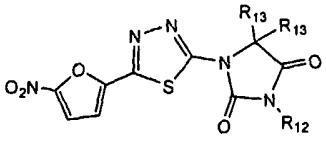
R11 = H, alkyl, alkoxy, nitro, halogen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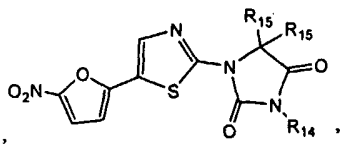
R12, R13 = H, alkyl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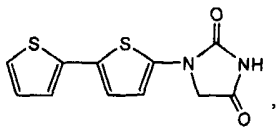
R14= H, alkyl, allyl, propargyl
R15 = H, alkyl,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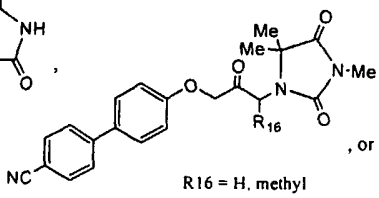
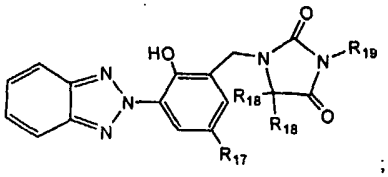
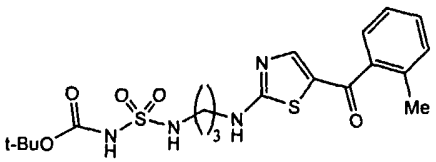

, or

R16 = H, methyl

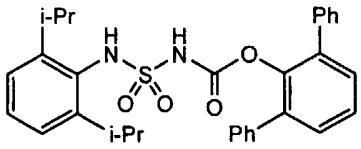

;

R17, R18 = alkyl
R19 = H, alkyl

when Q is Q-10, t is 0, and E is phenyl, then any R_7 on E is not an *o*-alkoxy;
when Q is Q-10, then the compound of formula (I) is not


;

when Q is Q-11, t is 0, and E is phenyl, then any R_7 on E is not an *o*-alkoxy;
when Q is Q-11, then the compound of formula (I) is not



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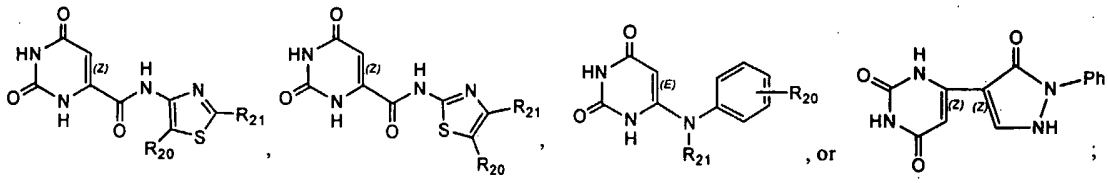
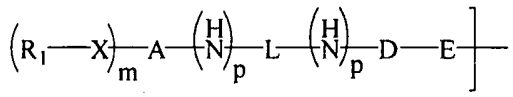
when Q is Q-15, then the compound of formula (I) is not

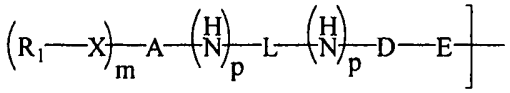


when Q is Q-16 and Y is -NH-, then



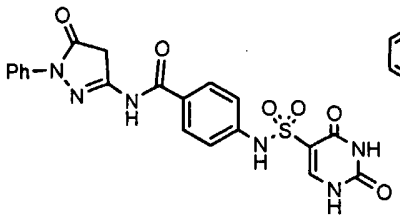
of formula (I) is not biphenyl;

when Q is Q-16 and Y is -S-, then



of formula (I) is not phenylsulfonylaminophenyl or phenylcarbonylaminophenyl;

when Q is Q-16 and Y is $-SO_2NH-$, then the compound of formula (I) is not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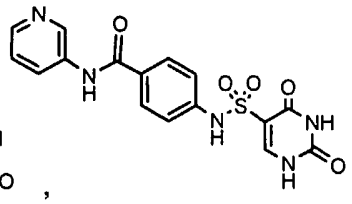
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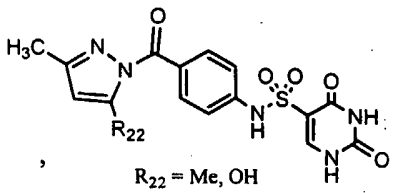
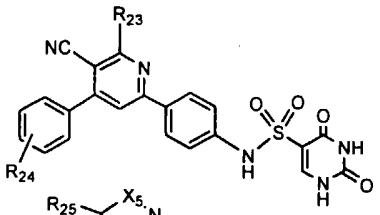

R_{22} = Me, OH ,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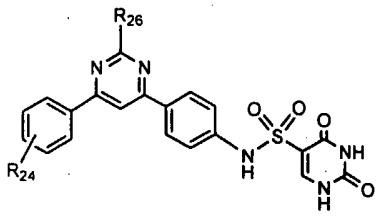
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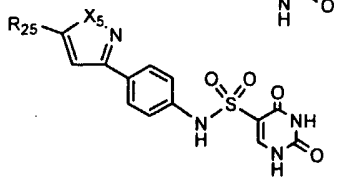
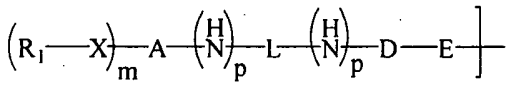

;

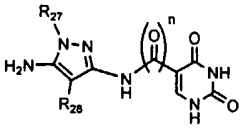
when Q is Q-16 and Y is -CONH-, then

R_{23} = OH, SH, NH2
R_{24} = hydrogen or one or more methoxy, hydroxy, fluoro, chloro, nitro, dimethylamino, or furanyl
R_{25} = substituted phenyl, furanyl
R_{26} = OH or Cl
X_5 = O, NH;



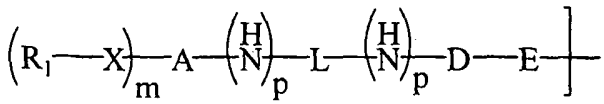
of formula (I) is not imidazophenyl;

when Q is Q-16 and Y is -CONH-, then the compound of formula (I) is not


;

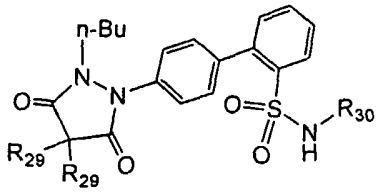
R_{27} = substituted phenyl, pyridylcarbonyl
R_{28} = CN, methoxycarbonyl
n = 0 or 1

when Q is Q-16 and t is 0, then



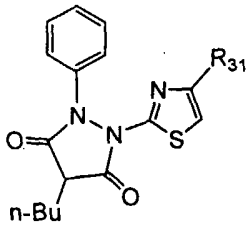
of formula (I) is not phenylcarbonylphenyl, pyrimidophenyl, phenylpyrimidyl, pyrimidyl, or N-pyrolyl;

when Q is Q-17, then the compound of formula (I) is not



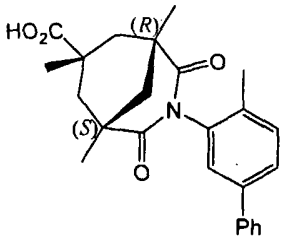
R_{29} = alkyl
R_{30} = H, t-Bu, benzoyl

or



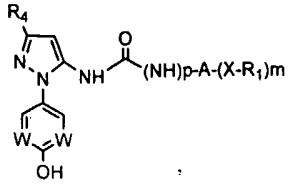
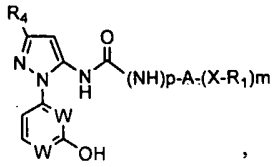
R_{31} = substituted phenyl ;

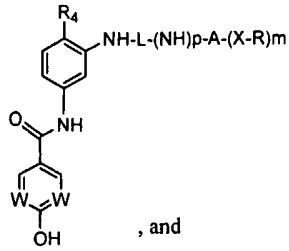
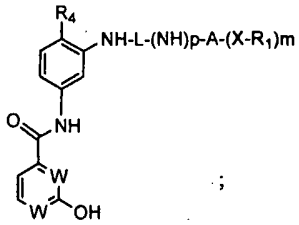
when Q is Q-21, then the compound of formula (I) is not



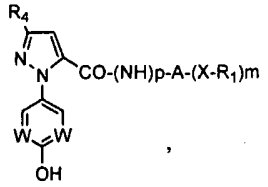
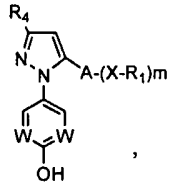
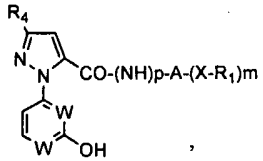
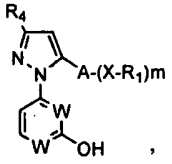
;

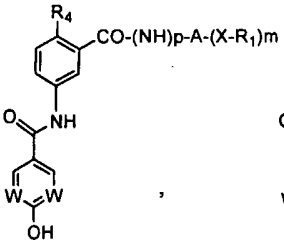
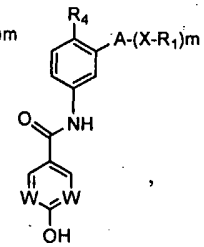
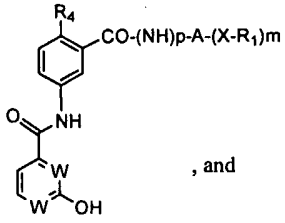
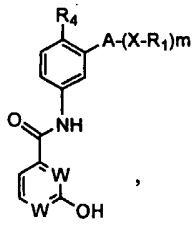
when Q is Q-22, then the compound of formula (I) is selected from the group consisting of

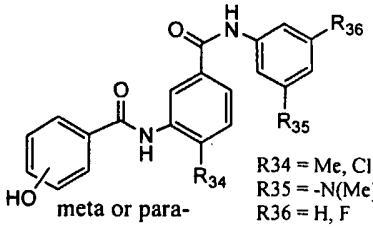



when Q is Q-22 and q is 0, then the compound of formula (I) is selected from the group consisting of

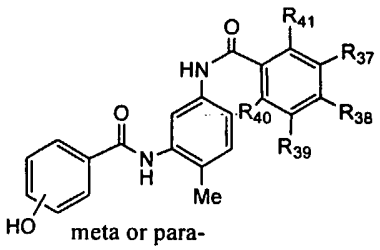
but excluding



meta or para-

R34 = Me, Cl
R35 = -N(Me)2, morpholino
R36 = H, F

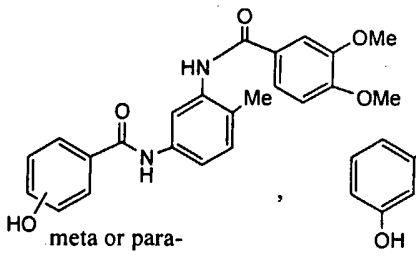
,



meta or para-

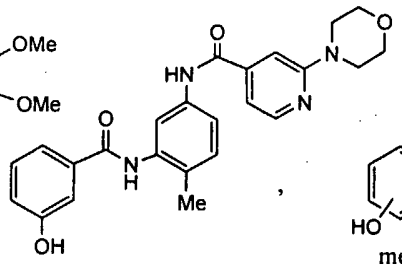
R37 = N(Me)2, morpholino, OMe, OH, H
R38 = H, CN, OMe, OH, benzyloxy, phenyl, nitro
R39 = H, OH
R40 = H, F
R41 = H, Cl

,



meta or para-

,



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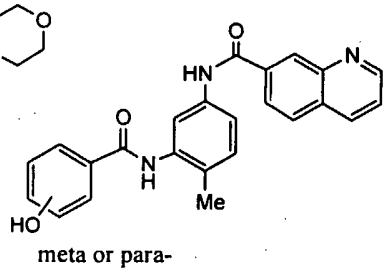
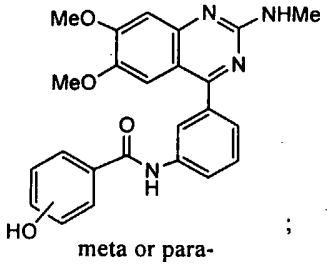


meta or para-

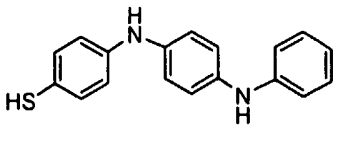
, and



meta or para-

;

when Q is Q-23, then the compound of formula (I) is not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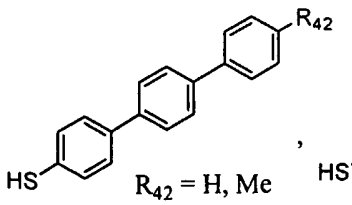
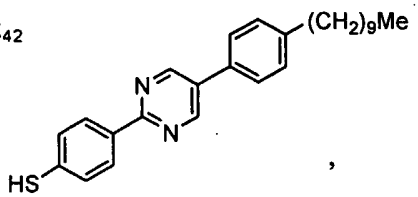

R_{42} = H, Me ,

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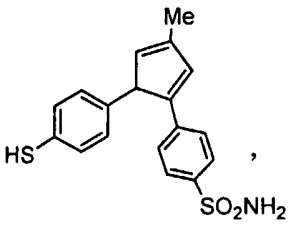
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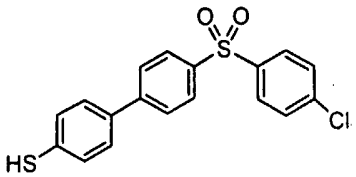
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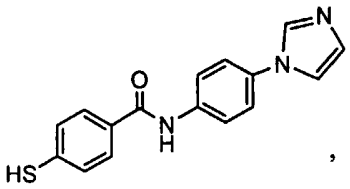
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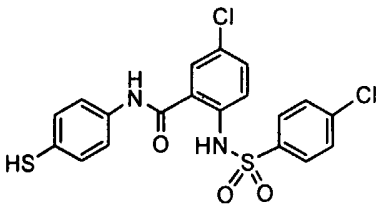
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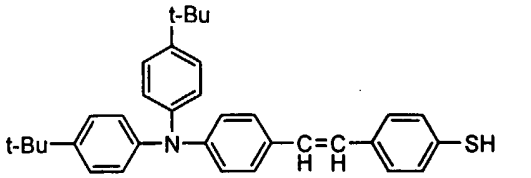
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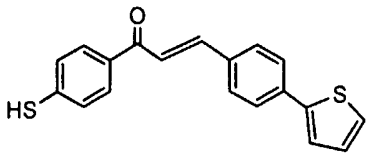
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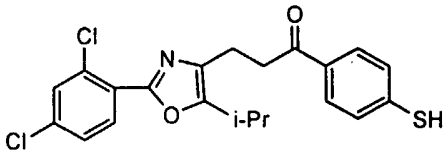
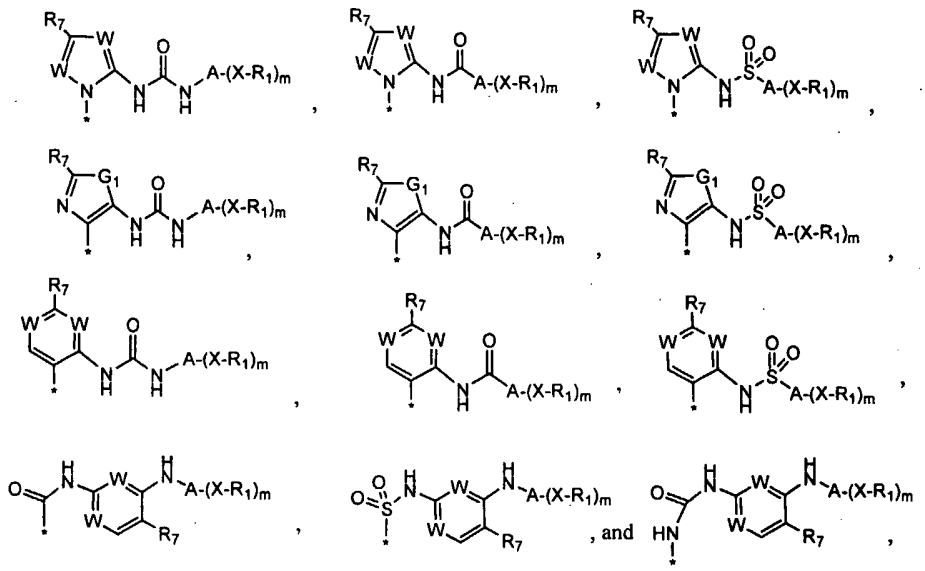

;

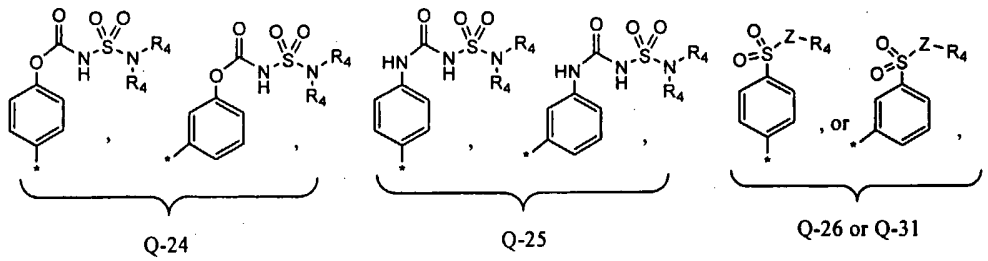
when Q is Q-24, Q-25, Q-26, or Q-31, then the compound of formula (I) is selected from the group consisting of



wherein each W is individually selected from the group consisting of -CH- and -N-;

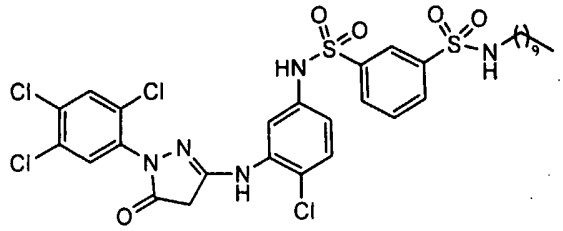
each G_1 is individually selected from the group consisting of -O-, -S-, and -N(R_4)-; and

* denotes the point of attachment to Q-24, Q-25, Q-26, or Q-31 as follows:



wherein each Z is individually selected from the group consisting of -O- and -N(R_4)-;

when Q is Q-31, then the compound of formula (I) is not



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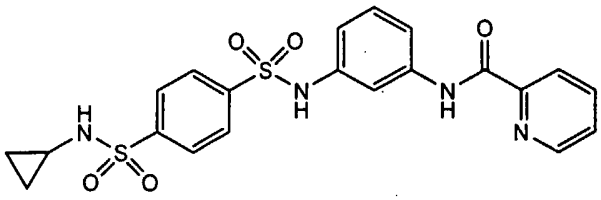
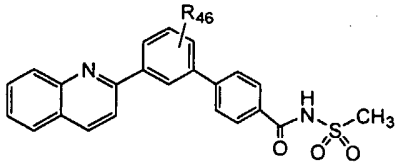


;

when Q is Q-28 or Q-29 and t is 0, then the compound of formula (I) is not



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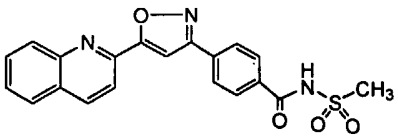
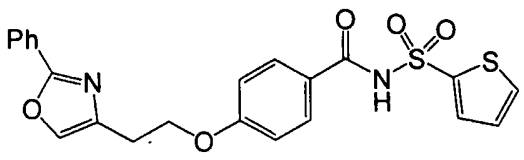


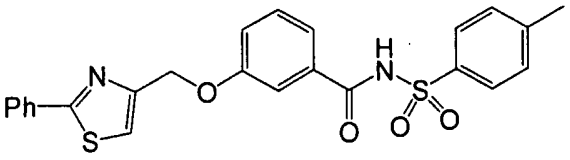
;

R_{46} = hydrogen, hydroxyalkyl, alkoxyalkyloxy, hydroxy

when Q is Q-28 or Q-29 and Y is an ether linkage, then the compound of formula (I) is not

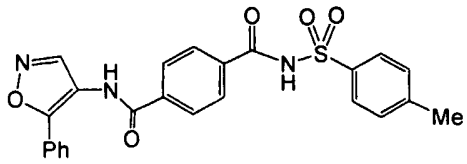


or



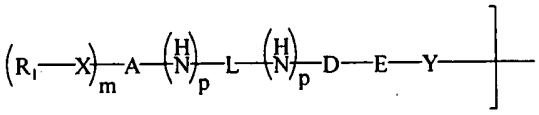
;

when Q is Q-28 or Q-29 and Y is -CONH-, then the compound of formula (I) is not



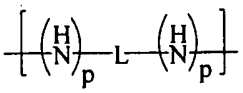
;

when Q is Q-32, then



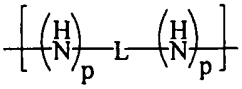
is not biphenyl, benzoxazolylphenyl, pyridylphenyl or bipyridyl;

when Q is Q-32, Y is -CONH-, q is 0, m is 0, and

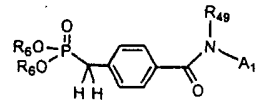


of formula (I) is -CONH-, then A is not phenyl;

when Q is Q-32, q is 0, m is 0, and



is -CONH-, then the compound of formula (I) is not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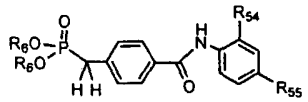
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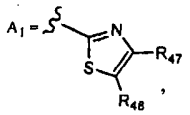
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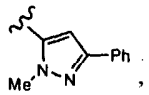
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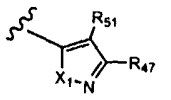
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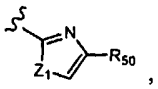

,

R_{47} = alkyl, substituted phenyl, thienyl, phenacetyl naphthyl
R_{48} = H, alkyl, Br, substituted phenyl, benzoyl, phenylsulfonyl
R_{49} = H, alkyl, phenyl
R_{50} = substituted phenyl

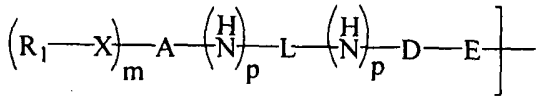
R_{54} = benzoyl, phenylalkylaminocarbonyl, substituted phenylaminocarbonyl H, Br
R_{55} = Cl, Br, SPh, benzoyl, phenylsulfonyl
R_{51} = H, phenylsulfonyl, phenyl, benzyl
R_6 = Et, i-Pr
R_{53} = substituted phenyl, substituted benzyl
X_1 = O, N-Ph, N-alkyl, N-carbamoyl
Z_1 = N(R50), O

when Q is Q-32, D is thiazolyl, q is 0, t is 0, p is 0, n is 0, and m is 0, then A is not phenyl or 2-pyridone;

when Q is Q-32, D is oxazolyl or isoxazolyl, q is 0, t is 0, p is 0, n is 0, and m is 0, then A is not phenyl;

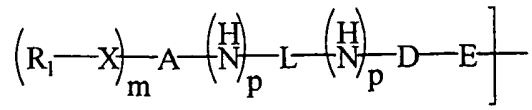
when Q is Q-32, D is pyrimidyl q is 0, t is 0, p is 0, n is 0, and m is 0, then A is not phenyl;

when Q is Q-32 and Y is an ether linkage, then



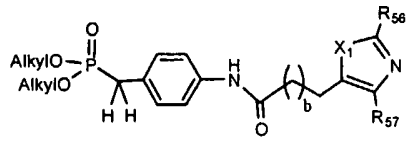
of formula (I) is not biphenyl or phenyloxazolyl;

when Q is Q-32 and Y is -CH=CH-, then

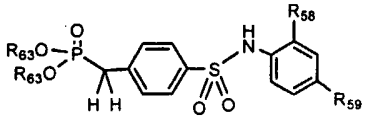


of formula (I) is not phenylaminophenyl;

when Q is Q-32, then the compound of formula (I) is not

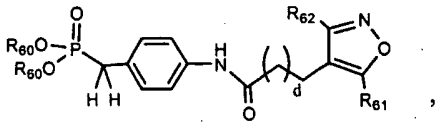


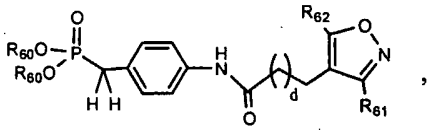
b = 0-1
X_1 = O, S
R56 = H, CF3, Cl, imidazolyl, amino, morpholino, phenylthio, cycloalkyl, benzyl, phenyl, phenoxy, thienyl, substituted alkyl, pyridylthio, pyrimidyl, benzylamino, N-benimidazolyl, pyridylcarbonylamino, ureido,N- thiourea, substituted alkanoylamino, phenylsulfonyl, substituted benzoyl, phenylalkenoyl, furanoyl, thienoyl, pyridinoyl,
R57 = substituted phenyl, substituted biphenyl

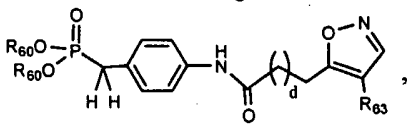


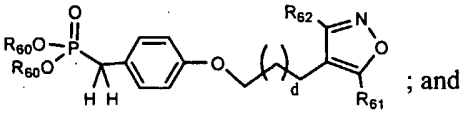
, or

R58 = substituted alkylaminocarbonyl, phenylaminocarbonyl
R59 = H, Cl





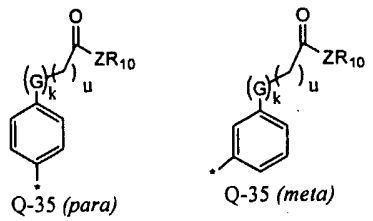




; and

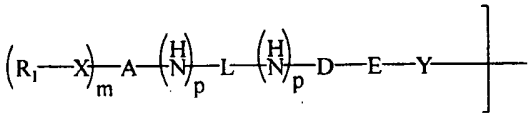
d = 0-2
R60 = H, alkyl
R61 = substituted phenyl, thienyl, Br
R62= H, alkyl, phenyl
R63 = substituted phenyl

when Q is Q-35 as shown

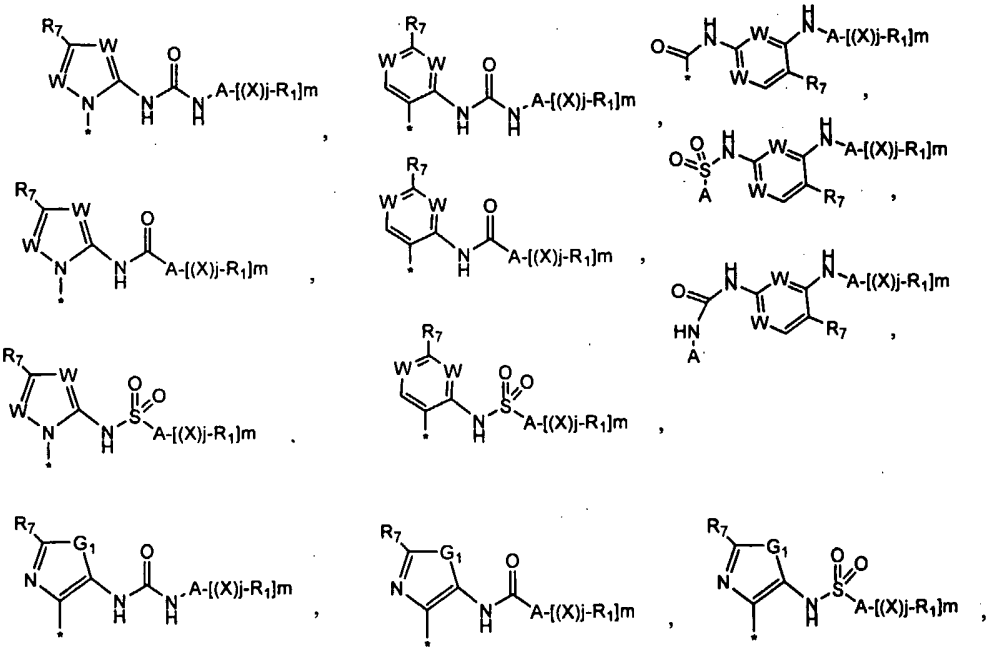


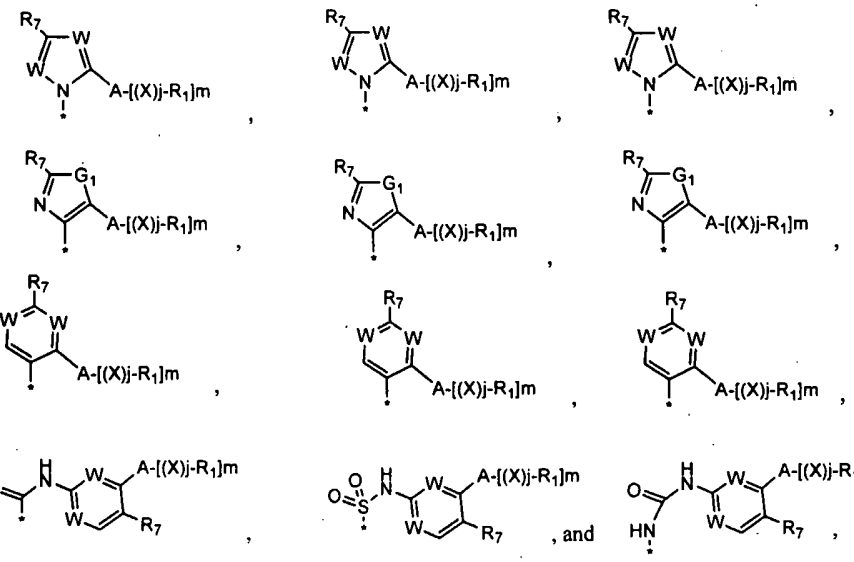
Q-35 *(para)* Q-35 *(meta)*

wherein G is selected from the group consisting of -O-, -S-, -NR_4-, and -CH_2-, k is 0 or 1, and u is 1, 2, 3, or 4, then

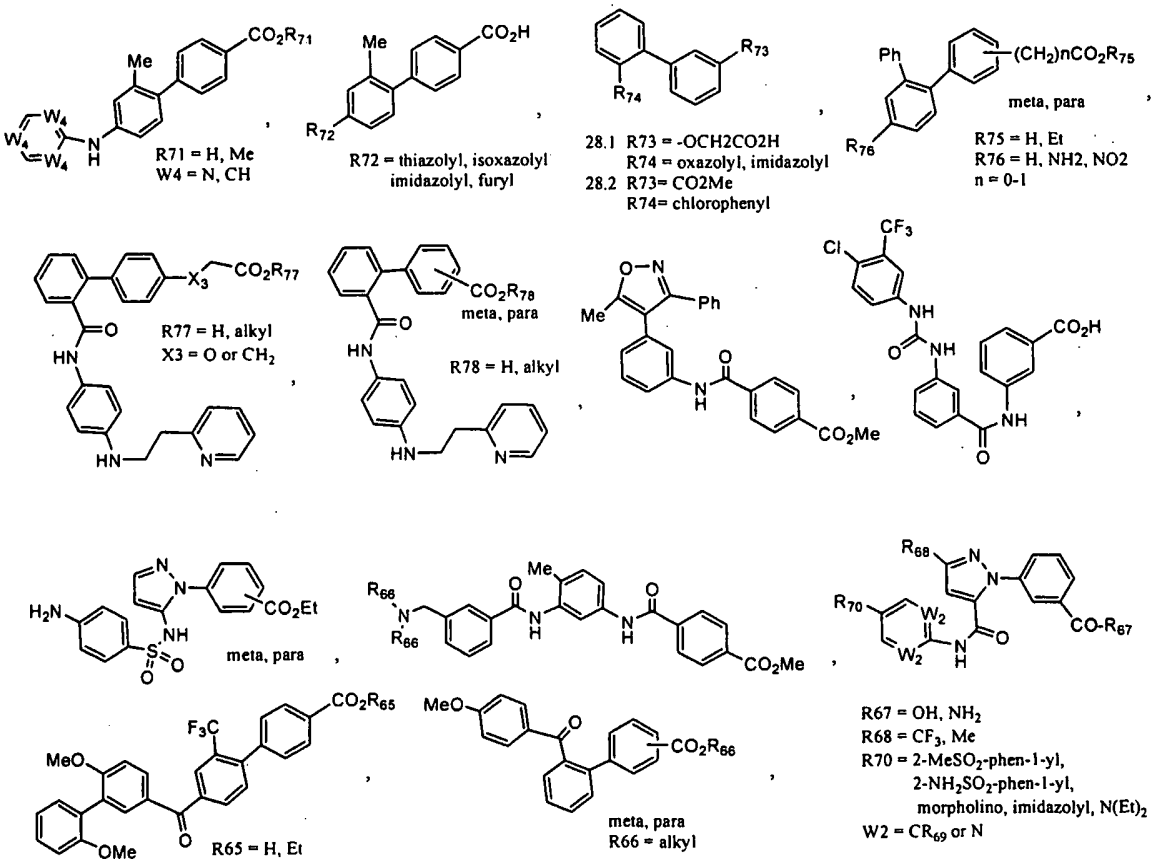


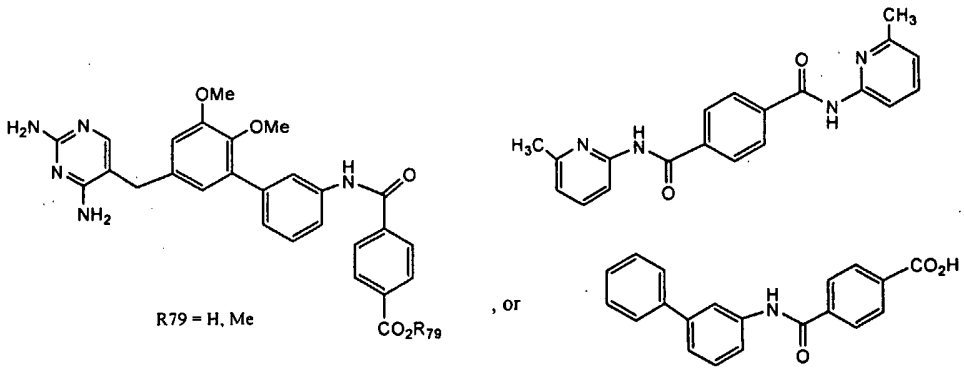
is selected from the group consisting of



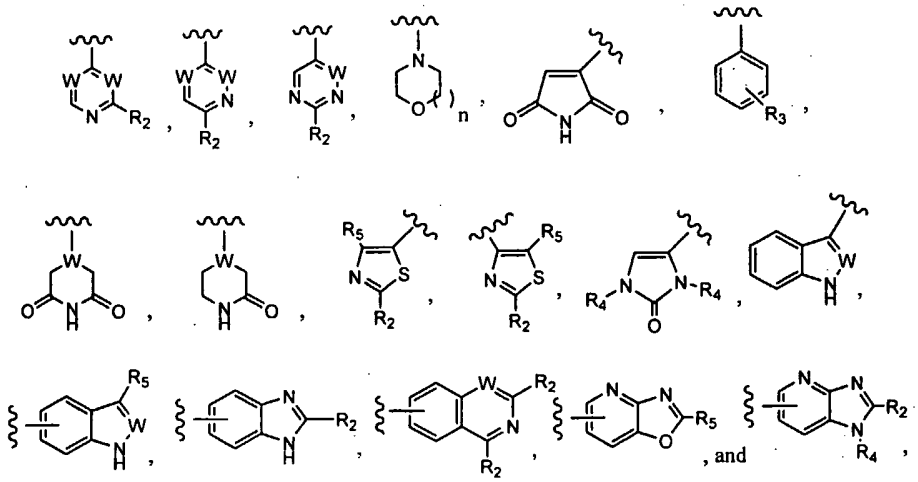


except that the compound of formula (I) is not





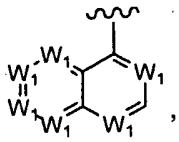
Even more preferably, R_1 as discussed above is selected from the group consisting of 6-5 fused heteroaryls, 6-5 fused heterocyclyls, 5-6 fused heteroaryls, and 5-6 fused heterocyclyls, and even more preferably, R_1 is selected from the group consisting of



each R_2 is individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aminos, alkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arylaminos (preferably C_6-C_{18}, and more preferably C_6-C_{12}), cycloalkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclylaminos, halogens, alkoxys (preferably C_1-C_{18}, and more preferably C_1-C_{12}), and hydroxys; and

each R_3 is individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arylaminos (preferably C_6-C_{18}, and more preferably C_6-C_{12}), cycloalkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclylaminos, alkoxys (preferably C_1-C_{18}, and more preferably C_1-C_{12}), hydroxys, cyanos, halogens, perfluoroalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylsulfinyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylsulfonyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), R_4NHSO_2-, and -$NHSO_2R_4$.

Finally, in another preferred embodiment, wherein A is selected from the group consisting of aromatic, monocycloheterocyclic, and bicycloheterocyclic rings; and most preferably phenyl, naphthyl, pyridyl, pyrimidyl, thienyl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, benzothienyl, pyrazolylpyrimidinyl, imidazopyrimidinyl, purinyl, and



where each W_1 is individually selected from the group consisting of -CH- and -N-.

An additional class of compounds useful in the invention have the formula

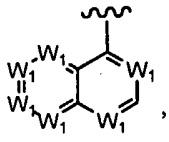
$$A\text{-}T\text{-}(L)_n\text{-}(NH)_p\text{-}D\text{-}(E)_q\text{-}(Y)_t\text{-}Q$$

(IB)

wherein:

Y is selected from the group consisting of -O-, -S-, -NR_6-, -NR_6SO_2-, -NR_6CO-, alkynyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkenyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylenes (preferably C_1-C_{18}, and more preferably C_1-C_{12}), -$O(CH_2)_h$-, and -$NR_6(CH_2)_h$-, where each h is individually selected from the group consisting of 1, 2, 3, or 4, and where for each of alkylenes (preferably C_1-C_{18}, and more preferably C_1-C_{12}), -$O(CH_2)_h$-, and -$NR_6(CH_2)_h$-, one of the methylene groups present therein may be optionally double-bonded to a side-chain oxo group except that where -$O(CH_2)_h$- the introduction of the side-chain oxo group does not form an ester moiety;

A is selected from the group consisting of aromatic (preferably C_6-C_{18}, and more preferably C_6-C_{12}), monocycloheterocyclic, and bicycloheterocyclic rings; and most preferably phenyl, naphthyl, pyridyl, pyrimidyl, thienyl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, benzothienyl, pyrazolylpyrimidinyl, imidazopyrimidinyl, purinyl, and



where each W1 is individually selected form the group consisting of –CH- and –N-.

D is phenyl or a five- or six-membered heterocyclic ring selected from the group consisting of pyrazolyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, furyl,

oxadiazolyl, thiadiazolyl, thienyl, pyridyl, and pyrimidyl;

E is selected from the group consisting of phenyl, pyridinyl, and pyrimidinyl;

L is selected from the group consisting of -C(O)- and -$S(O)_2$-;

T is NR_6, O, alkylene (preferably C_1-C_{12}, more preferably C_1-C_4), -$O(CH_2)_h$-, or -$NR_6(CH_2)_h$-, where each h is individually selected from the group consisting of 1, 2, 3, or 4, or T is absent wherein A is directly bonded to $-(L)_n(NH)_p$ -D-$(E)_q$ -$(Y)_t$ -Q;

n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

t is 0 or 1;

v is 1,2, or 3;

x is 1 or 2;

Q is selected from the group consisting of formulae Q_{36} – Q_{59}, inclusive;

each R_4 group is individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aminoalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkoxyalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aryls (preferably C_6-C_{18}, and more preferably C_6-C_{12}), aralkyls (preferably C_6-C_{18}, and more preferably C_6-C_{12} and preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclyls, and heterocyclylalkyls except when the R_4 substituent places a heteroatom on an *alpha*-carbon directly attached to a ring nitrogen on Q;

when two R_4 groups are bonded with the same atom, the two R_4 groups optionally form an alicyclic or heterocyclic 4-7 membered ring;

each R_6 is individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), allyls, and B-trimethylsilylethyl;

each R_8 is individually selected from the group consisting of alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), phenyl, naphthyl, aralkyls (wherein the aryl is preferably C_6-C_{18}, and more preferably C_6-C_{12}), wherein alkyl is preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclyls, and heterocyclylalkyls (wherein the alkyl is preferably C_1-C_{18}, and more preferably C_1-C_{12});

each R_9 group is individually selected from the group consisting of -H, -F, and alkyls

(preferably C_1-C_{18}, and more preferably C_1-C_{12}), wherein when two R_9 groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring;

each $R_{9'}$ group is individually selected from the group consisting of -F, and alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), wherein when two $R_{9'}$ groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring;

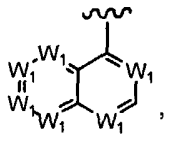
each R_{10} is alkyl or perfluoroalkyl;

G is alkylene (preferably C_1-C_8, and more preferably C_1-C_4), $N(R_6)$, O;

each Z is individually selected from the group consisting of -O- and $-N(R_4)-$; and each ring of formula (I) optionally includes one or more of $R_{7'}$, where $R_{7'}$ is a substituent individually selected from the group consisting of -H, alkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aryls (preferably C_6-C_{18}, and more preferably C_6-C_{12}), heterocyclyls, alkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arylaminos (preferably C_6-C_{18}, and more preferably C_6-C_{12}), cycloalkylaminos (preferably C_1-C_{18}, and more preferably C_1-C_{12}), heterocyclylaminos, hydroxys, alkoxys (preferably C_1-C_{18}, and more preferably C_1-C_{12}), perfluoroalkoxys (preferably C_1-C_8, more preferably C_1-C_4), aryloxys (preferably C_6-C_{18}, and more preferably C_6-C_{12}), alkylthios (preferably C_1-C_{18}, and more preferably C_1-C_{12}), arthylthios, cyanos, halogens, nitrilos, nitros, alkylsulfinyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), alkylsulfonyls (preferably C_1-C_{18}, and more preferably C_1-C_{12}), aminosulfonyls, perfluoroalkyls (preferably C_1-C_{18}, and more preferably C_1-C_{12});

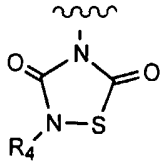
aminooxaloylamino; alkylaminooxaloylamino; dialkylaminooxaloylamino; morpholinooxaloylamino; piperazinooxaloylamino; alkoxycarbonylamino; heterocyclyloxycarbonylamino; heterocyclylalkyloxycarbonylamino; heterocyclylcarbonylamino; heterocyclylalkylcarbonylamino; aminoalkyloxycarbonylamino; alkylaminoalkyloxycarbonylamino; or dialkylaminoalkyloxycarbonylamino.

In a preferred embodiment, A as described above is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrimidyl, thienyl, furyl, pyrrolyl, pyrazolyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, imidazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, benzothienyl, pyrazolylpyrimidinyl, imidazopyrimidinyl, purinyl, and

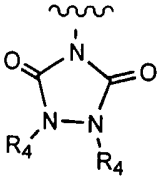


where each W_1 is individually selected from the group consisting of -CH- and -N-.

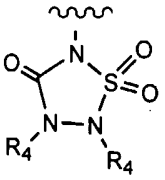
Q groups Q-36 through Q-59 are set forth below. In an additionally preferred embodiment, Q is taken from Q-37, Q-39, Q-41, Q-42, Q-43, Q-44, Q-47, Q-48, Q-54, and Q-57; in a more preferred embodiment, Q is taken from Q-39, Q-41, Q-42, Q-43, Q-44, Q-47, Q-48, and Q-54.



Q-36



Q-37



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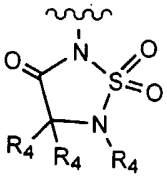

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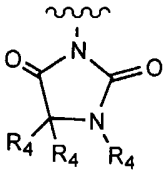

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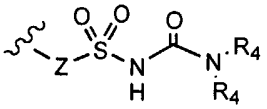

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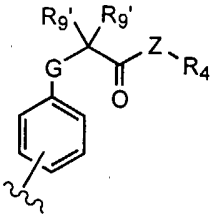

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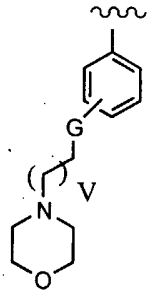

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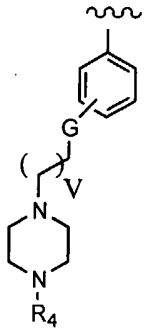

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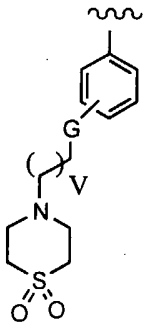
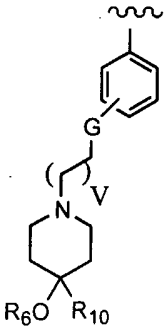


Q-45



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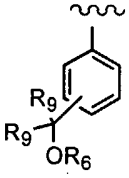

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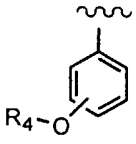

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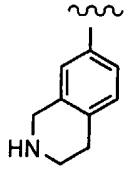

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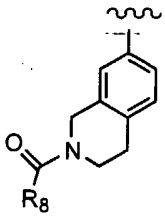
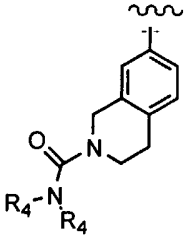


Q-50



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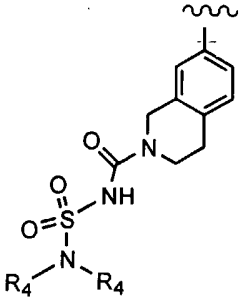

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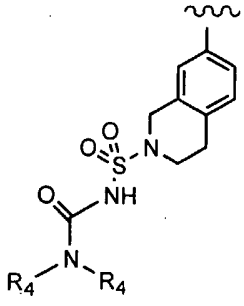

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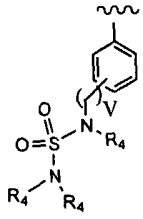

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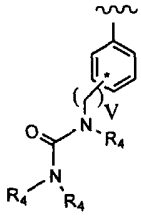
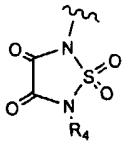
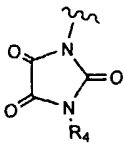


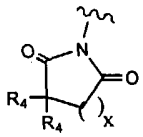
Q-55



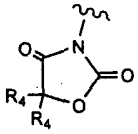
Q-56



Q-57



Q-58



Q-59

With respect to the method of using the novel compounds, the activation state of a kinase is determined by the interaction of switch control ligands and complemental switch control pockets. One conformation of the kinase may result from the switch control ligand's interaction with a particular switch control pocket while another conformation may result from the ligand's interaction with a different switch control pocket. Generally interaction of the ligand with one pocket, such as the "on" pocket, results in the kinase assuming an active conformation wherein the kinase is biologically active. Similarly, an inactive conformation (wherein the kinase is not biologically active) is assumed when the ligand interacts with another of the switch control pockets, such as the "off" pocket. The switch control pocket can be selected from the group consisting of simple, composite and combined switch control pockets. Interaction between the switch control ligand and the switch control pockets is dynamic and therefore, the ligand is not always interacting with a switch control pocket. In some instances, the ligand is not in a switch control pocket (such as occurs when the protein is changing from an active conformation to an inactive conformation). In other instances, such as when the ligand is interacting with the environment surrounding the protein in order to determine with which switch control pocket to interact, the ligand is not in a switch control pocket. Interaction of the ligand with particular switch control pockets is controlled in part by the charge status of the amino acid residues of the switch control ligand. When the ligand is in a neutral charge state, it interacts with one of the switch control pockets and when it is in a charged state, it interacts with the other of the switch control pockets. For example, the switch control ligand may have a plurality of OH groups and be in a neutral charge state. This neutral charge state results in a ligand that is more likely to interact with one of the switch control pockets through hydrogen boding between the OH groups and selected residues of the pocket, thereby resulting in whichever protein conformation results from that interaction. However, if the OH groups of the switch control ligand become charged through phosphorylation or some other means, the propensity of the ligand to interact with the other of the switch control pockets will increase and the ligand will interact with this other switch control pocket through complementary covalent binding between the negatively or positively charged residues of the pocket and ligand. This will result in the protein assuming the opposite conformation assumed when the ligand was in a neutral charge state and interacting with the other switch control pocket.

Of course, the conformation of the protein determines the activation state of the protein

and can therefore play a role in protein-related diseases, processes, and conditions. For example, if a metabolic process requires a biologically active protein but the protein's switch control ligand remains in the switch control pocket (i.e. the "off" pocket) that results in a biologically inactive protein, that metabolic process cannot occur at a normal rate. Similarly, if a disease is exacerbated by a biologically active protein and the protein's switch control ligand remains in the switch control pocket (i.e. the "on" pocket) that results in the biologically active protein conformation, the disease condition will be worsened. Accordingly, as demonstrated by the present invention, selective modulation of the switch control pocket and switch control ligand by the selective administration of a molecule will play an important role in the treatment and control of protein-related diseases, processes, and conditions.

One aspect of the invention provides a method of modulating the activation state of a kinase, preferably p38 α-kinase and including both the consensus wild type sequence and disease polymorphs thereof. The activation state is generally selected from an upregulated or downregulated state. The method generally comprises the step of contacting the kinase with a molecule having the general formula (I). When such contact occurs, the molecule will bind to a particular switch control pocket and the switch control ligand will have a greater propensity to interact with the other of the switch control pockets (i.e., the unoccupied one) and a lesser propensity to interact with the occupied switch control pocket. As a result, the protein will have a greater propensity to assume either an active or inactive conformation (and consequenctly be upregulated or downregulated), depending upon which of the switch control pockets is occupied by the molecule. Thus, contacting the kinase with a molecule modulates that protein's activation state. The molecule can act as an antagonist or an agonist of either switch control pocket. The contact between the molecule and the kinase preferably occurs at a region of a switch control pocket of the kinase and more preferably in an interlobe oxyanion pocket of the kinase. In some instances, the contact between the molecule and the pocket also results in the alteration of the conformation of other adjacent sites and pockets, such as an ATP active site. Such an alteration can also effect regulation and modulation of the active state of the protein. Preferably, the region of the switch control pocket of the kinase comprises an amino acid residue sequence operable for binding to the Formula I molecule. Such binding can occur between the molecule and a specific region of the switch control pocket with preferred regions including the α-C helix, the α-D helix, the catalytic loop, the activation loop, and the C-terminal residues or C-lobe residues

(all residues located downstream (toward the C-end) from the Activation loop), the glycine rich loop, and combinations thereof. When the binding region is the α-C helix, one preferred binding sequence in this helix is the sequence IIHXKRXXREXXLLXXM, (SEQ ID NO. 2). When the binding region is the catalytic loop, one preferred binding sequence in this loop is DIIHRD (SEQ ID NO. 3). When the binding region is the activation loop, one preferred binding sequence in this loop is a sequence selected from the group consisting of DFGLARHTDD (SEQ ID NO.4), EMTGYVATRWYR (SEQ ID NO. 5), and combinations thereof. When the binding region is in the C-lobe residues, one preferred binding sequence is WMHY (SEQ ID NO. 6). When the binding region is in the glycine rich loop one preferred binding sequence is YGSV (SEQ ID NO. 7). When a biologically inactive protein conformation is desired, molecules which interact with the switch control pocket that normally results in a biologically active protein conformation (when interacting with the switch control ligand) will be selected. Similarly, when a biologically active protein conformation is desired, molecules which interact with the switch control pocket that normally results in a biologically inactive protein conformation (when interacting with the switch control ligand) will be selected. Thus, the propensity of the protein to assume a desired conformation will be modulated by administration of the molecule. In preferred forms, the molecule will be administered to an individual undergoing treatment for a condition selected from the group consisting of human inflammation, rheumatoid arthritis, rheumatoid spondylitis, ostero-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof. In such forms, it will be desired to select molecules that interact with the switch control pocket that generally leads to a biologically active protein conformation so that the protein will have the propensity to assume the biologically inactive form and thereby alleviate the condition. It is contemplated that the molecules of the present invention will be administerable in any conventional form including oral, parenteral, inhalation, and subcutaneous. It is preferred for the administration to be in the oral form. Preferred molecules include the preferred compounds of formula (I), as discussed above.

Another aspect of the present invention provides a method of treating an inflammatory condition of an individual comprising the step of administering a molecule having the general formula (I) to the individual. Such conditions are often the result of an overproduction of the biologically active form of a protein, including kinases. The administering step generally includes the step of causing said molecule to contact a kinase involved with the inflammatory process, preferably p38 α-kinase. When the contact is between the molecule and a kinase, the contact preferably occurs in an interlobe oxyanion pocket of the kinase that includes an amino acid residue sequence operable for binding to the Formula I molecule. Preferred binding regions of the interlobe oxyanion pocket include the α-C helix region, the α-D helix region, the catalytic loop, the activation loop, the C-terminal residues, the glycine rich loop residues, and combinations thereof. When the binding region is the α-C helix, one preferred binding sequence in this helix is the sequence IIHXKRXXREXXLLXXM, (SEQ ID NO. 2). When the binding region is the catalytic loop, one preferred binding sequence in this loop is DIIHRD (SEQ ID NO. 3). When the binding region is the activation loop, one preferred binding sequence in this loop is a sequence selected from the group consisting of DFGLARHTDD (SEQ ID NO.4), EMTGYVATRWYR (SEQ ID NO. 5), and combinations thereof. Such a method permits treatment of the condition by virtue of the modulation of the activation state of a kinase by contacting the kinase with a molecule that associates with the switch control pocket that normally leads to a biologically active form of the kinase when interacting with the switch control ligand. Because the ligand cannot easily interact with the switch control pocket associated with or occupied by the molecule, the ligand tends to interact with the switch control pocket leading to the biologically inactive form of the protein, with the attendant result of a decrease in the amount of biologically active protein. Preferably, the inflammatory condition is selected from the group consisting of human inflammation, rheumatoid arthritis, rheumatoid spondylitis, ostero-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof. As with the other methods of the invention, the molecules may be administered in any conventional form, with any convention excipients or ingredients. However, it is preferred to administer the molecule in an oral dosage form.

Preferred molecules are again selected from the group consisting of the preferred formula (I) compounds discussed above.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of a naturally occurring mammalian protein in accordance with the invention including "on" and "off" switch control pockets 102 and 104, respectively, a transiently modifiable switch control ligand 106, and an active ATP site 108;

Fig. 2 is a schematic representation of the protein of Fig. 1, wherein the switch control ligand 106 is illustrated in a binding relationship with the off switch control pocket 104, thereby causing the protein to assume a first biologically downregulated conformation;

Fig. 3 is a view similar to that of Fig. 1, but illustrating the switch control ligand 106 in its charged-modified condition wherein the OH groups 110 of certain amino acid residues have been phosphorylated;

Fig. 4 is a view similar to that of Fig. 2, but depicting the protein wherein the phosphorylated switch control ligand 106 is in a binding relationship with the on switch control pocket 102, thereby causing the protein to assume a second biologically-active conformation different than the first conformation of Fig. 2;

Fig. 4a is an enlarged schematic view illustrating a representative binding between the phosphorylated residues of the switch control ligand 106, and complemental residues Z+ from the on switch control pocket 102;

Fig. 5 is a view similar to that of Fig. 1, but illustrating in schematic form possible small molecule compounds 116 and 118 in a binding relationship with the off and on switch control pockets 104 and 102, respectively;

Fig. 6 is a schematic view of the protein in a situation where a composite switch control pocket 120 is formed with portions of the switch control ligand 106 and the on switch control pocket 102, and with a small molecule 122 in binding relationship with the composite pocket; and

Fig. 7 is a schematic view of the protein in a situation where a combined switch control pocket 124 is formed with portions of the on switch control pocket 102, the switch control ligand sequence 106, and the active ATP site 108, and with a small molecule 126 in binding relationship with the combined switch control pocket.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a way of rationally developing new small molecule modulators which interact with naturally occurring proteins (e.g., mammalian, and especially human proteins) in order to modulate the activity of the proteins. Novel protein-small molecule adducts are also provided. The invention preferably makes use of naturally occurring proteins having a conformational property whereby the proteins change their conformations *in vivo* with a corresponding change in protein activity. For example, a given enzyme protein in one conformation may be biologically upregulated, while in another conformation, the same protein may be biologically downregulated. The invention preferably makes use of one mechanism of conformation change utilized by naturally occurring proteins, through the interaction of what are termed "switch control ligands" and "switch control pockets" within the protein.

As used herein, "switch control ligand" means a region or domain within a naturally occurring protein and having one or more amino acid residues therein which are transiently modified *in vivo* between individual states by biochemical modification, typically phosphorylation, sulfation, acylation or oxidation. Similarly, "switch control pocket" means a plurality of contiguous or non-contiguous amino acid residues within a naturally occurring protein and comprising residues capable of binding *in vivo* with transiently modified residues of a switch control ligand in one of the individual states thereof in order to induce or restrict the conformation of the protein and thereby modulate the biological activity of the protein, and/or which is capable of binding with a non-naturally occurring switch control modulator molecule to induce or restrict a protein conformation and thereby modulate the biological activity of the protein.

A protein-modulator adduct in accordance with the invention comprises a naturally occurring protein having a switch control pocket with a non-naturally occurring molecule bound to the protein at the region of said switch control pocket, said molecule serving to at least partially regulate the biological activity of said protein by inducing or restricting the conformation of the protein. Preferably, the protein also has a corresponding switch control ligand, the ligand interacting *in vivo* with the pocket to regulate the conformation and biological activity of the protein such that the protein will assume a first conformation and a first biological activity upon the ligand-pocket interaction, and will assume a second, different conformation and biological activity in the absence of the ligand-pocket interaction.

The nature of the switch control ligand/switch control pocket interaction may be understood from a consideration of schematic Figs. 1-4. Specifically, in Fig. 1, a protein 100 is illustrated in schematic form to include an "on" switch control pocket 102, and "off" switch control pocket 104, and a switch control ligand 106. In addition, the schematically depicted protein also includes an ATP active site 108. In the exemplary protein of Fig. 1, the ligand 106 has three amino acid residues with side chain OH groups 110. The off pocket 104 contains corresponding X residues 112 and the on pocket 102 has Z residues 114. In the exemplary instance, the protein 100 will change its conformation depending upon the charge status of the OH groups 110 on ligand 106, i.e., when the OH groups are unmodified, a neutral charge is presented, but when these groups are phosphorylated a negative charge is presented.

The functionality of the pockets 102, 104 and ligand 106 can be understood from a consideration of Figs. 2-4. In Fig. 2, the ligand 106 is shown operatively interacted with the off pocket 104 such that the OH groups 110 interact with the X residues 112 forming a part of the pocket 104. Such interaction is primarily by virtue of hydrogen bonding between the OH groups 110 and the residues 112. As seen, this ligand/pocket interaction causes the protein 100 to assume a conformation different from that seen in Fig. 1 and corresponding to the off or biologically downregulated conformation of the protein.

Fig. 3 illustrates the situation where the ligand 106 has shifted from the off pocket interaction conformation of Fig. 2 and the OH groups 110 have been phosphorylated, giving a negative charge to the ligand. In this condition, the ligand has a strong propensity to interact with on pocket 102, to thereby change the protein conformation to the on or biologically upregulated state (Fig. 4). Fig. 4a illustrates that the phosphorylated groups on the ligand 106 are attracted to positively charged residues 114 to achieve an ionic-like stabilizing bond. Note that in the on conformation of Fig. 4, the protein conformation is different than the off conformation of Fig. 2, and that the ATP active site is available and the protein is functional as a kinase enzyme.

Figs. 1-4 illustrate a simple situation where the protein exhibits discrete pockets 102 and 104 and ligand 106. However, in many cases a more complex switch control pocket pattern is observed. Fig. 6 illustrates a situation where an appropriate pocket for small molecule interaction is formed from amino acid residues taken both from ligand 106 and, for example, from pocket 102. This is termed a "composite switch control pocket" made up of residues from both the ligand 106 and a pocket, and is referred to by the numeral 120. A small molecule 122 is

illustrated which interacts with the pocket 120 for protein modulation purposes.

Another more complex switch pocket is depicted in Fig. 7 wherein the pocket includes residues from on pocket 102, and ATP site 108 to create what is termed a "combined switch control pocket." Such a combined pocket is referred to as numeral 124 and may also include residues from ligand 106. An appropriate small molecule 126 is illustrated with pocket 124 for protein modulation purposes.

It will thus be appreciated that while in the simple pocket situation of Figs.1-4, the small molecule will interact with the simple pocket 102 or 104, in the more complex situations of Figs. 6 and 7 the interactive pockets are in the regions of the pockets 120 or124. Thus, broadly the the small molecules interact "at the region" of the respective switch control pocket.

MATERIALS AND METHODS

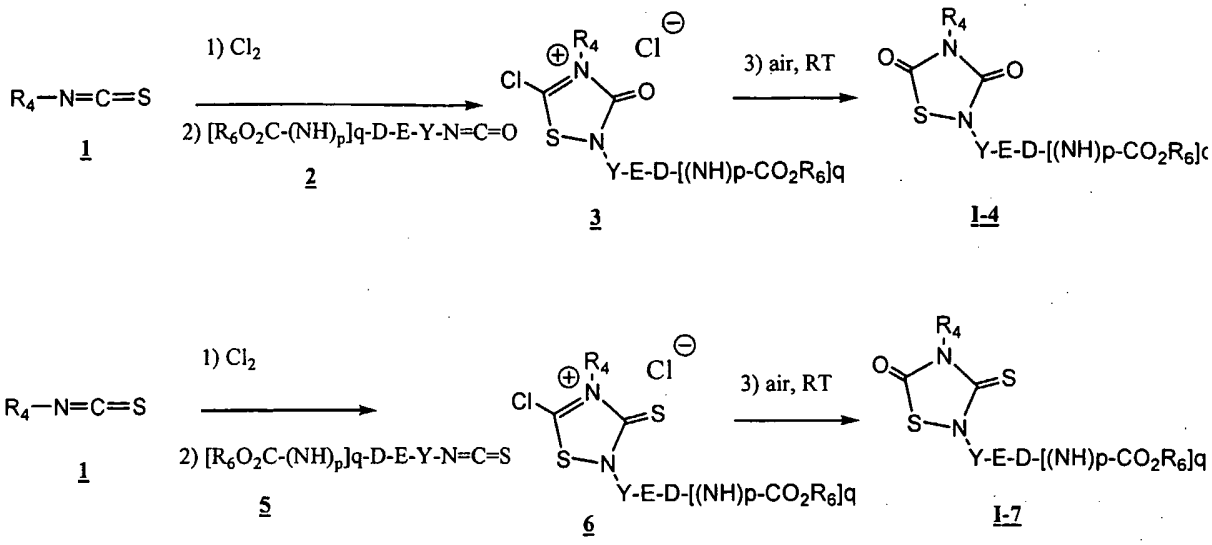
General Synthesis of Compounds.

In the synthetic schemes of this section, q is 0 or 1. When q = 0, the substituent is replaced by a synthetically non-interfering group R_7.

Compounds of Formula **I** wherein Q is taken from Q-1 or Q-2 and Y is alkylene are prepared according to the synthetic route shown in Scheme 1.1. Reaction of isothiocyanate **1** with chlorine, followed by addition of isocyanate **2** affords 3-oxo-thiadiazolium salt **3**. Quenching of the reaction with air affords compounds of Formula **I-4**. Alternatively, reaction of isothiocyanate **1** with isothiocyanate **5** under the reaction conditions gives rise to compounds of Formula **I-7**. See A. Martinez *et al*, *Journal of Medicinal Chemistry* (2002) 45: 1292.

Intermediates **1**, **2** and **5** are commercially available or prepared according to Scheme 1.2. Reaction of amine **8** with phosgene or a phosgene equivalent affords isocyanate **2**. Similarly, reaction of amine **8** with thiophosgene affords isothiocyanate **5**. Amine **8** is prepared by palladium(0)-catalyzed amination of **9**, wherein M is a group capable of oxidative insertion into palladium(0), according to methodology reported by S. Buchwald. See M. Wolter et al, *Organic Letters* (2002) 4:973; B.H. Yang and S. Buchwald, *Journal of Organometallic Chemistry* (1999) 576(1-2):125. In this reaction sequence, P is a suitable amine protecting group. Use of and removal of amine protecting groups is accomplished by methodology reported in the literature (**Protective Groups in Organic Synthesis,** Peter G.M. Wutts, Theodora Greene (Editors) 3rd edition (April 1999) Wiley, John & Sons, Incorporated; ISBN: 0471160199). Starting compounds **9** are commercially available or readily prepared by one of ordinary skill in the art: See **March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure**, Michael B. Smith & Jerry March (Editors) 5th edition (January 2001) Wiley John & Sons; ISBN : 0471585890.

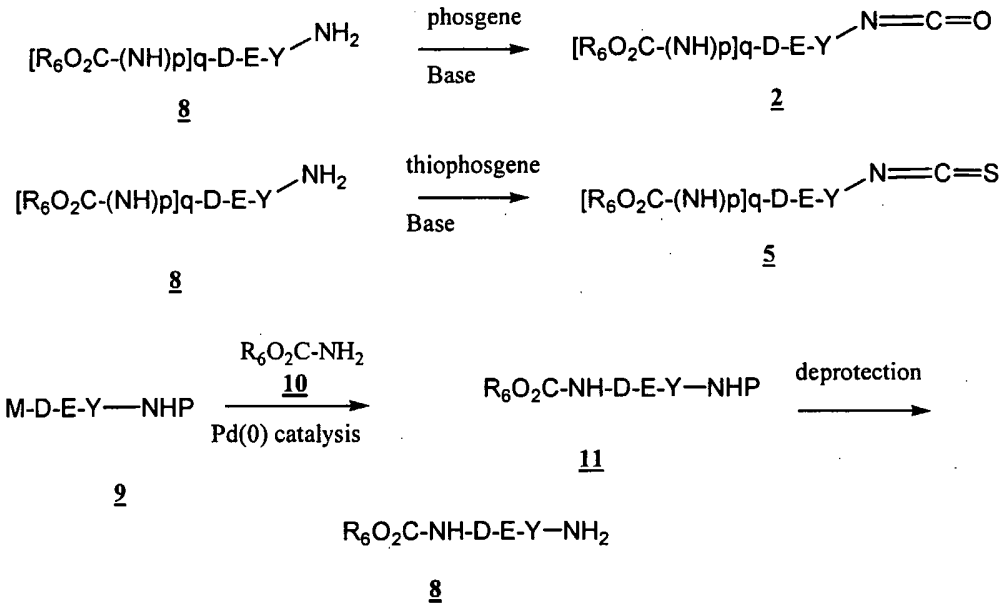
Scheme 1.1



1 2 3 I-4

1 5 6 I-7

Scheme 1.2

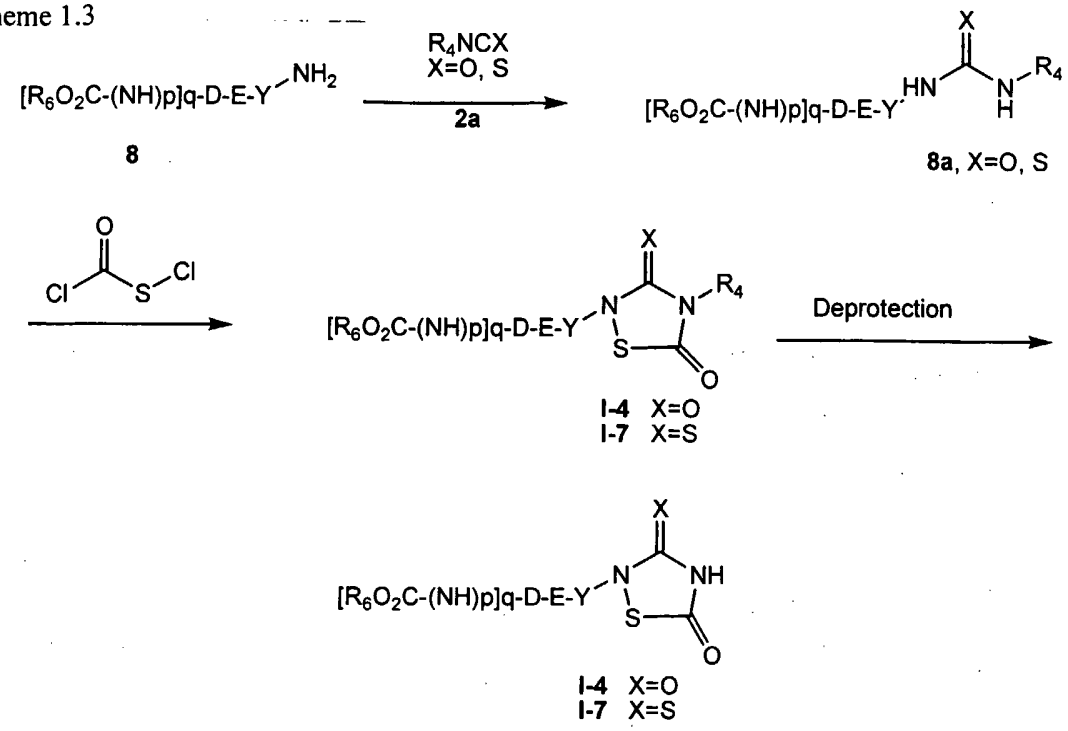


8 2 8 5 9 11 8

Compounds of Formula I wherein Q is taken from Q1 or Q-2 and Y is alkylene are also available via the synthetic route shown in Scheme 1.3. Reaction of amine **8** with isocyanate or isothiocyanate **2a** yields the urea/thiourea **8a** which can be cyclized by the addition of chlorocarbonyl sulfenyl chloride. See GB1115350 and US3818024, Revankar et. al US Patent 4,093,624, and Klayman et. al *JOC* **1972**, *37(10), 1532* for further details.

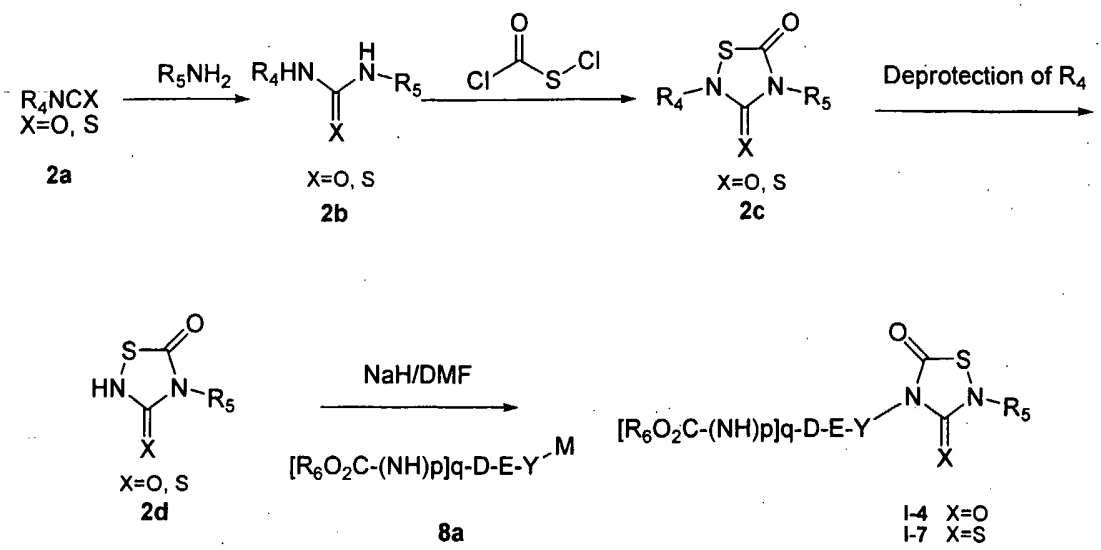
Where R_4 is a readily removable protecting group (e.g. R = 3,4-d-methoxybenzyl amine), the action of mild, acidic deprotection conditions such as CAN or TFA will reveal the parent ring system of **I-4** (X=O) and **I-7** (X=S).

Scheme 1.3



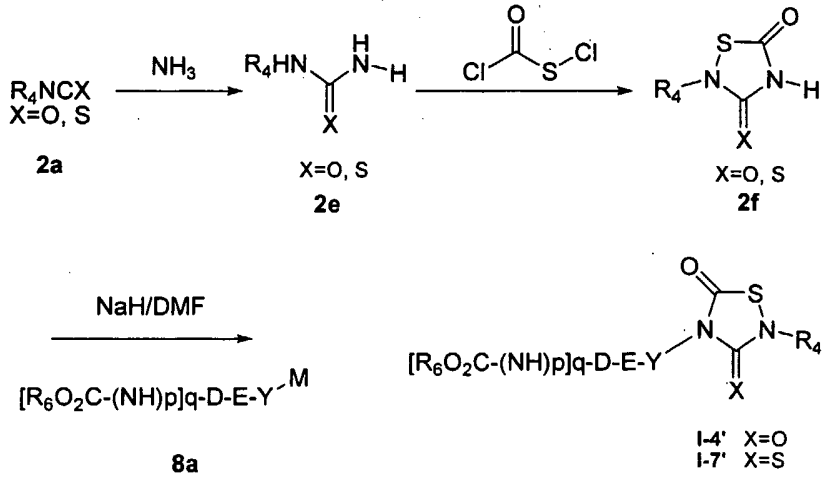
I-7 is also available as shown in Scheme 1.4. Condensation of isocyanate or isothiocyanate **2a** with amine R_5NH_2 yields urea/thiourea **2b**, which, when reacted with chlorocarbonyl sulfenyl chloride according to GB1115350 and US3818024 yields **2c**. Where R_4 is a readily removable protecting group (e.g. R = 3,4-d-methoxybenzyl amine), the action of mild, acidic deprotection conditions such as CAN or TFA will reveal the parent ring system of **2d**. Reaction of **2d** with NaH in DMF, and displacement wherein M is a suitable leaving group such as chloride, bromide or iodide yields **I-4** (X=O) and **I-7** (X=S).

Scheme 1.4



Compounds of Formula I wherein Q is taken from Q-1' or Q-2' and Y is alkylene are available via the synthetic route shown in Scheme 1.3. Condensation of isocyanate or isothiocyanate **2a** with ammonia yields urea/thiourea **2e**, which, when reacted with chlorocarbonyl sulfenyl chloride according to GB1115350 and US3818024 yields **2f**. Reaction of **2f** with NaH in DMF, and displacement wherein M is a suitable leaving group such as chloride, bromide or iodide yields yields **I-4'** (X=O) and **I-7'** (X=S).

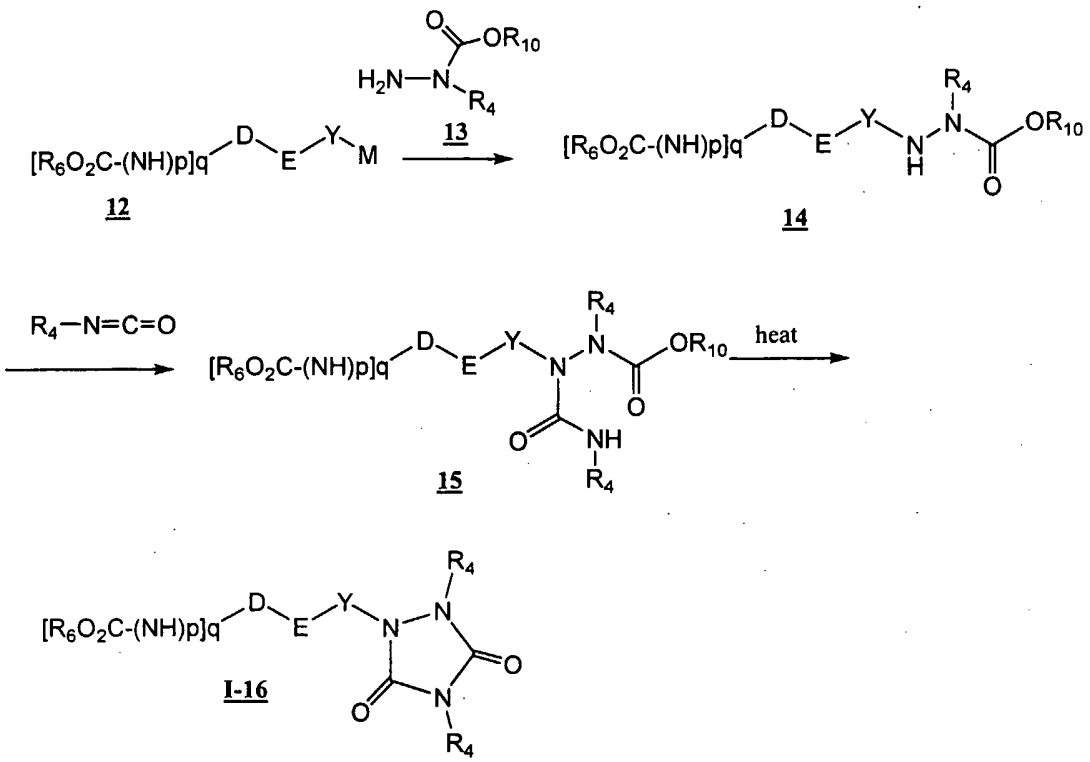
Scheme 1.5



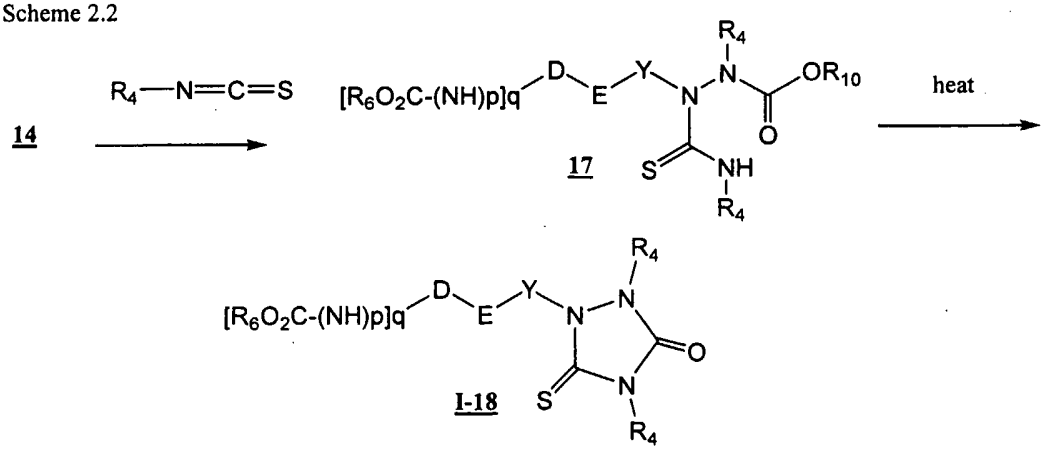
Compounds of Formula I wherein Q is taken from Q-3 or Q-4 and Y is alkylene, are prepared according to the synthetic route shown in Schemes 2.1 and 2.2, respectively. Reaction of 12, wherein M is a suitable leaving group, with the carbamate-protected

hydrazine **13** affords intermediate **14**. Reaction of **14** with an isocyanate gives rise to intermediate **15**. Thermal cyclization of **15** affords 1,2,4-triazolidinedione of Formula **I-16**. By analogy, scheme 2.2 illustrates the preparation of 3-thio-5-oxo-1,2,4-triazolidines of Formula **I-18** by reaction of intermediate **14** with an isothiocyanate and subsequent thermal cyclization.

Scheme 2.1

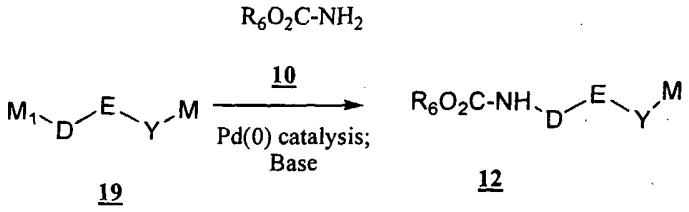


Scheme 2.2



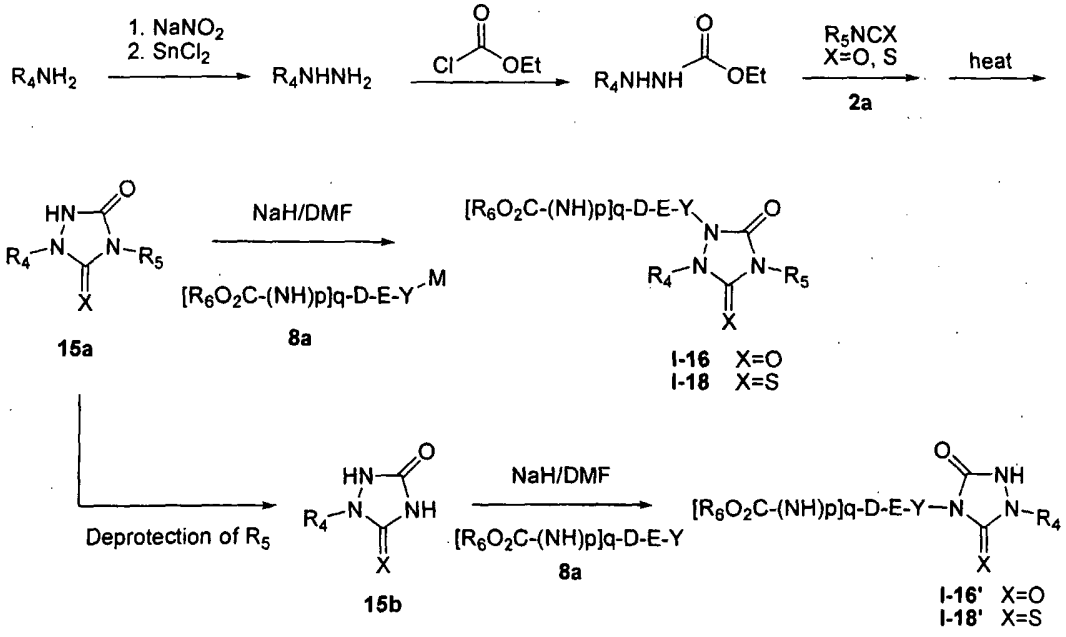
Intermediates **12** wherein p is 1 are readily available or are prepared by reaction of **19** with carbamates **10** under palladium(0)-catalyzed conditions. M_1 is a group which oxidatively inserts palladium(0), preferably iodo or bromo, and is of greater reactivity than M. Compounds **19** are either commercially available or prepared by one of ordinary skill in the art.

Scheme 2.3



Compounds of Formula **I** wherein D is taken from Q-3 or Q-4 and Y is alkylene, are also prepared according to the synthetic route shown in Scheme 2.4. Oxidation of amine R_4NH_2 to the corresponding hydrazine, condensation with ethyl chloroformate subsequent heating yields1,2,4-triazolidinedione **15a**. After the action of NaH in DMF, displacement wherein M is a suitable leaving group such as chloride, bromide or iodide yields **I-16** (X=O) and **I-18** (X=S).

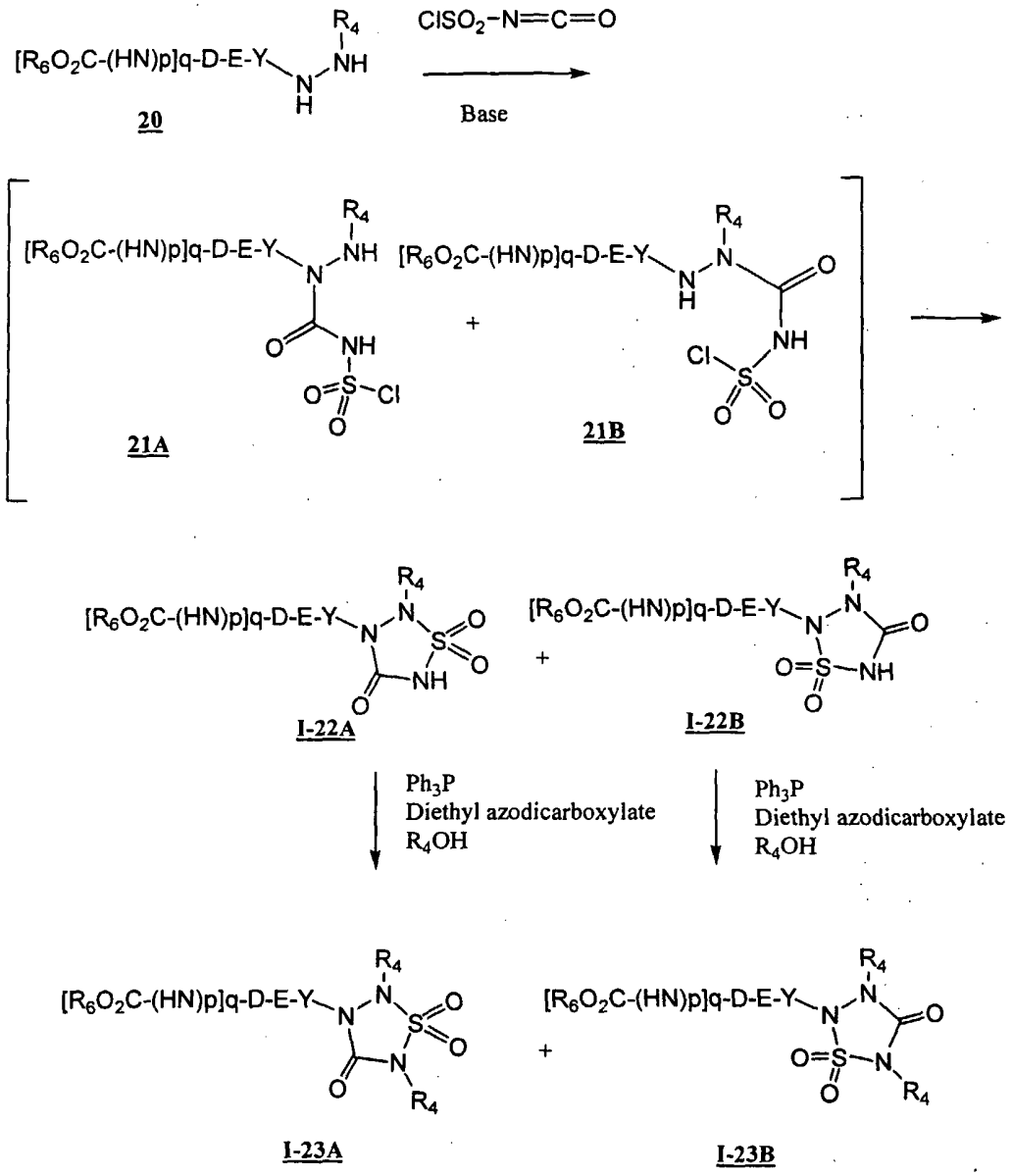
Scheme 2.4



Compounds of Formula **I** wherein D is taken from D-3' or D-4' and Y is alkylene, are also prepared according to the synthetic route shown in Scheme 2.4. When R_5 is a readily removable protecting group (e.g. R = 3,4-d-methoxybenzyl amine), the action of mild, acidic deprotection conditions such as CAN or TFA on **15a** will reveal 1,2,4-triazolidinedione **15b**. After deprotonation of **15b** by NaH in DMF, displacement wherein M is a suitable leaving group such as chloride, bromide or iodide yields **I-16'** (X=O) and **I-18'** (X=S).

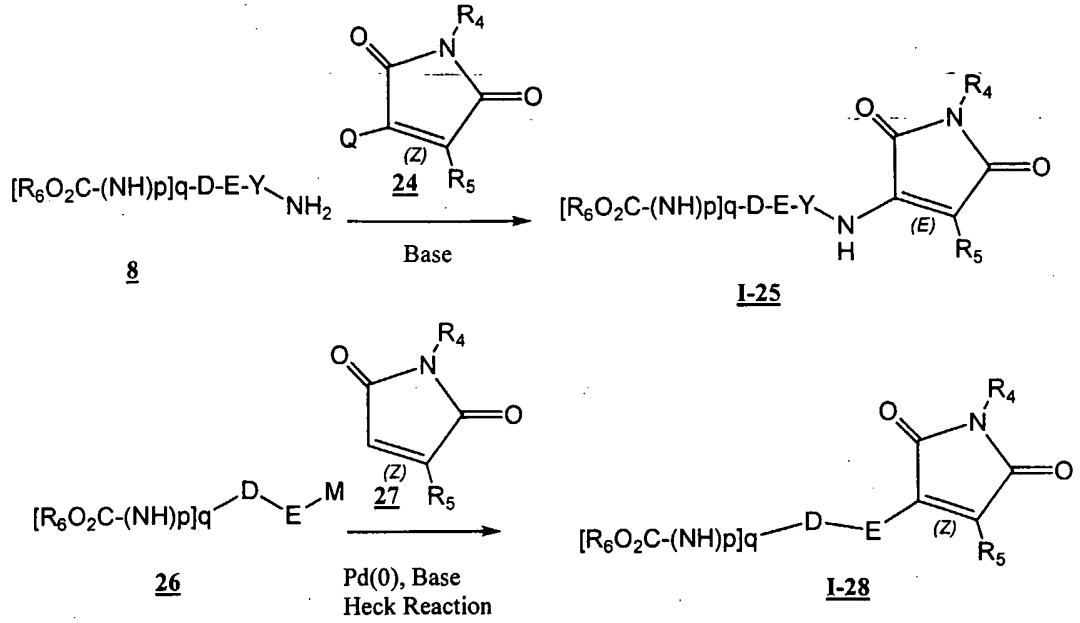
Compounds of Formula **I** wherein Q is taken from Q-5 or Q-6 and Y is alkylene are prepared according to the synthetic route shown in Scheme 3. Reaction of hydrazine **20** with chlorosulfonylisocyanate and base, such as triethylamine, gives rise to a mixture of intermediates **21A** and **21B** which are not isolated but undergo cyclization *in situ* to afford compounds of Formulae **I-22A** and **I-22B**. Compounds **I-22A** and **I-22B** are separated by chromatography or fractional crystallization. Optionally, compounds **I-22A** and **I-22B** can undergo Mitsunobu reaction with alcohols R_4OH to give compounds of Formulae **I-23A** and **I-23B**. Compounds **20** are prepared by acid-catalyzed deprotection of t-butyl carbamates of structure **14**, wherein R_{10} is t-butyl.

Scheme 3



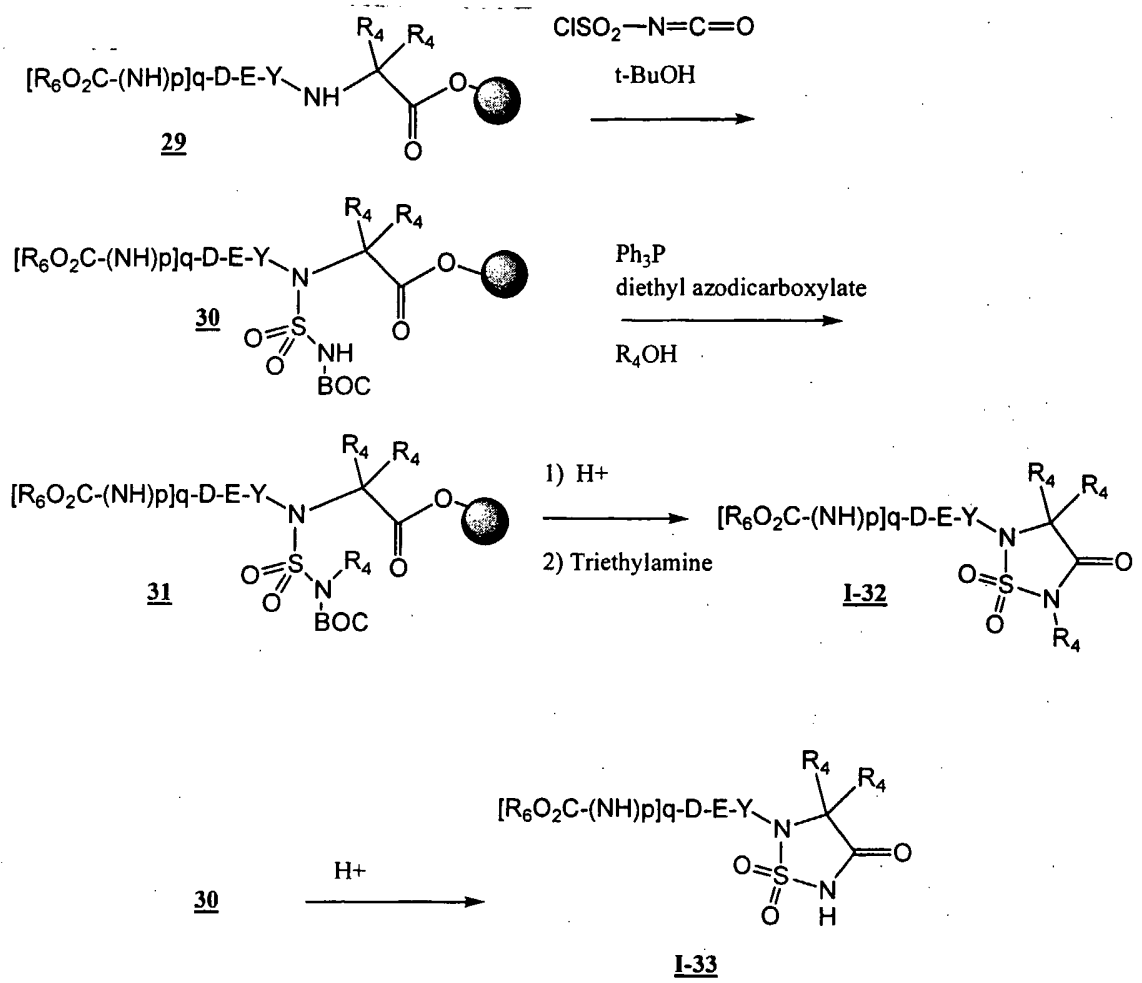
Compounds of Formula I wherein Q is Q-7 and Y is alkylene are prepared as shown in Scheme 4. Reaction of amine 8 with maleimide 24, wherein M is a suitable leaving group, affords compounds of Formula I-25. Reaction of compound 26, wherein M is a group which can oxidatively insert Pd(0), can participate in a Heck reaction with maleimide 27, affording compounds of Formula I-28. Maleimides 24 and 27 are commercially available or prepared by one of ordinary skill in the art.

Scheme 4



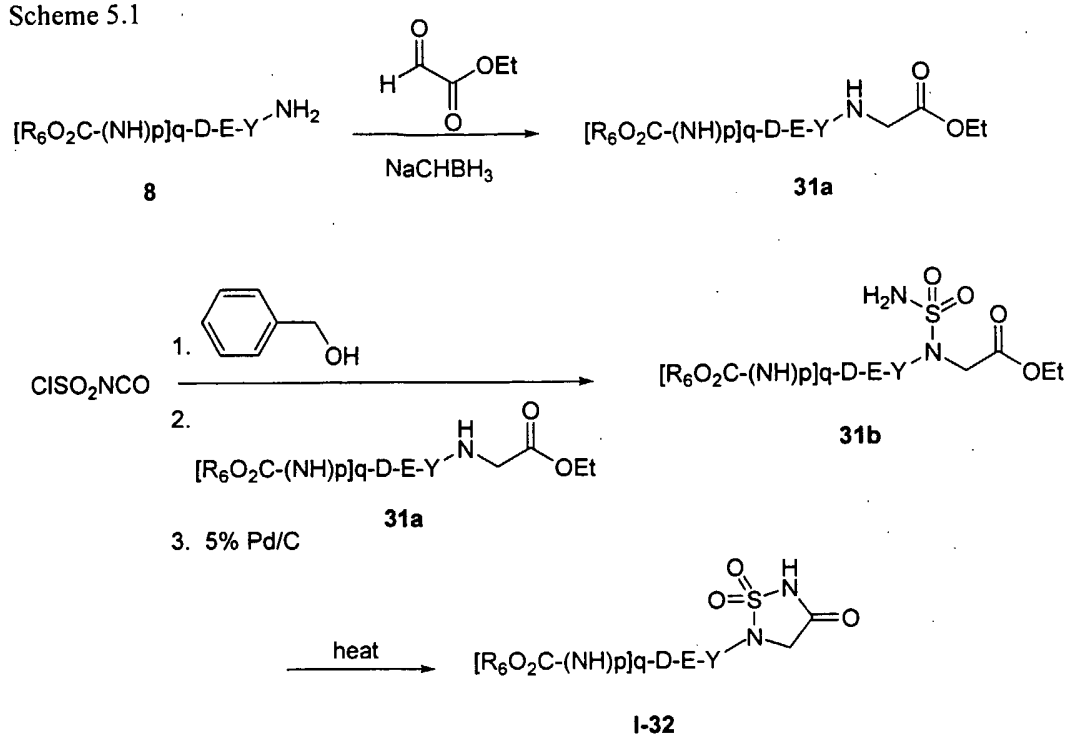
Compounds of Formula **I** wherein Q is Q-8 and Y is alkylene are prepared as shown in Scheme 5, according to methods reported by M. Tremblay *et al*, *Journal of Combinatorial Chemistry* (2002) 4:429. Reaction of polymer-bound activated ester **29** (polymer linkage is oxime activated-ester) with chlorosulfonylisocyante and t-butanol affords N-BOC sulfonylurea **30**. Subjection of **30** to the Mitsunobu reaction with R_4OH gives rise to **31**. BOC-group removal with acid, preferably trifluoroacetic acid, and then treatment with base, preferably triethylamine, provides the desired sulfahydantoin **I-32**. Optionally, intermediate **30** is treated with acid, preferably trifluoroacetic acid, to afford the N-unsubstituted sulfahydantoin **I-33**.

Scheme 5



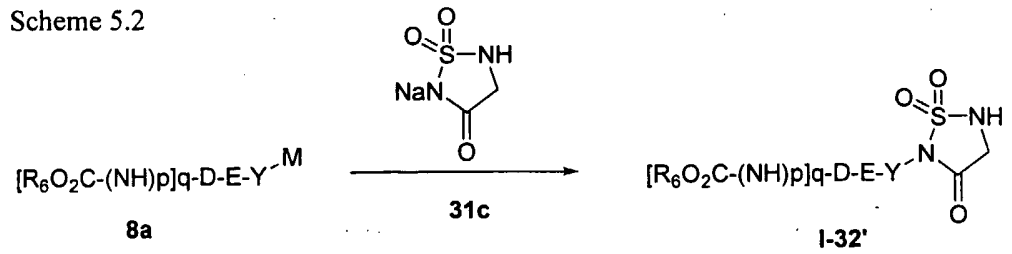
Compounds of Formula **I** wherein Q is Q-8 and Y is alkylene are also prepared as shown in Scheme 5a. Amine **8** is condensed with the glyoxal hemiester to yield **31a**. Reaction of chlorosulphonyl isocyanate first with benzyl alcohol then **31a** yields **31b**, which after heating yields **I-32**.

Scheme 5.1

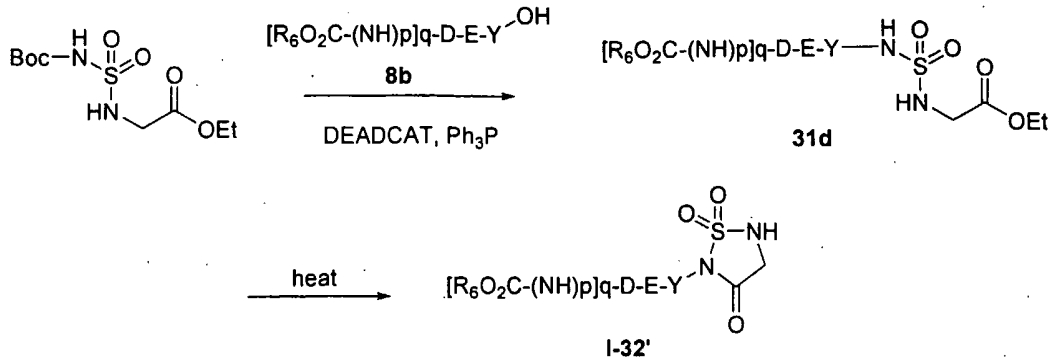


Compounds of Formula I wherein Q is taken from Q-8', are prepared according to the synthetic route shown in Scheme 5.2. Formation of **31c** by the method of Muller and DuBois *JOC* **1989**, *54,* 4471 and its deprotonation with NaH/DMF or NaH/DMF and subsequently alkylation wherein M is a suitable leaving group such as chloride, bromide or iodide yields **I-32'**. Alternatively, **I-32'** is also available as shown in Scheme 5.3. Mitsunobu reaction of boc-sulfamide amino ethyl ester with alcohol **8b** (made by methods analogous to that for amine **8**) yields **31c**, which after Boc removal with 2N HCl in dioxane is cyclized by the action of NaH on **31d** results in **I-32'**.

Scheme 5.2

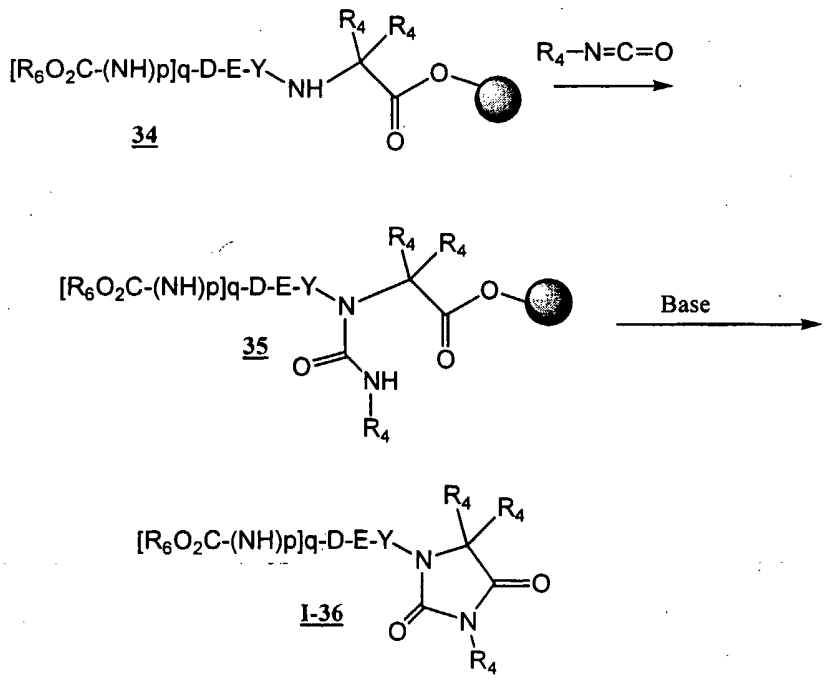


Scheme 5.3



Compounds of Formula I wherein Q is Q-9 and Y is alkylene are prepared as shown in Scheme 6. Reaction of polymer-bound amino acid ester **34** with an isocyanate affords intermediate urea **35**. Treatment of **35** with base, preferably pyridine or triethylamine, with optional heating, gives rise to compounds of Formula **I-36**.

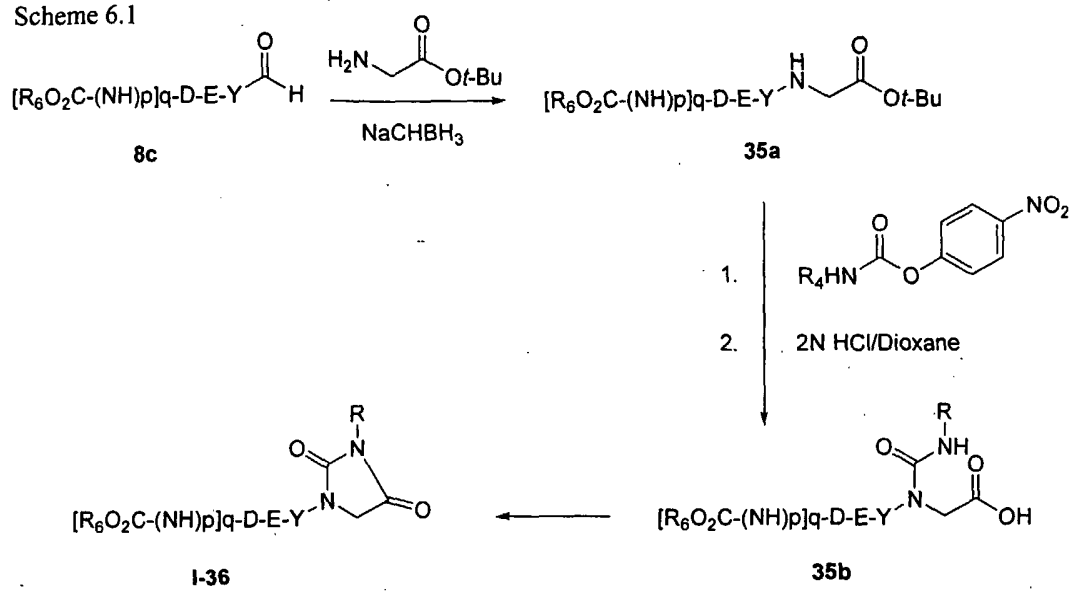
Scheme 6



Compounds of Formula I wherein Q is Q-9 and Y is alkylene are also prepared as shown in Scheme 6.1. Reaction of aldehyde **8c** under reductive amination conditions with the t-butyl ester of glycine yields **35a**. Isocyanate **2a** is condensed with p-nitrophenol (or the corresponding R_4NH_2 amine is condensed with p-nitrophenyl chloroformate) to yield the carbamic acid p-nitrophenyl ester, which when reacted with deprotonated **35a** and yields the

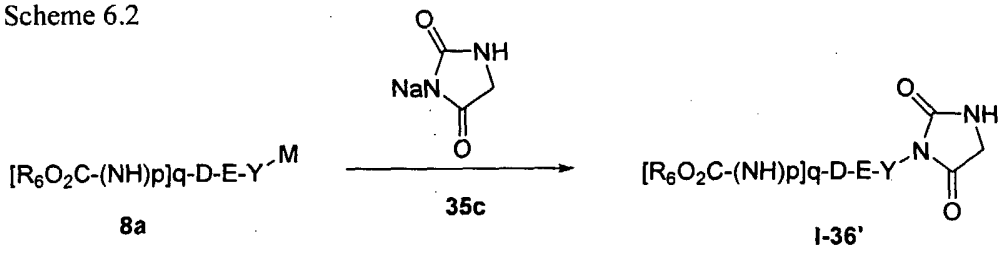
urea that when deprotected with acid yields **35b**. Formula **I-36** is directly available from **35b** by the action of NaH and heat.

Scheme 6.1



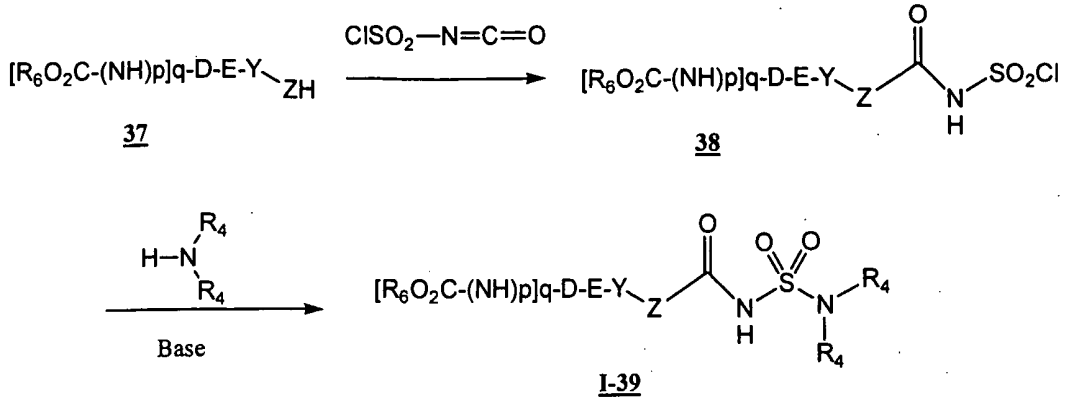
Compounds of Formula **I** wherein Q is taken from Q-9', are prepared according to the synthetic route shown in Scheme 6.2. Formation of **35c** by the method described in JP10007804A2 and Zvilichovsky and Zucker, Israel Journal of Chemistry, **1969**, *7(4)*, 547-54 and its deprotonation with NaH/DMF or NaH/DMF and its subsequent displacement of M, wherein M is a suitable leaving group such as chloride, bromide or iodide, yields **I-36'**.

Scheme 6.2

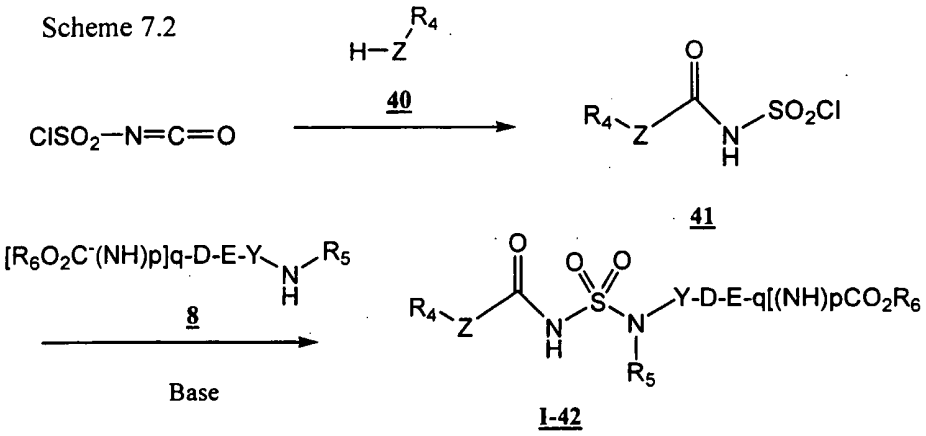


Compounds of Formula **I** wherein Q is Q-10 or Q-11, and Y is alkylene are prepared as shown in Schemes 7.1 and 7.2, respectively. Treatment of alcohol **37** (Z = O) or amine **37** (Z = NH) with chlorosulfonylisocyanate affords intermediate carbamate or urea of structure **38**. Treatment of **38** with an amine of structure $HN(R_4)_2$ and base, preferably triethylamine or pyridine, gives sulfonylureas of Formula **I-39**. Reaction of chlorosulonylisocyanate with an alcohol (Z = O) or amine (Z = NR_4) **40** affords intermediate **41**. Treatment of **41** with an amine **8** and base, preferably triethylamine or pyridine, gives sulfonylureas of Formula **I-42**.

Scheme 7.1

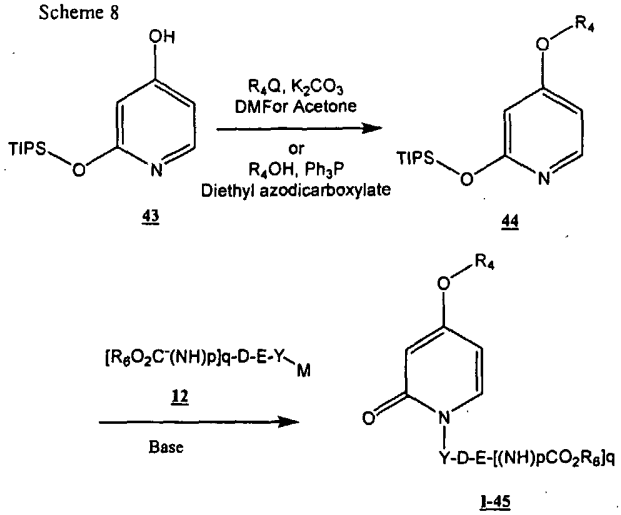


Scheme 7.2



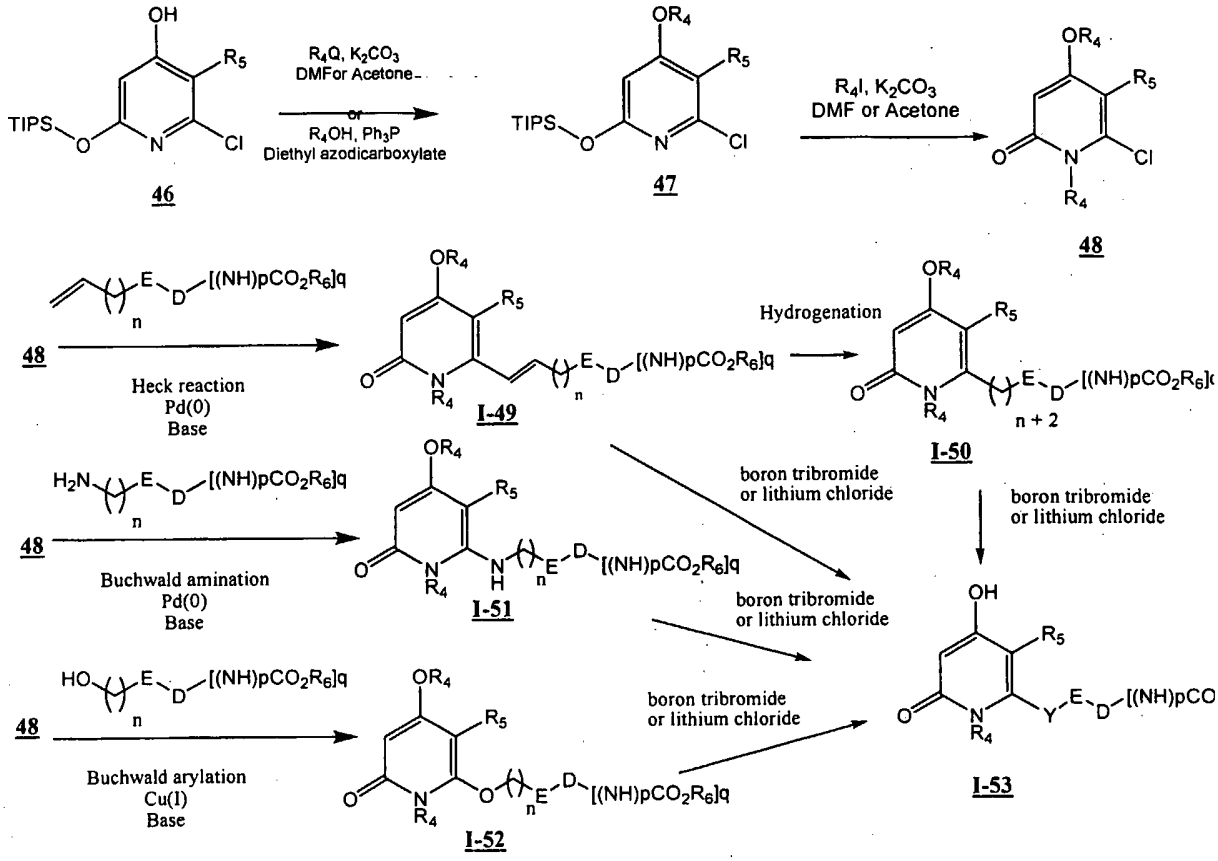
Compounds of Formula **I** wherein Q is taken from Q-12 are prepared according to the synthetic route shown in Scheme 8. Alkylation of pyridine **43**, wherein TIPS is tri-isopropylsilyl, under standard conditions (K_2CO_3, DMF, R_4-I or Mitsunobu conditions employing R_4-OH) yields pyridine derivative **44** which is reacted with compound **12**, wherein M is a suitable leaving group, to afford pyridones of formula **I-45**.

Scheme 8



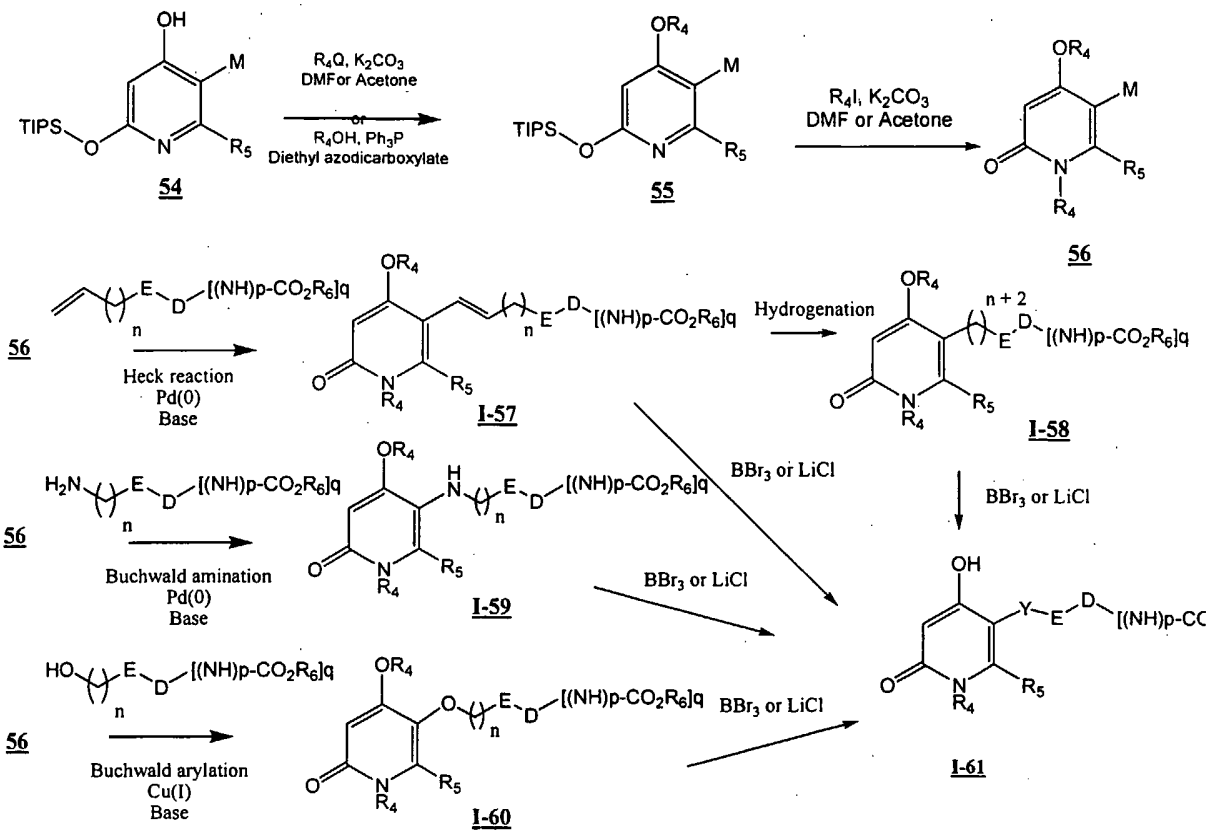
Compounds of Formula **I** wherein Q is taken from Q-13 are prepared according to the synthetic route shown in Scheme 9. Starting from readily available pyridine **46**, alkylation under standard conditions (K_2CO_3, DMF, R_4-I or Mitsunobu conditions employing R_4-OH) yields pyridine derivative **47**. N-alkylation with K_2CO_3, DMF, R_4-I affords pyridones of formula **48**. Intermediate **48** is partitioned to undergo a Heck reaction, giving **I-49**; a Buchwald amination reaction, giving **I-51**; or a Buchwald Cu(I) catalyzed O-arylation reaction, to give **I-52**. The Heck reaction product **I-49** may be optionally hydrogenated to afford the saturated compound **I-50**. Wherein the phenyl ether R_4 group is methyl, compounds of formula **I-49**, **I-50**, **I-51**, or **I-52** are treated with boron tribromide or lithium chloride to afford compounds of Formula **I-53**, wherein R_4 is hydrogen.

Scheme 9



Compounds of Formula I wherein Q is taken from Q-14 are prepared according to the synthetic route shown in Scheme 10. Starting from readily available pyridine 54, alkylation under standard conditions (K_2CO_3, DMF, R_4-I or Mitsunobu conditions employing R_4-OH) yields pyridine derivative 55. N-alkylation with K_2CO_3, DMF, R_4-I affords pyridones of formula 56. Intermediate 56, wherein M is a suitable leaving group, preferably bromine or chlorine, is partitioned to undergo a Heck reaction, giving I-57; a Buchwald amination reaction , giving I-59; or a Buchwald Cu(I) catalyzed O-arylation reaction, to give I-60. The Heck reaction product I-57 may be optionally hydrogenated to afford the saturated compound I-58. Wherein R_4 is methyl, compounds of formula I-57, I-58, I-59, or I-60 are treated with boron tribromide or lithium chloride to afford compounds of Formula I-61, wherein R_4 is hydrogen.

Scheme 10

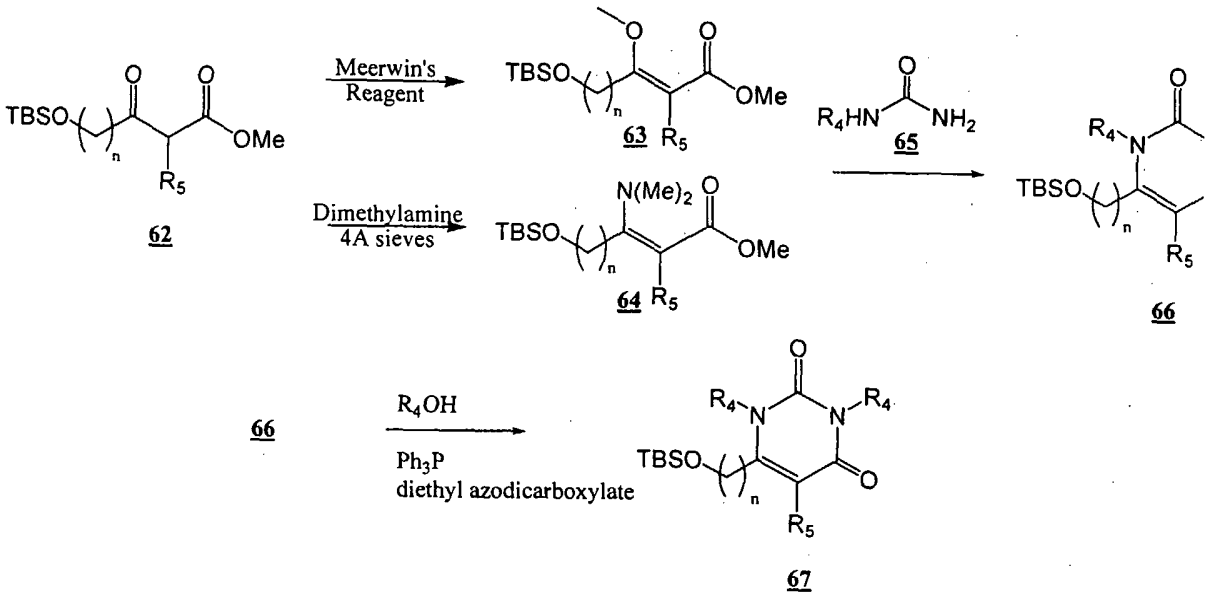


Compounds of Formula **I** wherein Q is taken from Q-15 are prepared according to the synthetic routes shown in Schemes 11 and 12. Starting esters **62** are available from the corresponding secoacids via TBS-ether and ester formation under standard conditions. Reaction of protected secoester **62** with Meerwin's salt produces the vinyl ether **63** as a pair of regioisomers. Alternatively, reaction of **62** with dimethylamine affords the vinylogous carbamate **64**. Formation of the dihydropyrimidinedione **66** proceeds by condensation with urea **65** with azeotropic removal of dimethylamine or methanol. Dihydropyrimidinedione **66** may optionally be further substituted by Mitsunobu reaction with alcohols R_4OH to give rise to compounds **67**.

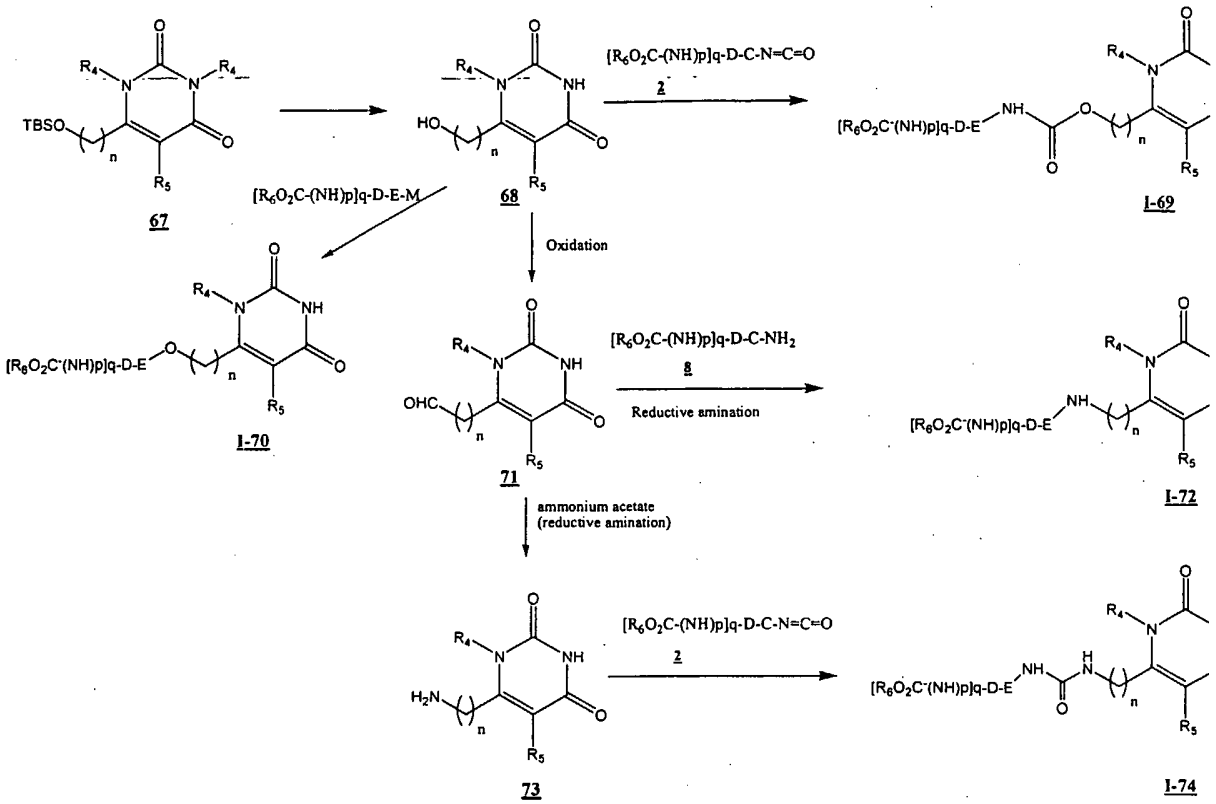
Scheme 12 illustrates the further synthetic elaboration of intermediates **67**. Removal of the silyl protecting group (TBS) is accomplished by treatment of **67** with flouride (tetra-n-butylammonium fluoride or cesium flouride) to give primary alcohols **68**. Reaction of **68** with isocyanates **2** gives rise to compounds of Formula **I-69**. Alternatively, reaction of **68** with $[R_6O_2C(NH)p]q$-D-E-M, wherein M is a suitable leaving group, affords compounds of Formula **I-70**. Oxidation of **68** using the Dess-Martin periodinane (D. Dess, J. Martin, *J. Am.*

Chem. Soc. (1991) 113:7277) or tetra-n-alkyl peruthenate (W. Griffith, S. Ley, *Aldrichimica Acta* (1990) 23:13) gives the aldehydes 71. Reductive amination of 71 with amines 8 gives rise to compounds of Formula I-72. Alternatively, aldehydes 71 may be reacted with ammonium acetate under reductive alkylation conditions to give rise to the primary amine 73. Reaction of 73 with isocyanates 2 affords compounds of Formula I-74.

Scheme 11

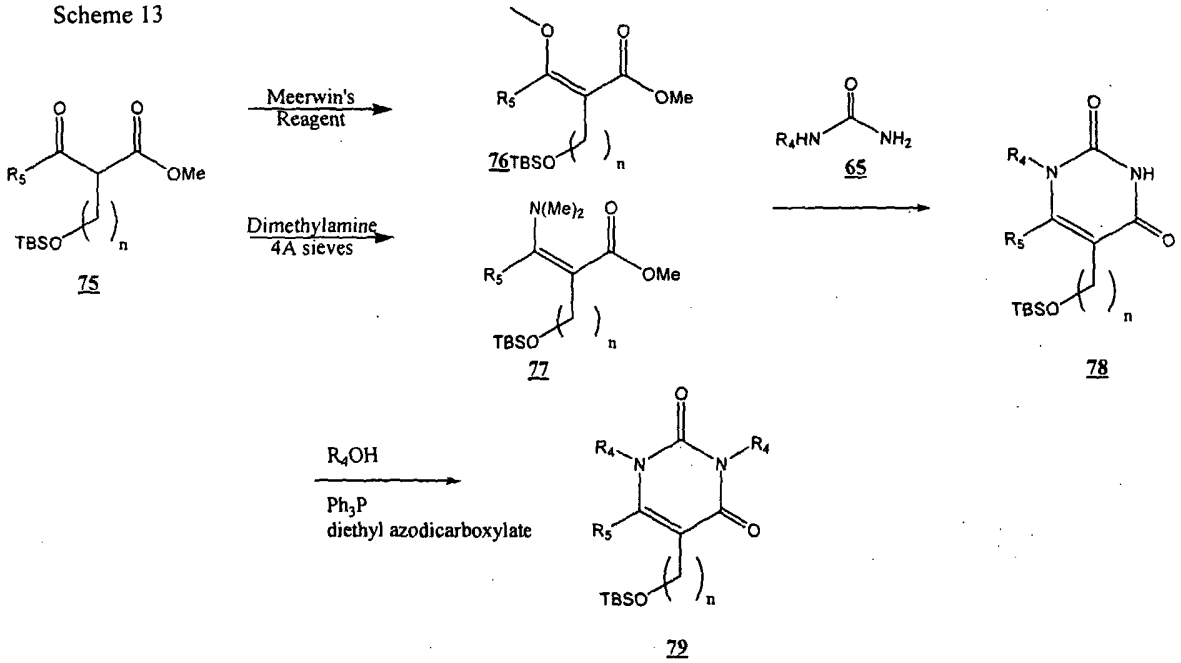


Scheme 12

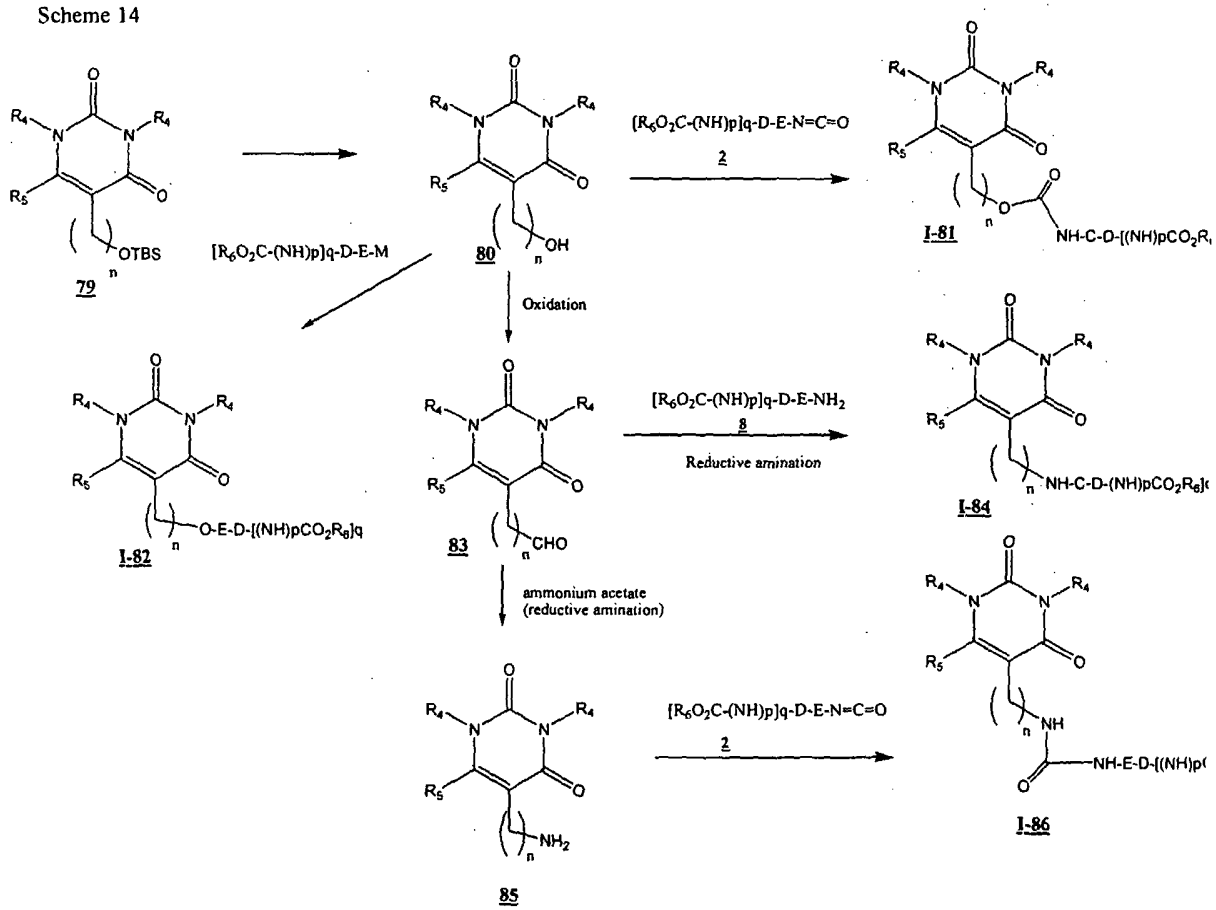


Compounds of Formula I wherein Q is taken from Q-16 are prepared according to the synthetic routes shown in Schemes 13 and 14. Starting esters 75 are available from the corresponding secoacids via TBS-ether and ester formation under standard conditions. Reaction of protected secoester 75 with Meerwin's salt produces the vinyl ether 76 as a pair of regioisomers. Alternatively, reaction of 75 with dimethylamine affords the vinylogous carbamate 77. Formation of the dihydropyrimidinedione 78 proceeds by condensation with urea 65 with azeotropic removal of dimethylamine or methanol. Dihydropyrimidinedione 78 may optionally be further substituted by Mitsunobu reaction with alcohols R_4OH to give rise to compounds 79. Compounds of Formulae I-81, I-82, I-84, and I-86 are prepared as shown in Scheme 14 by analogy to the sequence previously described in Scheme 12.

Scheme 13

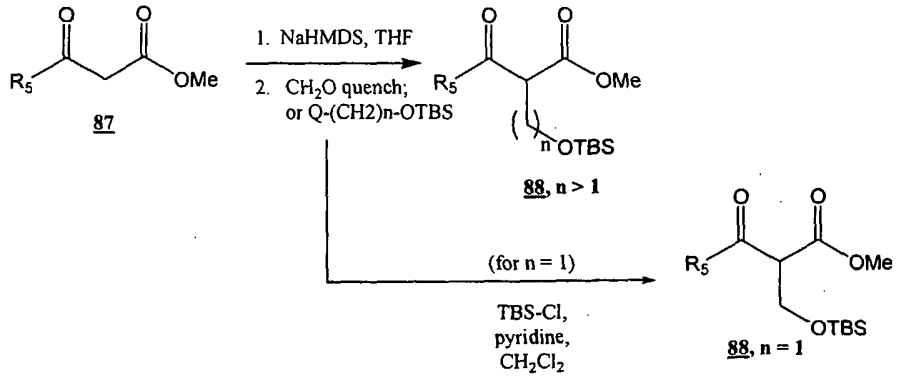


Scheme 14



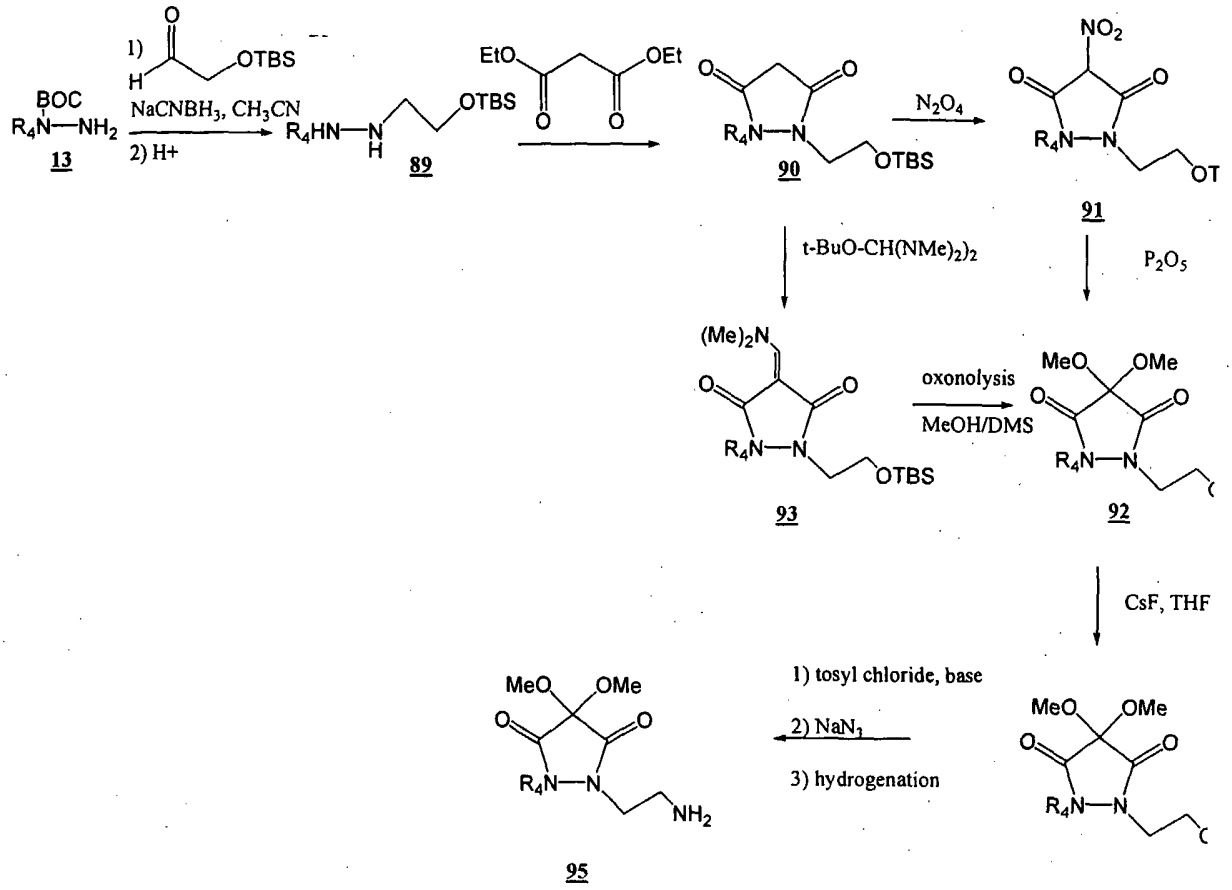
Alkyl acetoacetates **87** are commercially available and are directly converted into the esters **88** as shown in Scheme 15. Treatment of **87** with NaHMDS in THF, followed by quench with formaldehyde and TBSCl (n = 1) or Q-(CH2)n-OTBS (n = 2-4), gives rise to compounds **88**.

Scheme 15



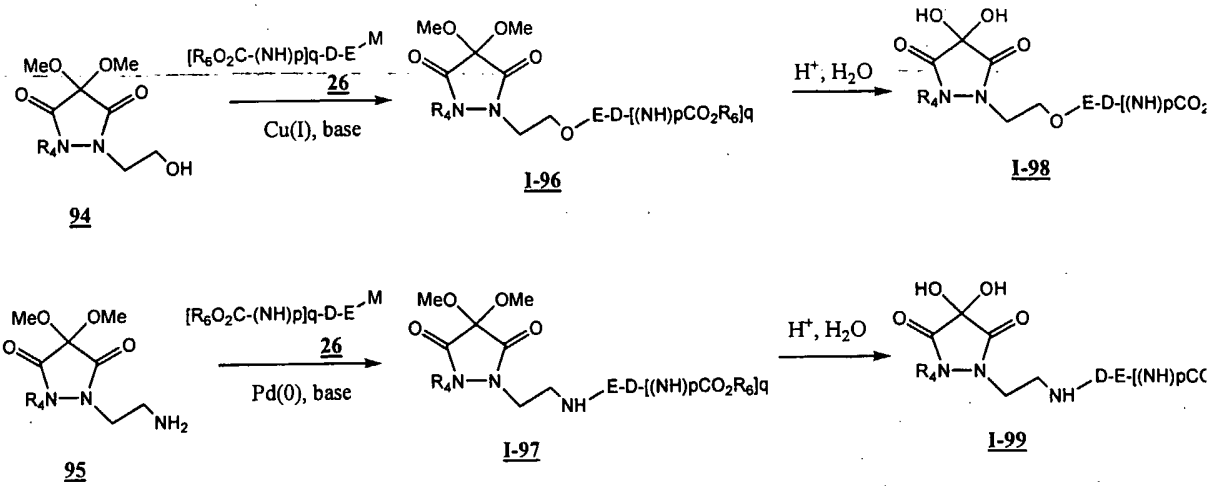
Compounds of Formula **I** wherein Q is taken from Q-17 are prepared according to the synthetic routes shown in Schemes 16.1 and 16.2, and starts with the BOC-protected hydrazine **13**, which is converted to the 1,2-disubstituted hydrazine **89** by a reductive alkylation with a glyoxal derivative mediated by sodium cyanoborohydride and acidic workup. Condensation of **89** with diethyl malonate in benzene under reflux yields the heterocycle **90**. Oxidation with N_2O_4 in benzene (see Cardillo, Merlini and Boeri *Gazz. Chim. Ital.*, (1966) 9:8) to the nitromalonohydrazide **91** and further treatment with P_2O_5 in benzene (see: Cardillo,G. et al, *Gazz.Chim.Ital.* (1966) 9:973-985) yields the tricarbonyl **92**. Alternatively, treatment of **90** with Brederick's reagent (t-BuOCH($N(Me_2)_2$, gives rise to **93**, which is subjected to ozonolysis, with a DMS and methanol workup, to afford the protected tricarbonyl **92**. Compound **92** is readily deprotected by the action of CsF in THF to yield the primary alcohol **94**. Alcohol **94** is optionally converted into the primary amine **95** by a sequence involving tosylate formation, azide displacement, and hydrogenation.

Scheme 16.1



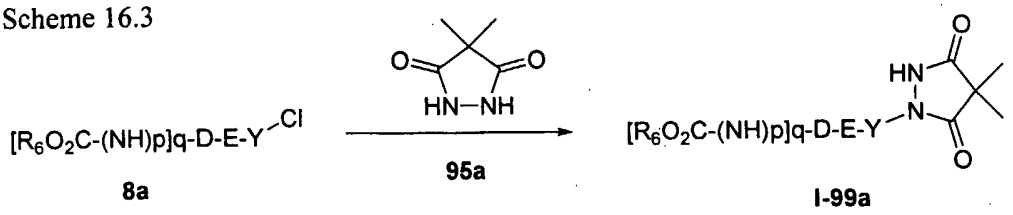
Reaction of **94** with (hetero)aryl halide **26**, wherein M is iodo, bromo, or chloro, under copper(I) catalysis affords compounds **I-96**. Optional deprotection of the di-methyl ketal with aqueous acid gives rise to compounds of Formula **I-98**. By analogy, reaction of amine **95** with **26** under palladium(0) catalysis affords compounds of Formula **I-97**. Optional deprotection of the di-methyl ketal with aqueous acid gives rise to compounds of Formula **I-99**.

Scheme 16.2



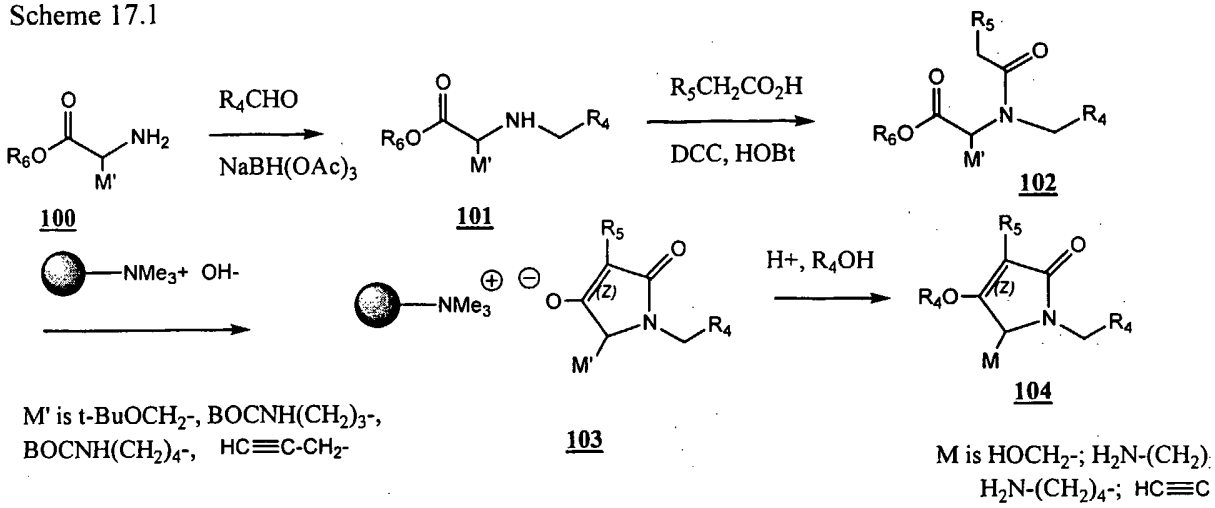
Compounds of Formula **I** wherein Q is taken from Q-17 are also prepared according to the synthetic route shown in Scheme 16.3. Deprotonation of 4,4-dimethyl-3,5-dioxo-pyrazolidine (**95a**, prepared according to the method described in Zinner and Boese, D. *Pharmazie* **1970**, *25(5-6)*, 309-12 and Bausch, M. J.et.al *J. Org. Chem.* **1991**, *56(19)*, 5643) with NaH/DMF or NaH/DMF and its subsequent displacement of M, wherein M is a suitable leaving group such as chloride, bromide or iodide yields **I-99a**.

Scheme 16.3



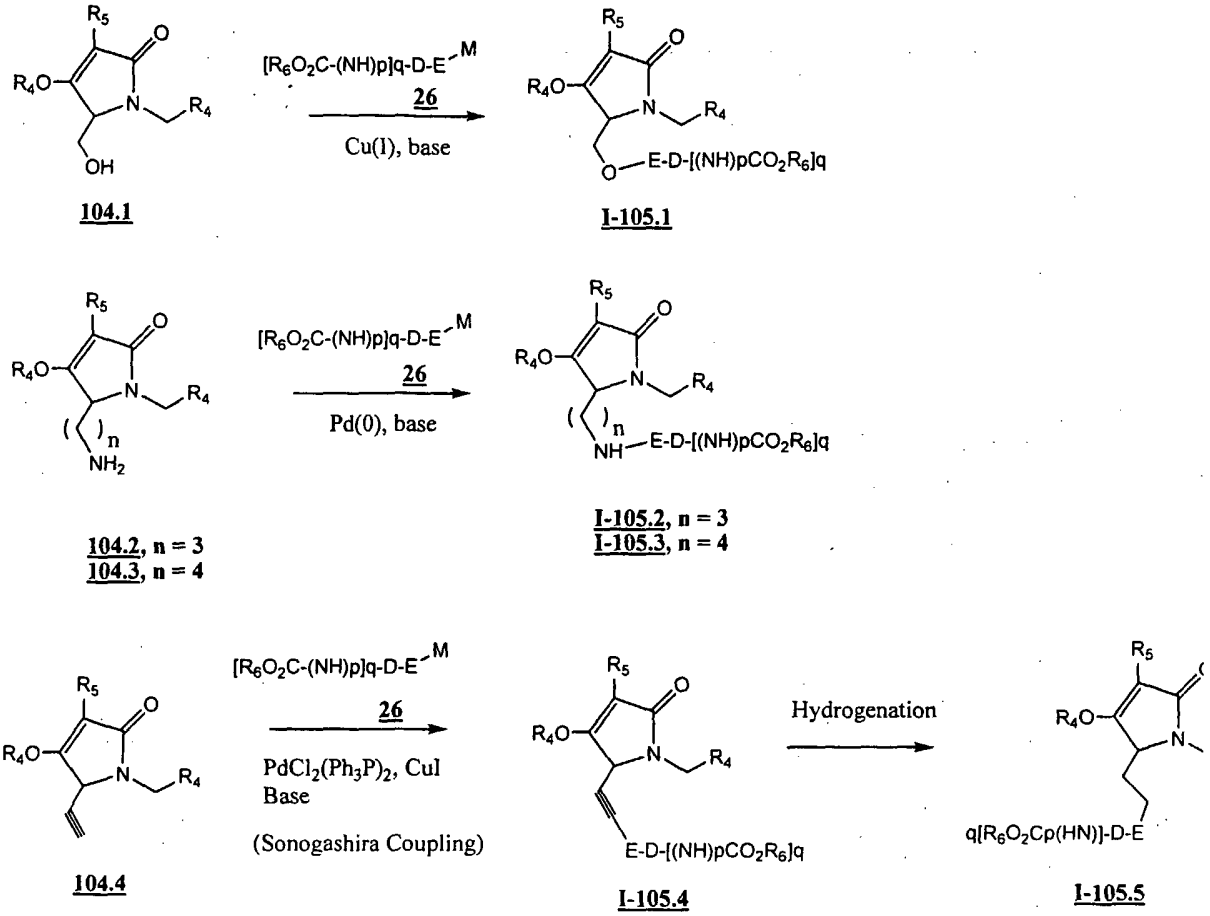
Compounds of Formula I wherein Q is taken from Q-18 are prepared as shown in Schemes 17.1 and 17.2. Aminoesters **100** are subjected to reductive alkylation conditions to give rise to intermediates **101**. Condensation of amines **101** with carboxylic acids using an acid activating reagent such as dicyclohexylcarbodiimide (DCC)/hydroxybenzotriazole (HOBt) affords intermediate amides **102**. Cyclization of amides **102** to tetramic acids **104** is mediated by Amberlyst A-26 hydroxide resin after trapping of the *in situ* generated alkoxide **103** and submitting **103** to an acetic acid-mediated resin-release.

Scheme 17.1



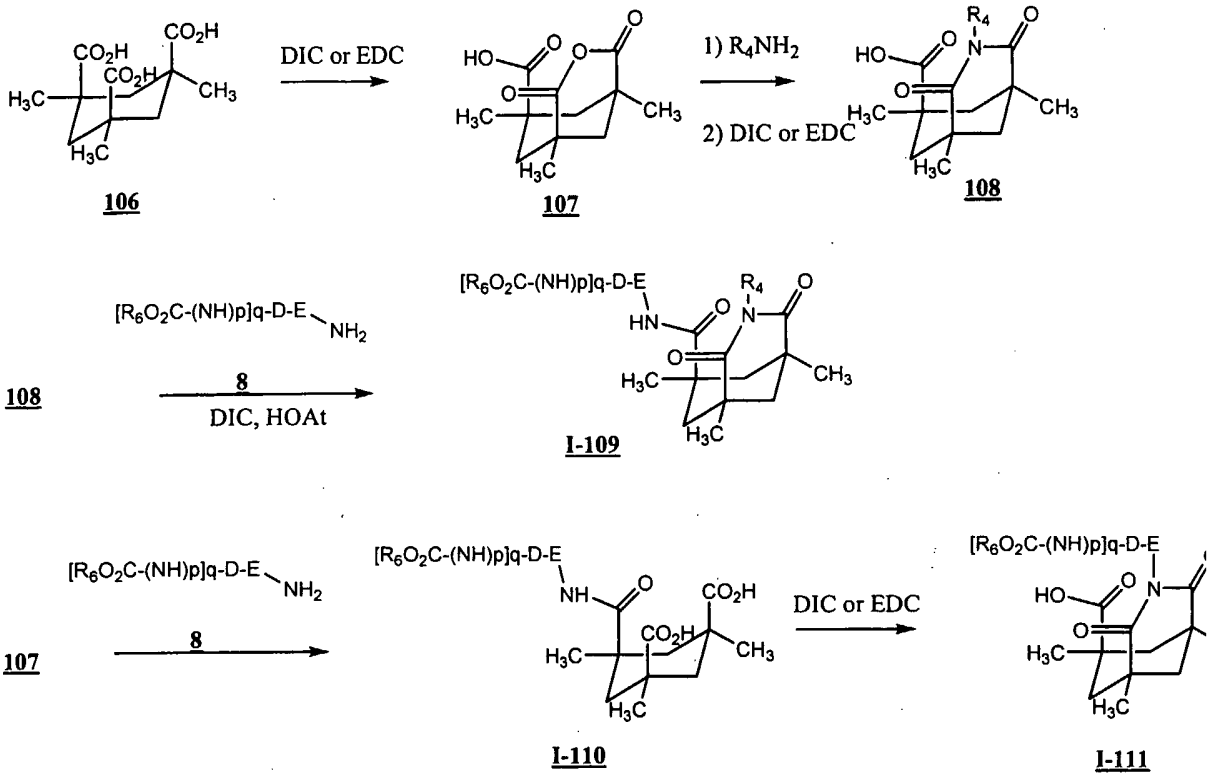
Scheme 17.2 illustrates the synthetic sequences for converting intermediates **104** to compounds of Formula **I**. Reaction of alcohol **104.1** with aryl or heteroaryl halide **26** (Q = halogen) under copper(I) catalysis gives rise to compounds of Formula **I-105.1**. Reaction of amines **104.2** and **104.3** with **26** under Buchwald palladium(0) catalyzed amination conditions affords compounds of Formulae **I-105.2** and **I-105.3**. Reaction of acetylene **104.4** with **26** under Sonogashira coupling conditions affords compounds of Formula **I-105.4**. Compounds **I-105.4** may optionally be reduced to the corresponding saturated analogs **I-105.5** by standard hydrogenation.

Scheme 17.2



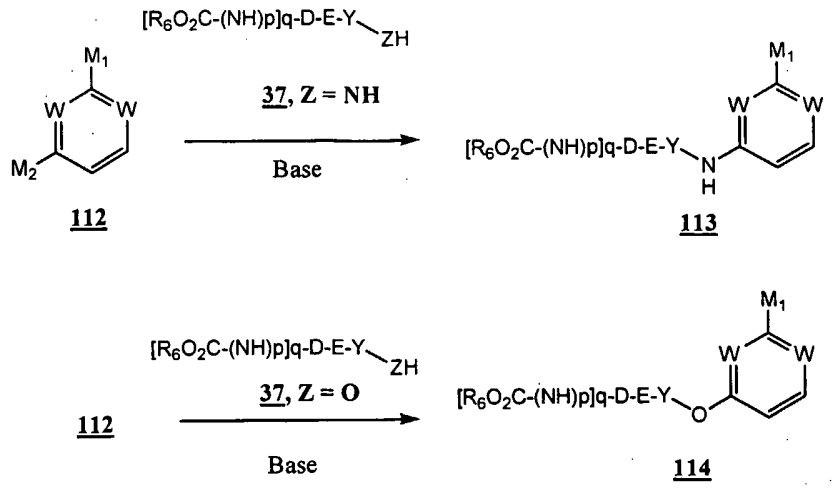
Compounds of Formula I wherein Q is taken from Q-19, Q-20, or Q-21 are prepared as illustrated in Scheme 18. Commercially available Kemp's acid **106** is converted to its anhydride **107** using a dehydrating reagent, preferably di-isopropylcarbodiimide (DIC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC). Reaction of **107** with amines R_4NH_2 affords the intermediate amides which are cyclized to the imides **108** by reaction with DIC or EDC. Alternatively, **107** is reacted with amines **8** to afford amides of Formula **I-110**. Amides **I-110** may optionally be further reacted with DIC or EDC to give rise to compounds of Formula **I-111**. Acid **108** is further reacted with amines **8** to give compounds of Formula **I-109**.

Scheme 18



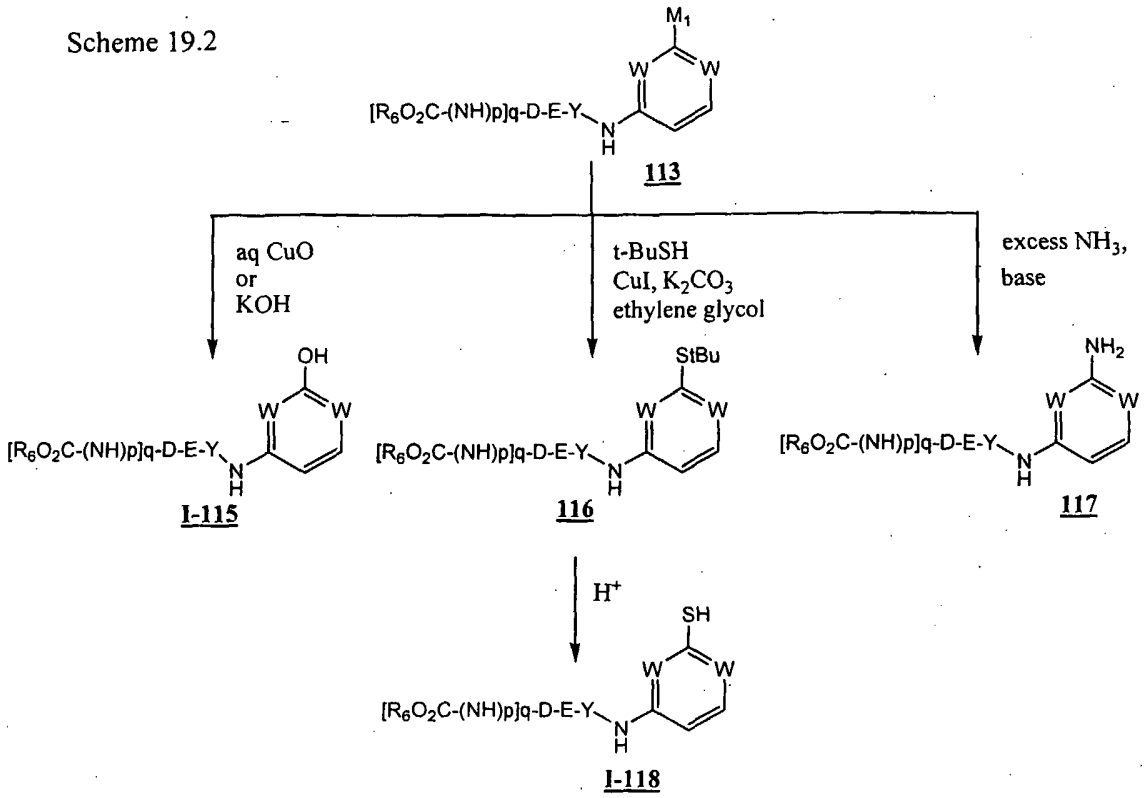
Compounds of Formula I wherein Q is taken from Q-22 or Q-23 are prepared as shown in Schemes 19.1 through 19.3. Preparation of intermediates **113** and **114** are prepared as shown in Scheme 19.1 from di-halo(hetero)aryls **112**, wherein M_2 is a more robust leaving group than M_1. Reaction of **112** with amines **37** (Z = NH) either thermally in the presence of base or by palladium(0) catalysis in the presence of base and phosphine ligand affords compounds **113**. Alternatively, reaction of **112** with alcohols **37** (X = O) either thermally in the presence of base or by copper(I) catalysis in the presence of base affords compounds **114**.

Scheme 19.1



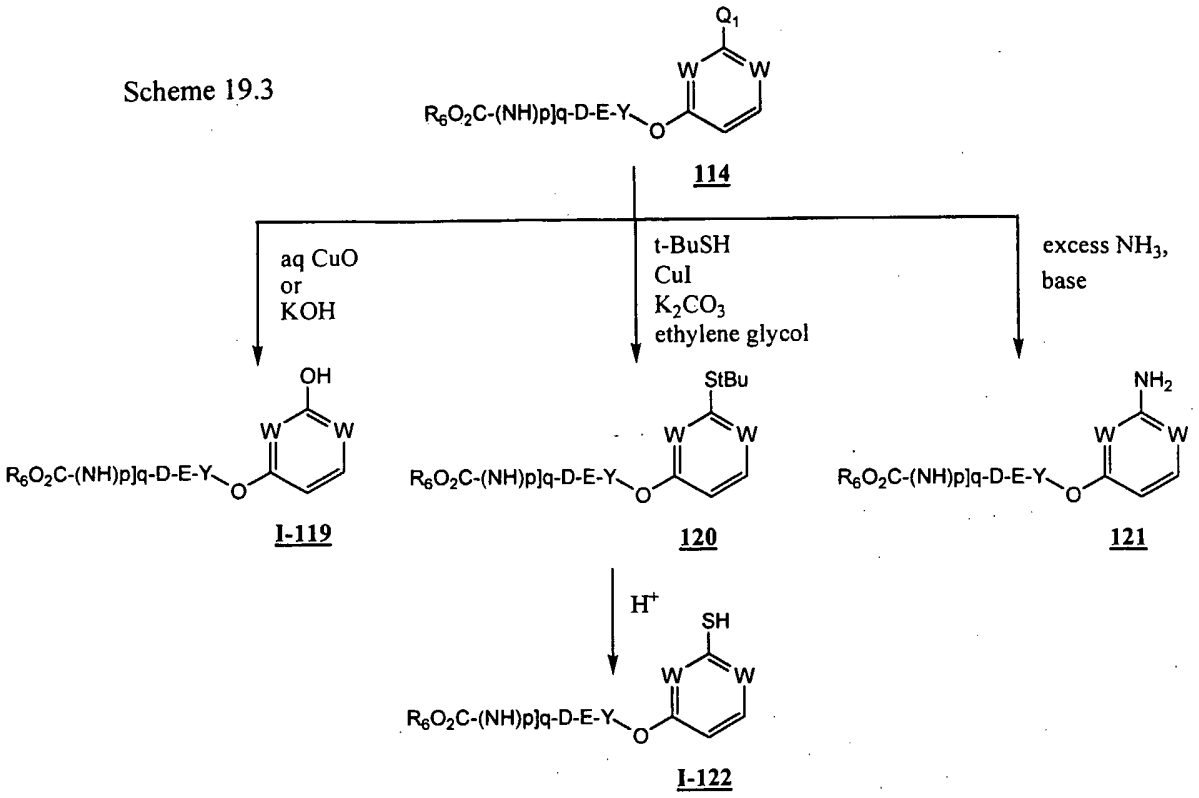
Scheme 19.2 illustrates the conversion of intermediates **113** into compounds of Formula **I-115**, **I-118**, or **117**. Treatment of **113** with aqueous copper oxide or an alkaline hydroxide affords compounds of Formula **I-115**. Alternatively, treatment of **113** with t-butylmercaptan under copper(I) catalysis in the presence of ethylene glycol and potassium carbonate gives rise to **116** (see F.Y. Kwong and S. L. Buchwald, *Organic Letters* (2002) 4:3517. Treatment of the t-butyl sulfide **116** with acid affords the desired thiols of Formula **I-118**. Alternatively, **113** may be treated with excess ammonia under pressurized conditions to afford compound **117**.

Scheme 19.2



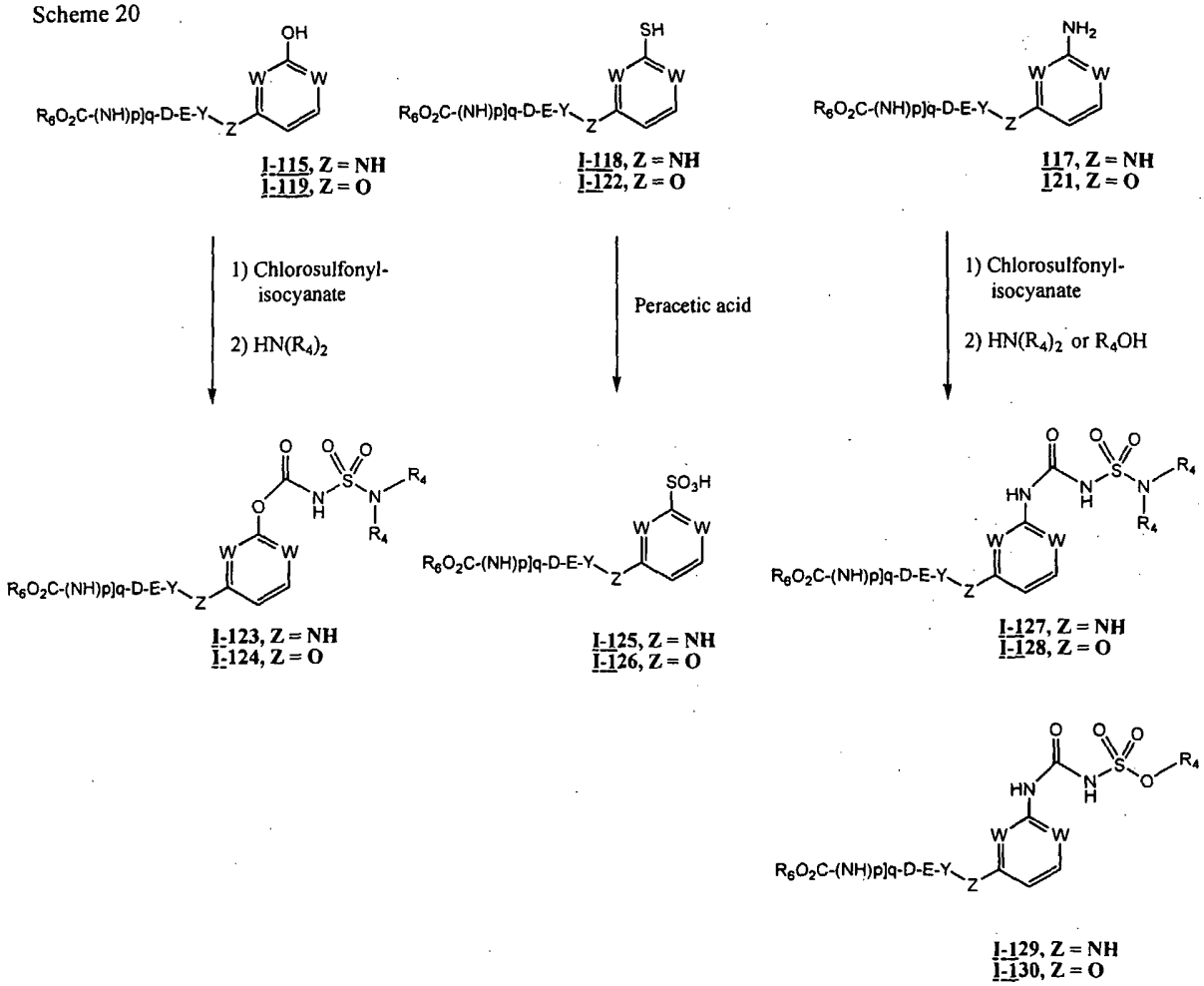
Scheme 19.3 illustrates the conversion of intermediate **114** into compounds of Formula **I-119**, **I-122**, and **121**, by analogy to the sequence described in Scheme 19.2.

Scheme 19.3



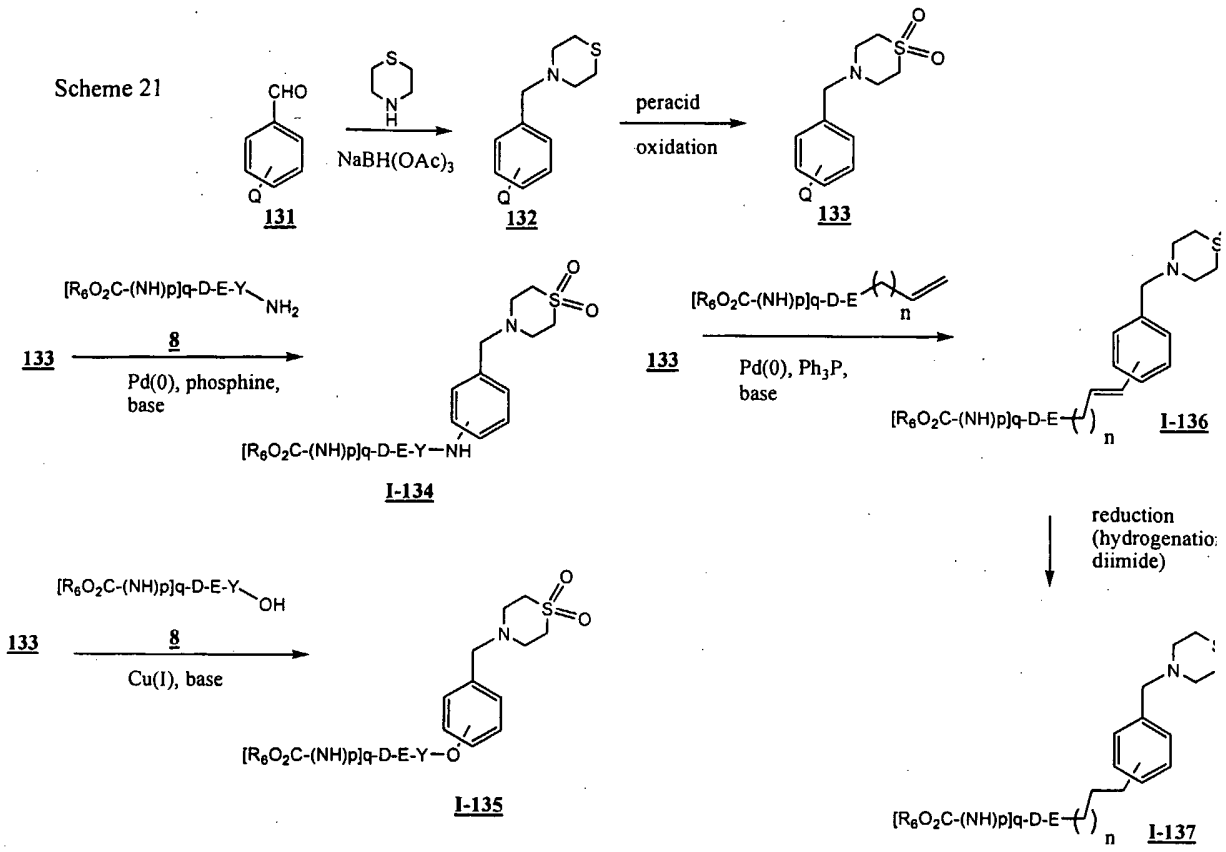
Compounds of Formula I wherein q is taken from Q-24, Q-25, or Q-26 are prepared as shown in Scheme 20. Reaction of compounds **I-115** or **I-119** with chlorosulfonylisocyanate, followed by *in situ* reaction with amines $HN(R_4)_2$ gives rise to compounds of Formulae **I-123** or **I-124**. Reaction of compounds **I-118** or **I-122** with a peracid, preferably peracetic acid or trifluoroperacetic acid, affords compounds of Formula **I-125** or **I-126**. Reaction of compounds **117** or **121** with chlorosulfonylisocyanate, followed by *in situ* reaction with amines $HN(R_4)_2$ or alcohols R_4OH, affords compounds of Formulae **I-127**, **I-128**, **I-129**, or **I-130**.

Scheme 20



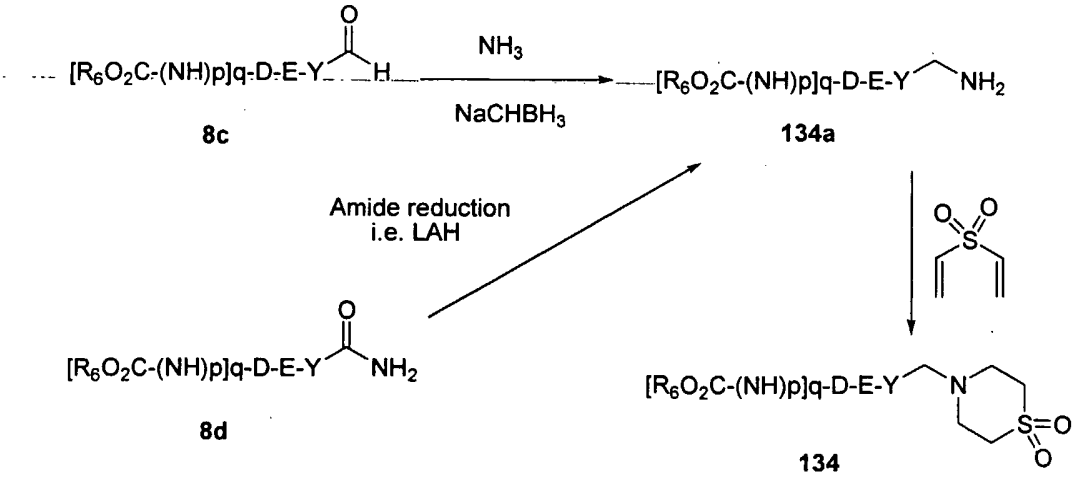
Compounds of Formula I wherein Q is taken from Q-27 are prepared as illustrated in Scheme 21. Reductive alkylation of thiomorpholine with aldehydes **131** affords benzylic amines **132**, which are then subjected to peracid oxidation to give rise to the thiomorpholine sulfones **133** (see C. R. Johnson et al, *Tetrahedron* (1969) 25: 5649). Intermediates **133** are reacted with amines **8** (Z = NH_2) under Buchwald palladium-catalyzed amination conditions to give rise to compounds of Formula **I-134**. Alternatively, compounds **133** are reacted with alcohols **8** (Z = OH) under Buchwald copper(I) catalyzed conditions to afford compounds of Formula **I-135**. Alternatively, intermediates **133** are reacted with alkenes under palladium(0)-catalyzed Heck reaction conditions to give compounds of Formula **I-136**. Compounds **I-136** are optionally reduced to the corresponding saturated analogs **I-137** by standard hydrogenation conditions or by the action of diimide.

Scheme 21



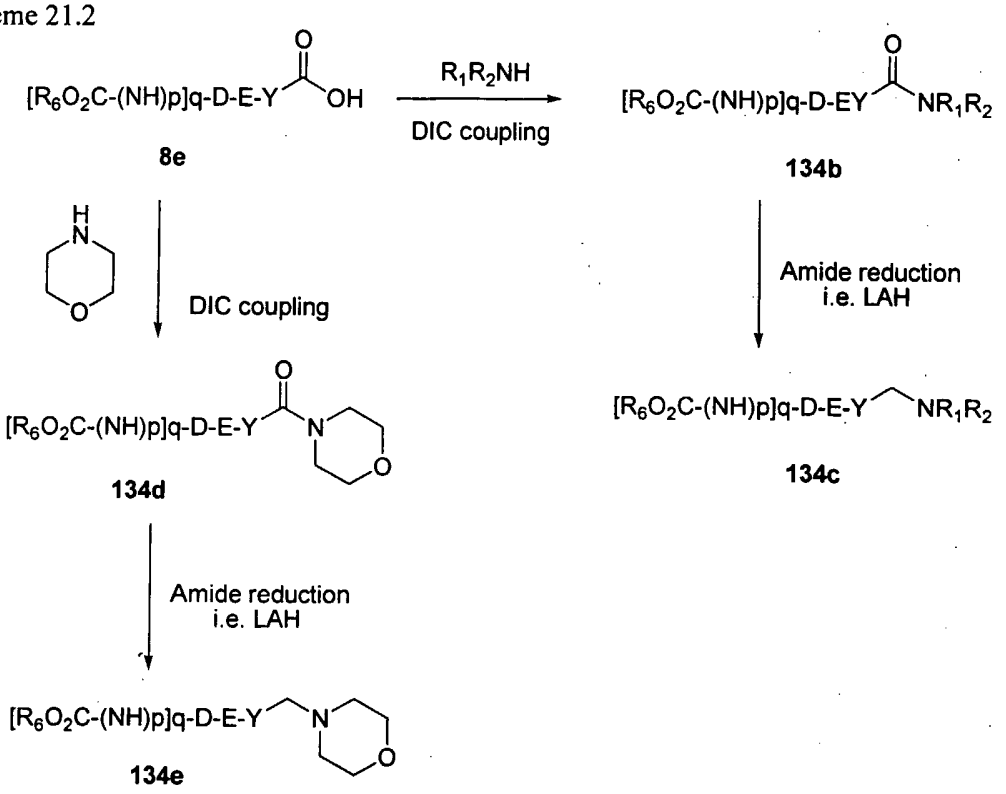
Compounds of Formula I wherein Q is taken from Q-27 are also prepared as illustrated in Scheme 21.1. Aldehyde **8c** is reductively aminated with ammonia, and the resultant amine condensed with divinyl sulphone to yield **I-134**. Intermediate **134a** is also available by reduction of amide **8d** under a variety of standard conditions.

Scheme 21.1



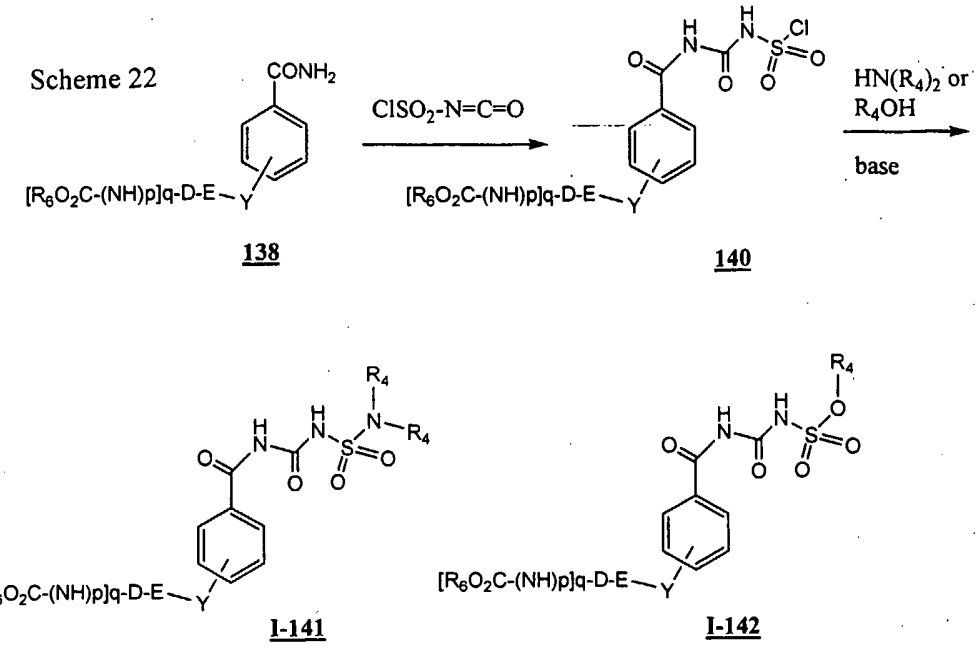
More generally, amines **134c** are available via the reduction of amides **134b** as shown in Scheme 21.2. The morpholine amide analogues **134d** and morpholine analogues **134e** are also available as shown in Scheme 21.2.

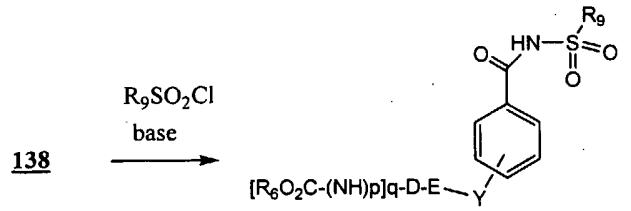
Scheme 21.2



Compounds of Formula I wherein Q is taken from Q-28 or Q-29 are prepared according to the sequences illustrated in Scheme 22. Readily available amides **138** are reacted with chlorosulfonylisocyanate to give intermediates **140**, which are reacted *in situ* with amines $HN(R_4)_2$ or alcohols R_4OH to afford compounds of Formulae **I-141** or **I-142**, respectively. Alternatively, amides **138** are reacted with sulfonylchlorides to give compounds of Formula **I-139**.

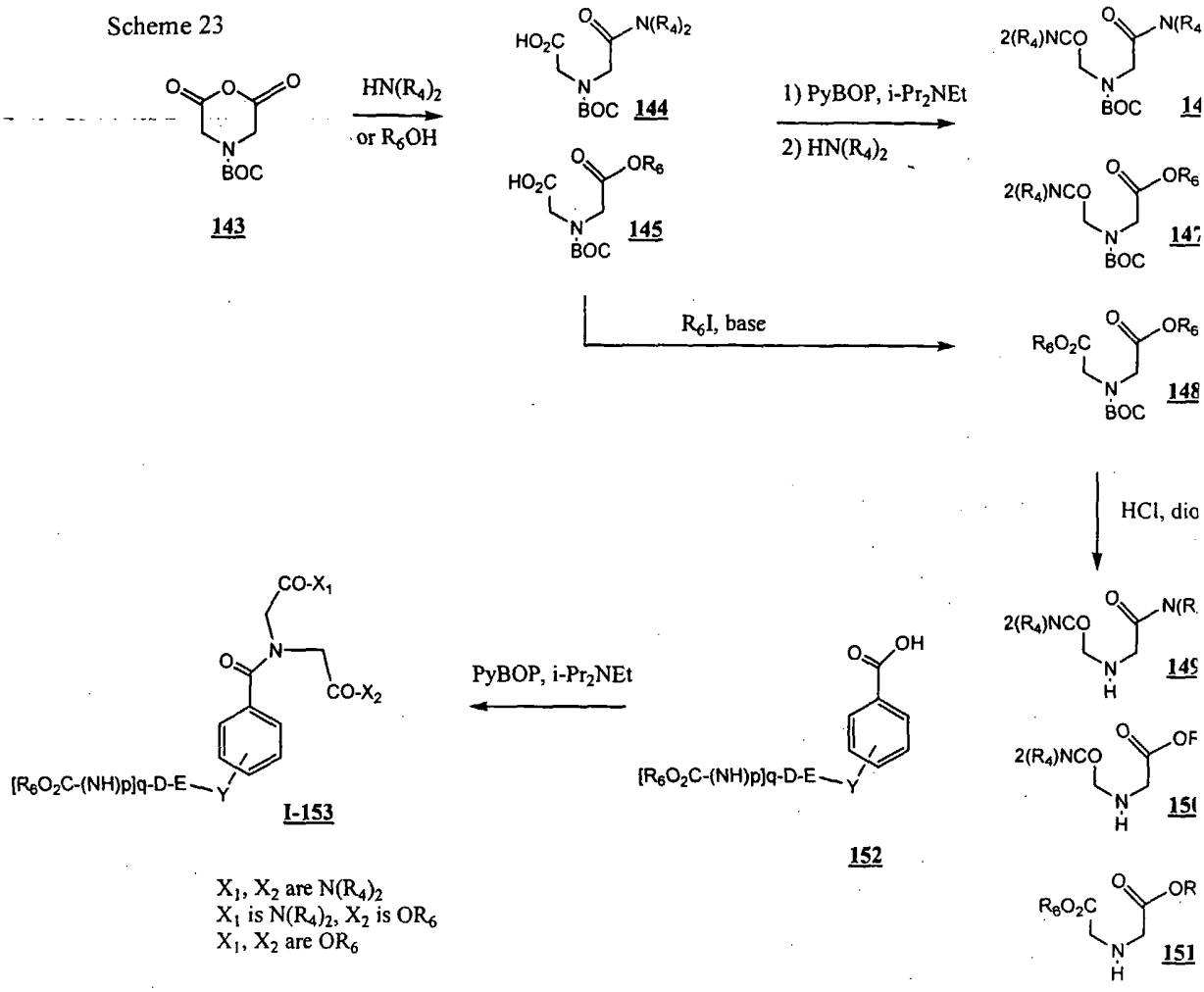
Scheme 22





Compounds of Formula I wherein Q is taken from Q-30 are prepared as shown in Scheme 23. Readily available N-BOC anhydride **143** (see S. Chen et al, *J. Am. Chem. Soc.* (1996) 118:2567) is reacted with amines $HN(R_4)_2$ or alcohols R_6OH to afford acids **144** or **145**, respectively. Intermediates **144** or **145** are further reacted with amines $HN(R_4)_2$ in the presence of an acid-activating reagent, preferably PyBOP and di-isopropylethylamine, to give diamides **146** or ester-amides **147**. Intermediate **145** is converted to the diesters **148** by reaction with an alkyl iodide in the presence of base, preferably potassium carbonate. Intermediates **146-148** are treated with HCl/dioxane to give the secondary amines **149-151**, which are then condensed with acids **152** in the presence of PyBOP and di-isopropylethylamine to give compounds of Formula **I-153**.

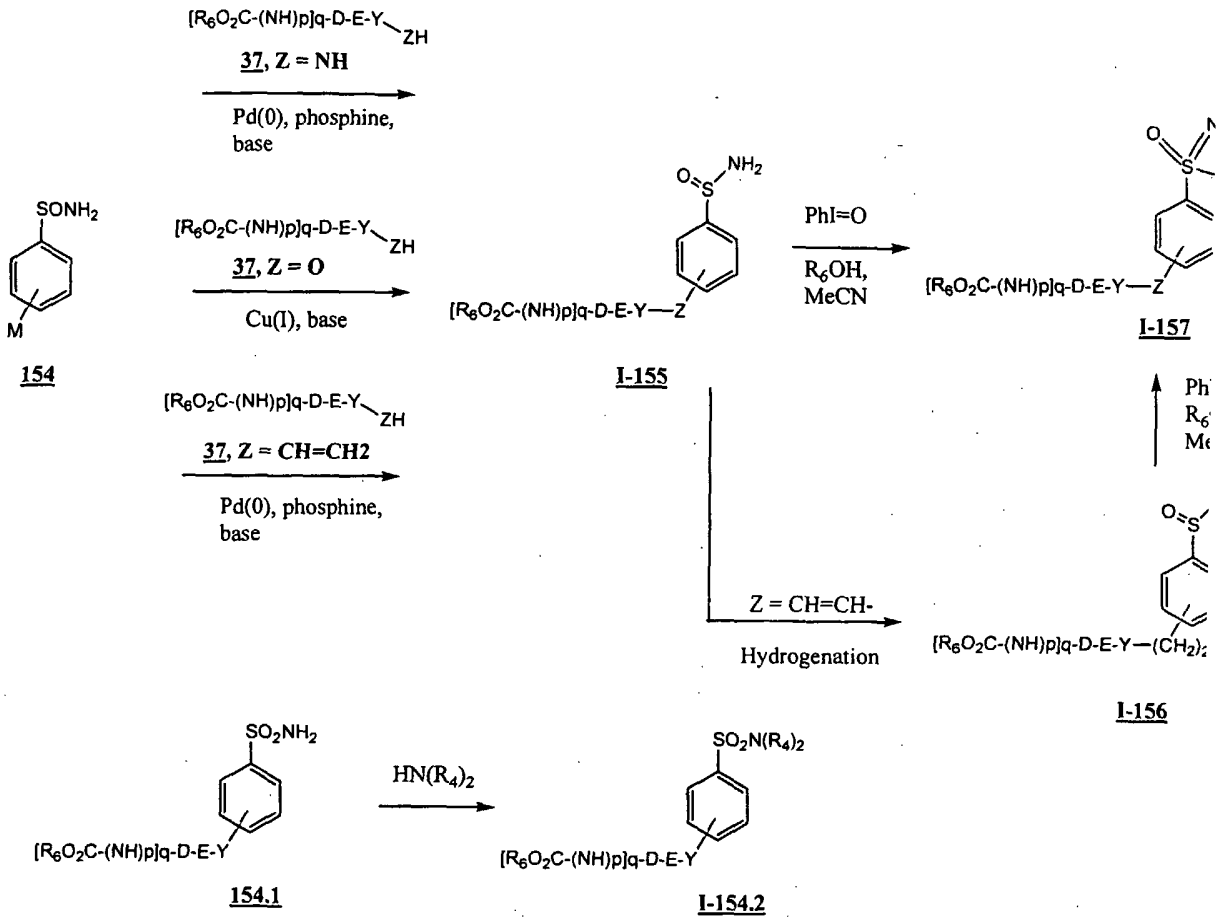
Scheme 23



Compounds of Formula I wherein Q is taken from Q-31 or Q-32 are prepared according to the sequences illustrated in Scheme 24. Treatment of readily available sulfenamides **154** with amines **37** (Z = NH), alcohols **37** (Z = O), or alkenes **37** (Z = -CH=CH_2), gives rise to compounds of Formula **I-155**. Treatment of sulfenamides **I-155** with iodosobenzene in the presence of alcohols R_6OH gives rise to the sulfonimidates of Formula **I-157** (see D. Leca et al, *Organic Letters* (2002) 4:4093). Alternatively, compounds **I-155** (Z = -CH=CH) may be optionally reduced to the saturated analogs **I-156** (Z = CH_2-CH_2-), which are converted to the corresponding sulfonimidates **I-157**.

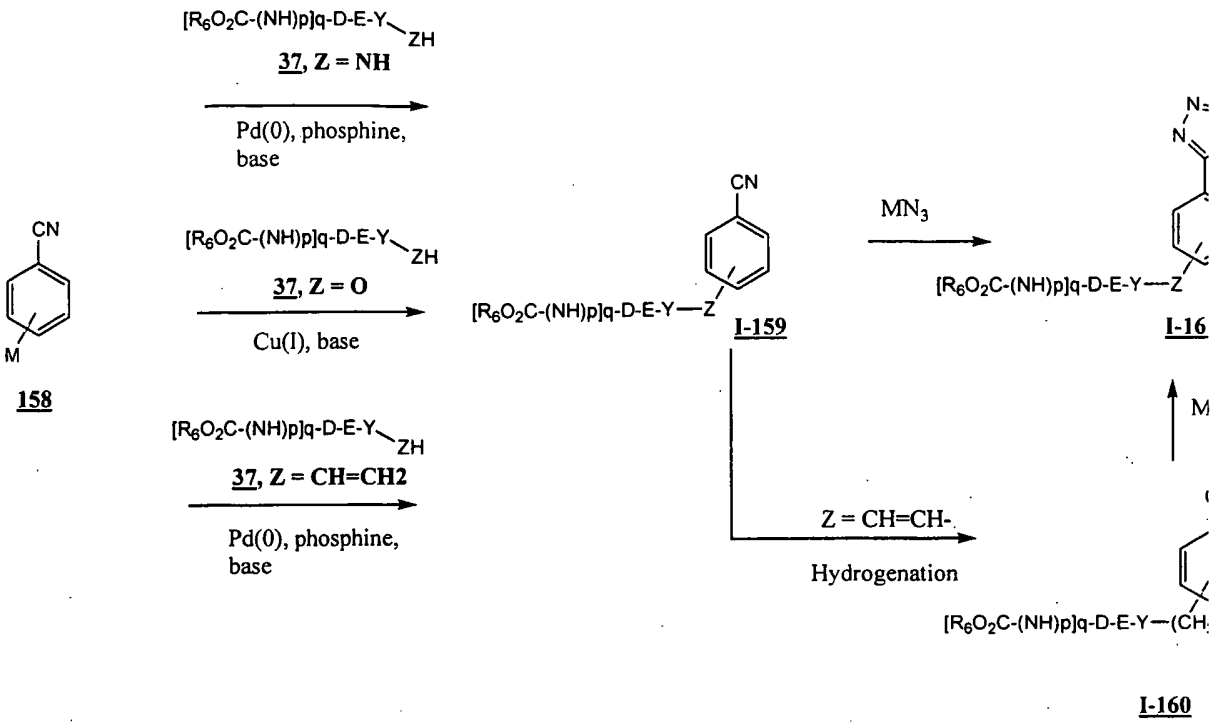
Treatment of readily available sulfonylchlorides **154.1** with amines $HN(R_4)_2$ and base gives rise to compounds of Formula **I-154.2**.

Scheme 24

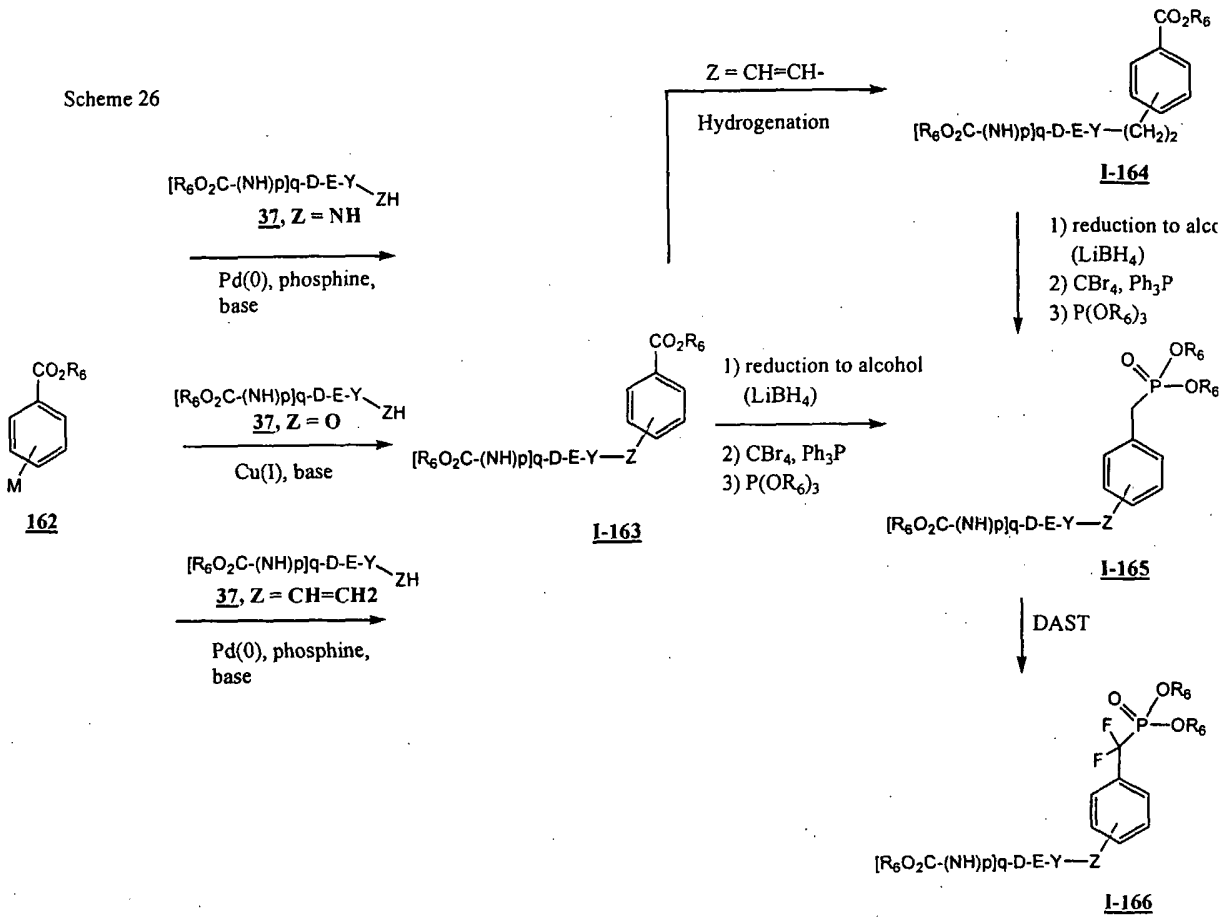


Compounds of Formula I wherein Q is taken from Q-33 are prepared as shown in Scheme 25. Readily available nitriles **158** are reacted with amines **37** (Z = NH), alcohols **37** (Z = O), or alkenes **37** (Z = -CH=CH_2) to afford compounds of Formula **I-159**. Compounds **I-159** (wherein Z = CH=CH-) are optionally reduced to their saturated analogs **I-160** by standard catalytic hydrogenation conditions. Treatment of compounds **I-159** or **I-160** with a metal azide (preferably sodium azide or zinc azide) gives rise to tetrazoles of Formula **I-161**.

Scheme 25

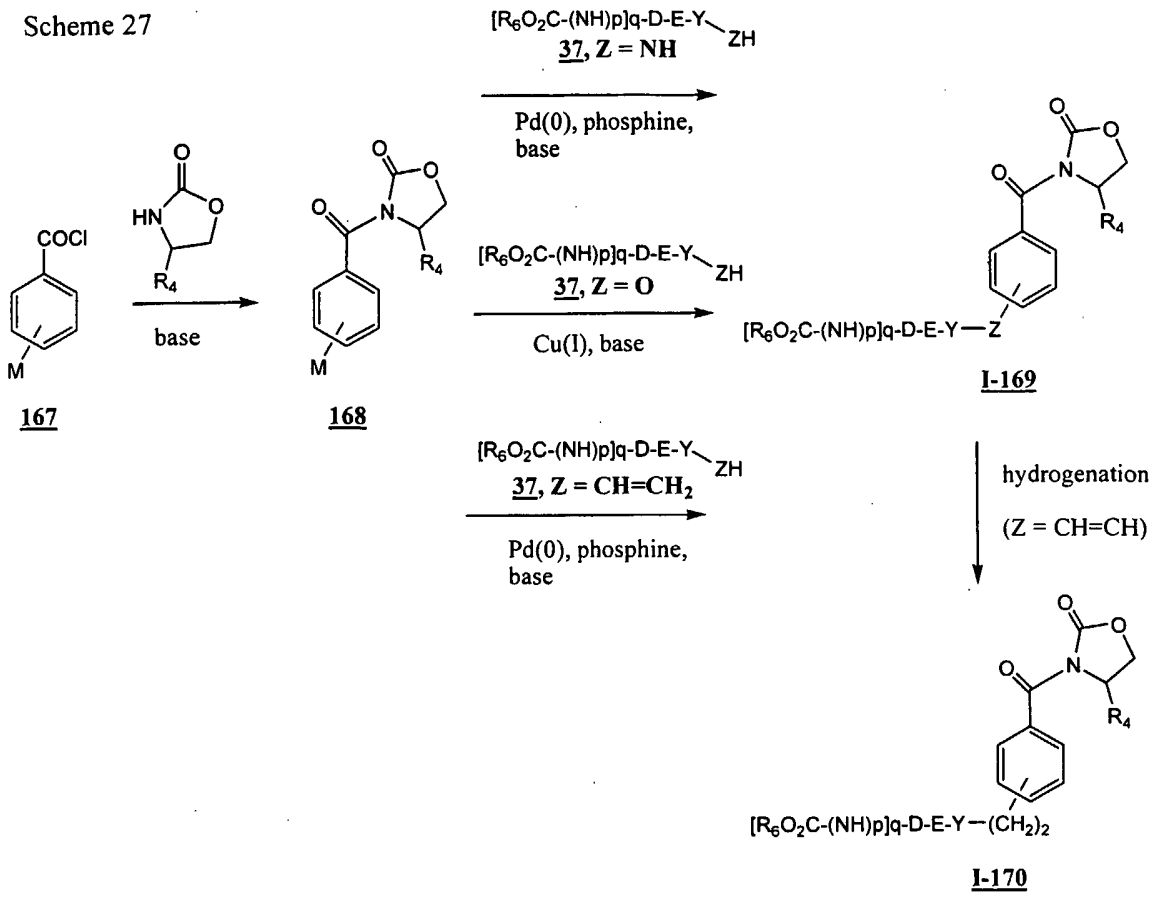


Compounds of Formula I wherein Q is taken from Q-34 are prepared as shown in Scheme 26. Readily available esters **162** are reacted with amines **37** (Z = NH), alcohols **37** (Z = O), or alkenes **37** (Z = -CH=CH_2) to afford compounds of Formula **I-163**. Compounds **I-163** (wherein Z is –CH=CH-) are optionally converted to the saturated analogs **I-164** by standard hydrogenation conditions. Compounds **I-163** or **I-164** are converted to the desired phosphonates **I-165** by an Arbuzov reaction sequence involving reduction of the esters to benzylic alcohols, conversion of the alcohols to the benzylic bromides, and treatment of the bromides with a tri-alkylphosphite. Optionally, phosphonates **I-165** are converted to the flourinated analogs **I-166** by treatment with diethylaminosulfur trifluoride (DAST).



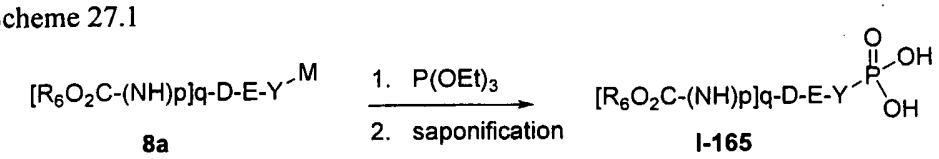
Compounds of Formula I wherein Q is taken from Q-35 are prepared according to Scheme 27. Readily available acid chlorides **167** are reacted with oxazolidones in the presence of base to afford the N-acyl oxazolidinones **168**. Intermediate **168** are reacted with amines **37** (Z = NH), alcohols **37** (Z = O), or alkenes **37** (Z = -CH=CH_2) to afford the N-acyl oxazolidinones of Formula **I-169**. Compounds **I-169** (wherein Z is –CH=CH-) are optionally converted to the saturated analogs **I-170** under standard hydrogenation conditions.

Scheme 27



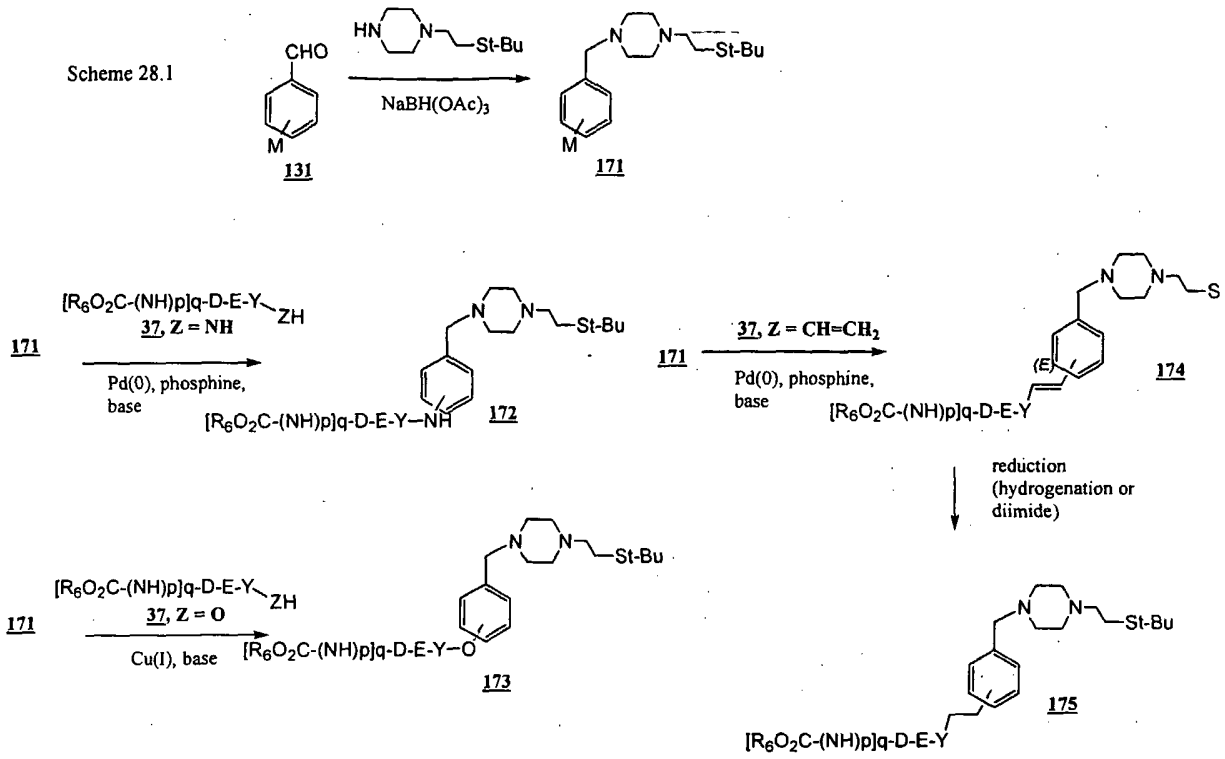
Compounds of Formula I wherein Q is taken from Q-35 are also prepared as illustrated in Scheme 27.1. Intermediate **8a**, wherein M is a suitable leaving group such as chloride, bromide or iodide, is refluxed with triethyl phosphite and the resulting phosphoryl intermediate saponified under mild conditions to yield **I-165**.

Scheme 27.1



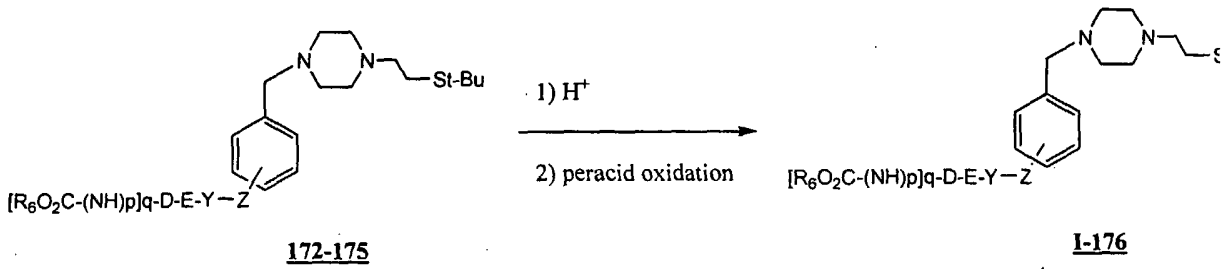
Compounds of Formula I wherein Q is taken from Q-36 are prepared as illustrated in Schemes 28.1 and 28.2. Reductive alkylation of the t-butylsulfide substituted piperazines with the readily available aldehydes 131 gives rise to the benzylic piperazines 171. Intermediates 171 are reacted with amines 37 (Z = NH), alcohols 37 (Z = O), or alkenes 37 (Z = -CH=CH$_2$) to give compounds 172, 173, or 174, respectively. Optionally, intermediates 174 are converted to the saturated analogs 175 under standard hydrogenation conditions.

Scheme 28.1



Scheme 28.2 illustrates the conversion of intermediate t-butylsulfides **172-175** to the sulfonic acids, employing a two step process involving acid-catalyzed deprotection of the t-butyl sulfide to the corresponding mercaptans, and subsequent peracid oxidation (preferably with peracetic acid or trifluoroperacetic acid) of the mercaptans to the desired sulfonic acids of Formula **I-176**.

Scheme 28.2

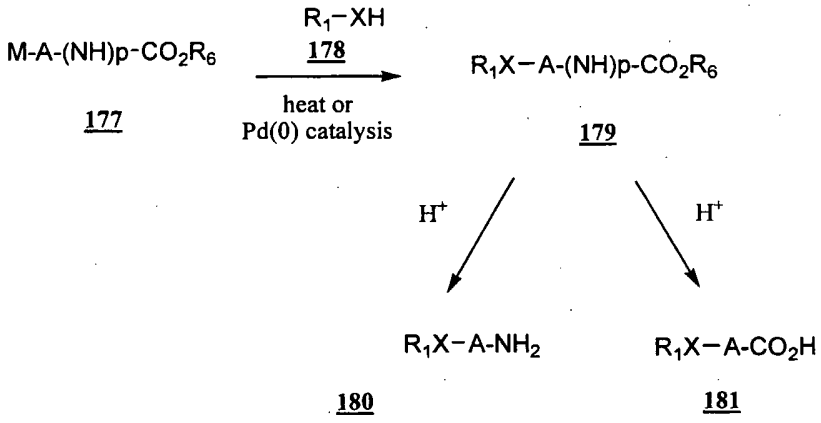


172-175 **I-176**

Z = NH, O, CH=CH, CH2-CH2

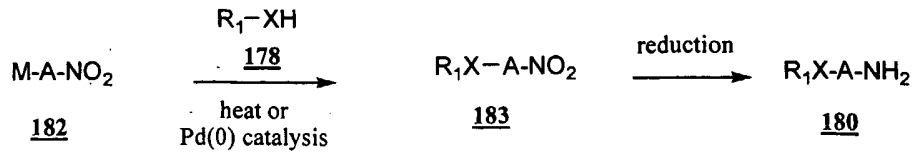
In some instances a hybrid p38-alpha kinase inhibitor is prepared which also contains an ATP-pocket binding moiety or an allosteric pocket binding moiety R_1-X-A. The synthesis of functionalized intermediates of formula R_1-X-A are accomplished as shown in Scheme 29. Readily available intermediates **177**, which contain a group M capable of oxidative addition to palladium(0), are reacted with amines **178** (X = NH) under Buchwald Pd(0) amination conditions to afford **179**. Alternatively amines or alcohols **178** (X = NH or O) are reacted thermally with **177** in the presence of base under nuclear aromatic substitution reaction conditions to afford **179**. Alternatively, alcohols **178** (X = O) are reacted with with **177** under Buchwald copper(I)-catalyzed conditions to afford **179**. In cases where p = 1, the carbamate of **179** is removed, preferably under acidic conditions when R_6 is t-butyl, to afford amines **180**. In cases where p = 0, the esters **179** are converted to the acids **181** preferably under acidic conditions when R_6 is t-butyl.

Scheme 29



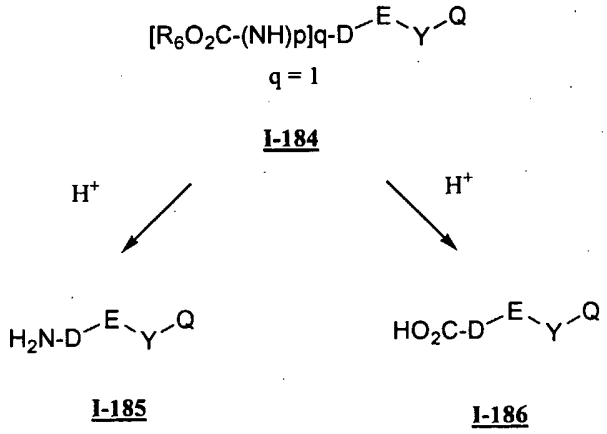
Another sequence for preparing amines **180** is illustrated in Scheme 30. Reaction of amines or alcohols **178** with nitro(hetero)arenes **182** wherein M is a leaving group, preferably M is fluoride, or M is a group capable of oxidative insertion into palladium(0), preferably M is bromo, chloro, or iodo, gives intermediates **183**. Reduction of the nitro group under standard hydrogenation conditions or treatment with a reducing metal, such as stannous chloride, gives amines **180**.

Scheme 30



In instances when hybrid p38-alpha kinase inhibitors are prepared, compounds of Formula **I-184** wherein q is 1 may be converted to amines **I-185** (p = 1) or acids **I-186** (p = 0) by analogy to the conditions described in Scheme 29. Compounds of Formula **I-184** are prepared as illustrated in previous schemes 1.1, 2.1, 2.2, 3, 4, 5, 6, 7.1, 7.2, 8, 9, 10, 12, 14, 16.2, 17.2, 18, 19.1, 19.2, 19.3, 20, 21, 22, 23, 24, 25, 26, 27, or 28.2.

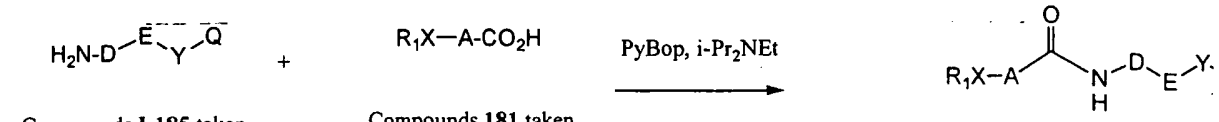
Scheme 31



Compounds **I-184** are taken from schemes 1.1, 2.1, 2.2, 3, 4, 5, 6, 7.1, 7.2, 8, 9, 10 12, 14, 16.2, 17.2, 18, 19.1, 19.2, 19.3, 20, 21, 22, 23, 24, 25, 26, 27, 28.2

The preparation of inhibitors of Formula **I** which contain an amide linkage –CO-NH- connecting the oxyanion pocket binding moieties and R_1-X-A moieties are shown in Scheme 32. Treatment of acids **181** with an activating agent, preferably PyBOP in the presence of di-iso-propylethylamine, and amines **I-185** gives compounds of Formula **I**. Alternatively, retroamides of Formula **I** are formed by treatment of acids **I-186** with PyBOP in the presence of di-iso-propylethylamine and amines **180**.

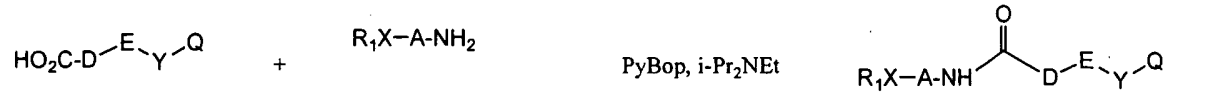
Scheme 32



Compounds **I-185** taken from scheme 31

Compounds **181** taken from scheme 29

Amides of Formula I
(hybrid inhibitors, possessing oxyanio
pocket-binding moiety Q and moiety R_1-)



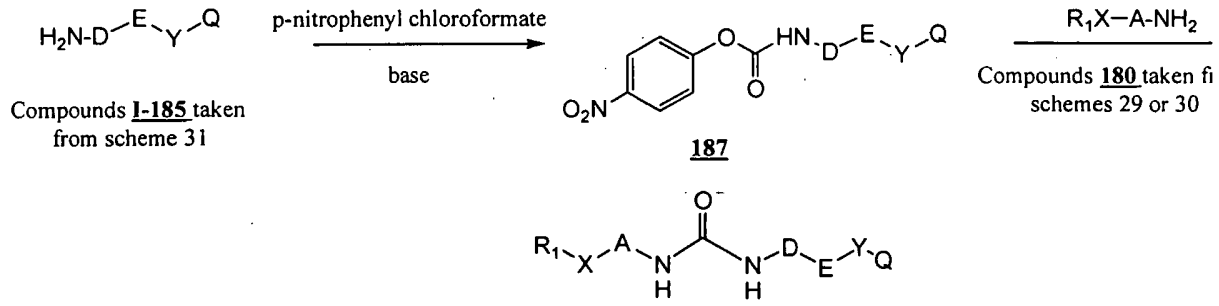
Compounds **I-186** taken from scheme 31

Compounds **180** taken from schemes 29 or 30

RetroamideFormula I
(hybrid inhibitors, possessing oxyanic
pocket-binding moiety Q and moiety R_1-

The preparation of inhibitors of Formula **I** which contain an urea linkage NH–CO-NH- connecting the oxyanion pocket binding moieties and the R_1-X-A moieties are shown in Scheme 33. Treatment of amines **I-185** with p-nitrophenyl chloroformate and base affords carbamates **187**. Reaction of **187** with amines **180** gives ureas of Formula **I**.

Scheme 33



Compounds **I-185** taken from scheme 31

187

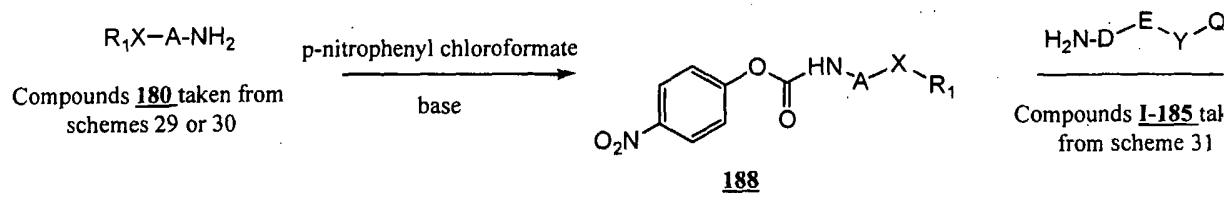
Compounds **180** taken fi schemes 29 or 30

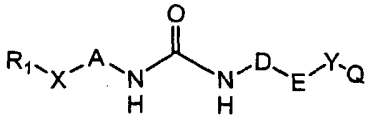
Formula I
(hybrid inhibitors, possessing oxyanion
pocket-binding moiety Q and moiety R_1-X-A)

Alternatively, inhibitors of Formula **I** which contain an urea linkage NH–CO-NH- connecting the oxyanion pocket binding moieties and the R_1-X-A moieties are prepared as

shown in Scheme 33. Treatment of amines **180** with p-nitrophenyl chloroformate and base affords carbamates **188**. Reaction of **188** with amines **I-185** gives ureas of Formula **I**.

Scheme 34

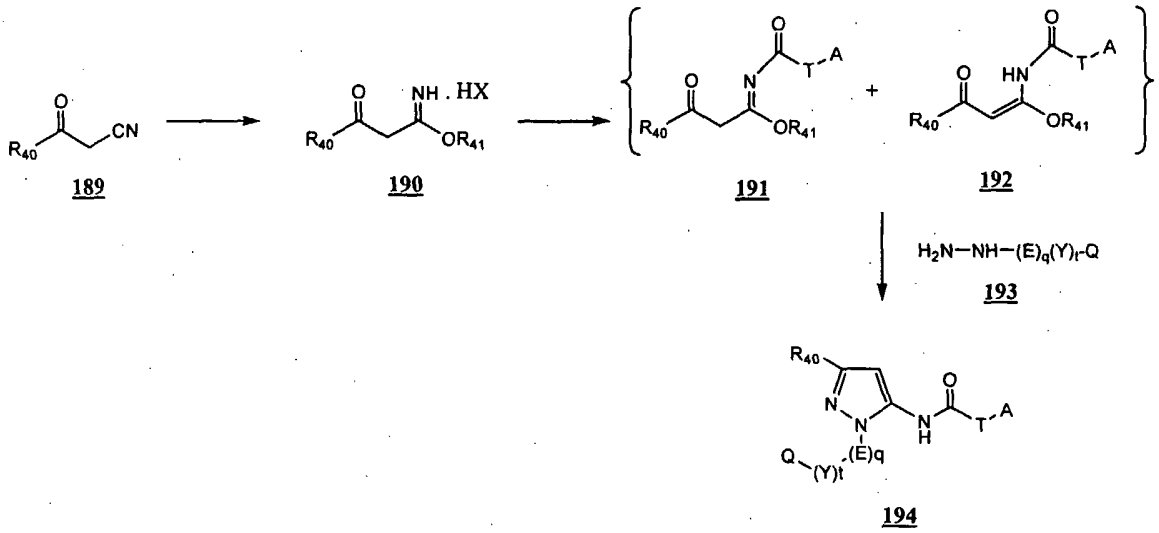




Formula I
(hybrid inhibitors, possessing oxyanion pocket-binding moiety Q and moiety R_1-X-A)

The preparation of inhibitors of Formula **I.B** can be generally accomplished starting from a variety of readily available *beta*-ketonitriles **189**, wherein R_{40} is alkyl, phenyl, or perfluoroalkyl. As illustrated in Scheme 35, reaction of **189** with an alcohol R_4OH, preferably methanol or ethanol, under anhydrous acidic conditions, preferably anhydrous HCl, leads to the formation of imidates **190**. Reaction of **190** with acyl chlorides, isocyanates, *para*-nitrophenylcarbamates, or substituted chloroformates in the presence of a base, preferably pyridine, triethylamine, di-*iso*-propylethylamine, Barton's base, or an alkali metal carbonate, affords key intermediates **191** and **192** as a mixture of tautomers, wherein T is alkylene, NH, O, or when T is absent, then the carbonyl side chain and A are connected by a direct bond.

Scheme 35

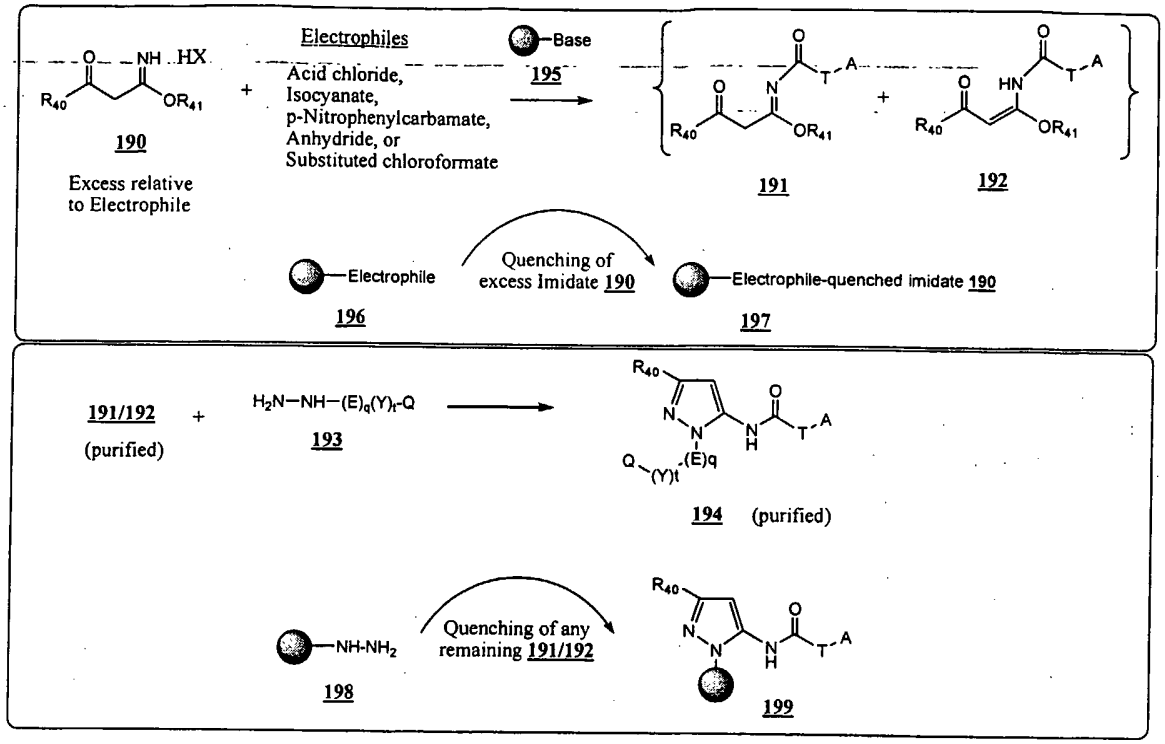


The mixture of tautomers **191/192** are not separated from each other, but are reacted as a mixture with a substituted hydrazine **193**, wherein the Q moiety is optionally protected by a protecting group that diminishes its reactivity with the **191/192** mixture. This cyclodehydration reaction is performed in the presence of base, acid catalysis, or under neutral conditions optionally in the presence of a dehydrating agent to afford the desired pyrazoles **194**. Preferable reaction solvents include dichloromethane, ethyl acetate, acetonitrile, or an alcoholic solvent taken from methanol, ethanol, or 2-propanol.

The reaction sequence initiating from **190** and yielding **194** may take place as two separate reactions, wherein the tautomeric mixture **191/192** is isolated, and then in a second reaction step this **191/192** mixture is reacted with a substituted hydrazine **193** to afford the desired pyrazoles **194**. Alternatively, the reaction sequence initiating from **190** and yielding **194** may take place in a one-pot procedure, without isolation of the intermediate **191/192** mixture.

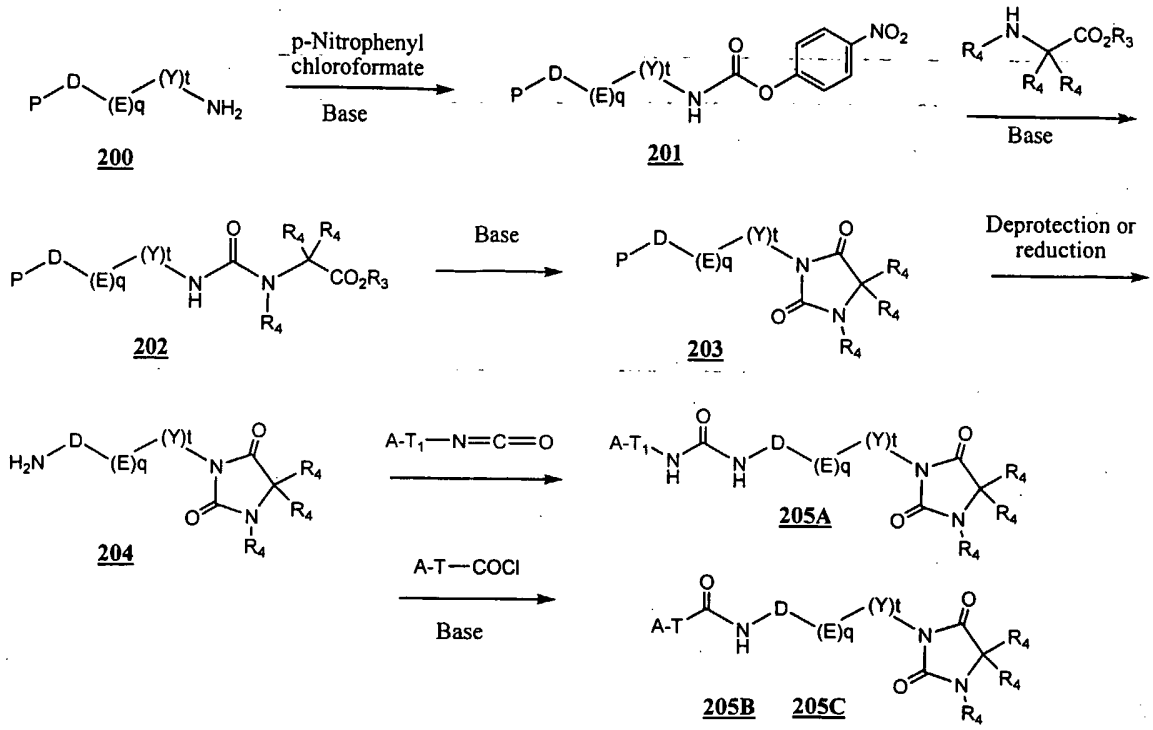
In a further modification, the reaction sequence initiating from **190** and yielding **194** may take place in a parallel array format, wherein phase-trafficking reagents, including scavenging reagents, are utilized to allow purification and isolation of intermediates and products. Scheme 36 illustrates this modification. Excess imidate **190** is reacted with a limiting amount of electrophile in the presence of a polymer-supported base **195** to afford the acylated imidates **191/192** as a mixture of tautomers. The crude mixture of **191/192** is optionally purified by incubation with a polymer-supported electrophile **196**, preferably a polymer-supported isocyanate or acid chloride. Reaction of **196** with any remaining imidate **190** sequesters this imidate as polymer-supported **197**. Filtration gives purified **191/192**. In the second step, purified acylated imidates **191/192** are reacted with the substituted hydrazines **193** to afford desired crude products **194**. A polymer-supported hydrazine **198** is optionally utilized to scavenge any remaining **191/192** from solution phase as derivatized **199**. Filtration gives rise to purified desired pyrazoles **194**.

Scheme 36



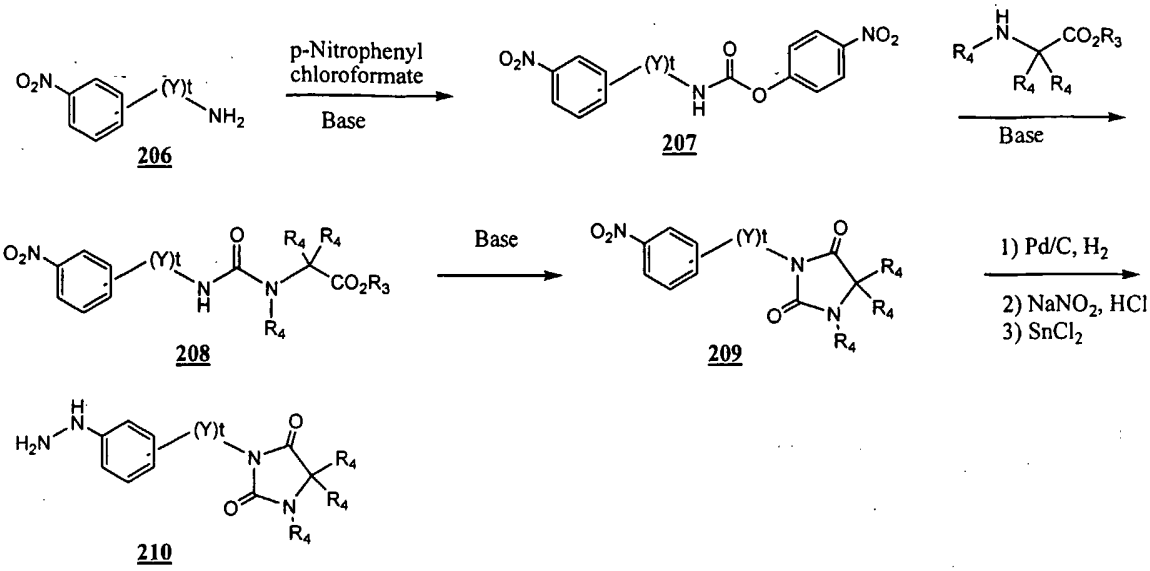
Scheme 37 illustrates the preparation of compounds wherein Q is Q-40. Readily available amine **200**, wherein P is a suitable amine-protecting group or a group convertible to an amine group, is reacted with p-nitrophenyl chloroformate to give rise to carbamate **201**. Intermediate **201** is reacted with a substituted amino acid ester with a suitable base to afford urea **202**. Further treatment with base results in cyclization to afford hydantoin **203**. The protecting group P is removed to afford the key amine-containing intermediate **204**. Alternatively, if P is a nitro group, then **203** is converted to **204** under reducing conditions such as iron/HCl, tin(II) chloride, or catalytic hydrogenation. Amine **204** is converted to **205A** by reaction with an isocyanate; **204** is converted to amide **205B** by reaction with an acid chloride, acid anhydride, or a suitable activated carboxylic acid in the presence of a suitable base; **204** is converted to carbamate **205C** by reaction with a substituted alkyl or aryl chloroformate in the presence of a suitable base.

Scheme 37



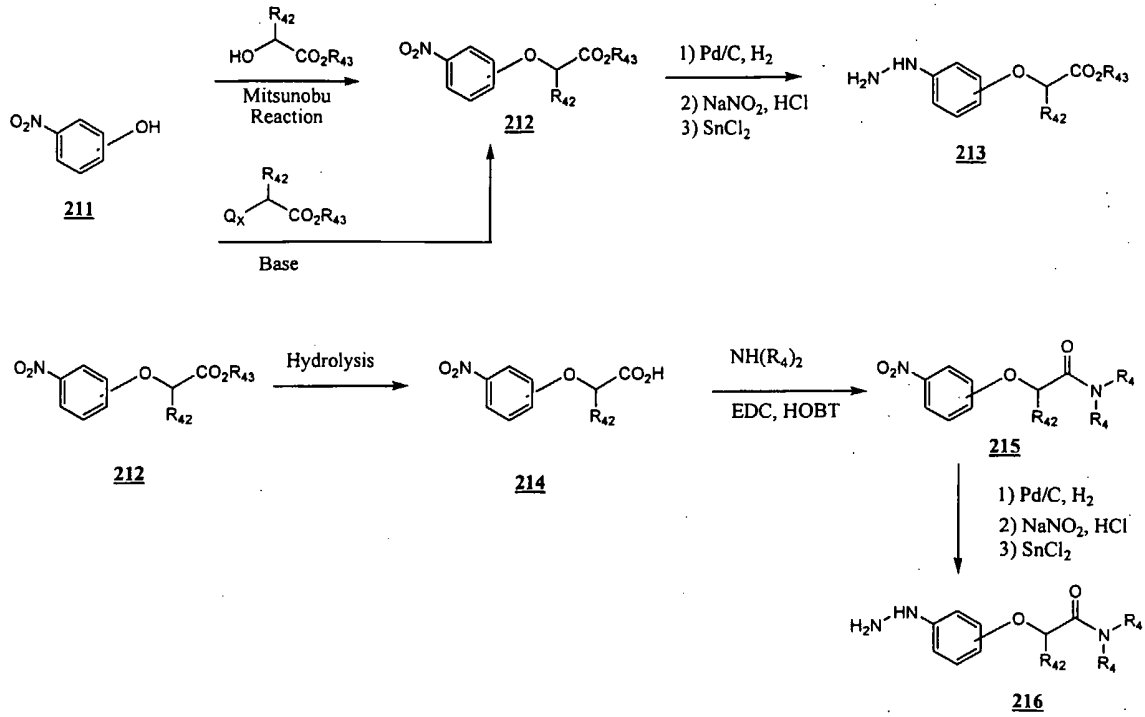
Scheme 38 illustrates the synthesis of key substituted hydrazine **210**. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36. The nitrophenyl substituted amine **206** is reacted with *p*-nitrophenyl chloroformate to give rise to carbamate **207**. Reaction of **207** with a suitable amino acid ester affords urea **208**, which is cyclized under basic conditions to give hydantoin **209**. Reduction of the nitro group of **209**, diazotization of the resulting amine, and reduction of the diazonium salt affords key hydrazine **210**.

Scheme 38



Scheme 39 illustrates the synthesis of key substituted hydrazines **213** and **216**, utilized to prepare compounds of formula **I.B** wherein Q is Q-42 and G is oxygen. Nitrophenol **211** is reacted with an alpha-hydroxy acid, wherein R_{42} is H or alkyl and R_{43} is alkyl, under Mitsunobu reaction conditions to give **212**; alternatively **211** is reacted under basic conditions with a carboxylic acid ester containing a displaceable Q_x group to afford **212**. Conversion of **212** to the hydrazine **213** is accomplished by standard procedures as described above.

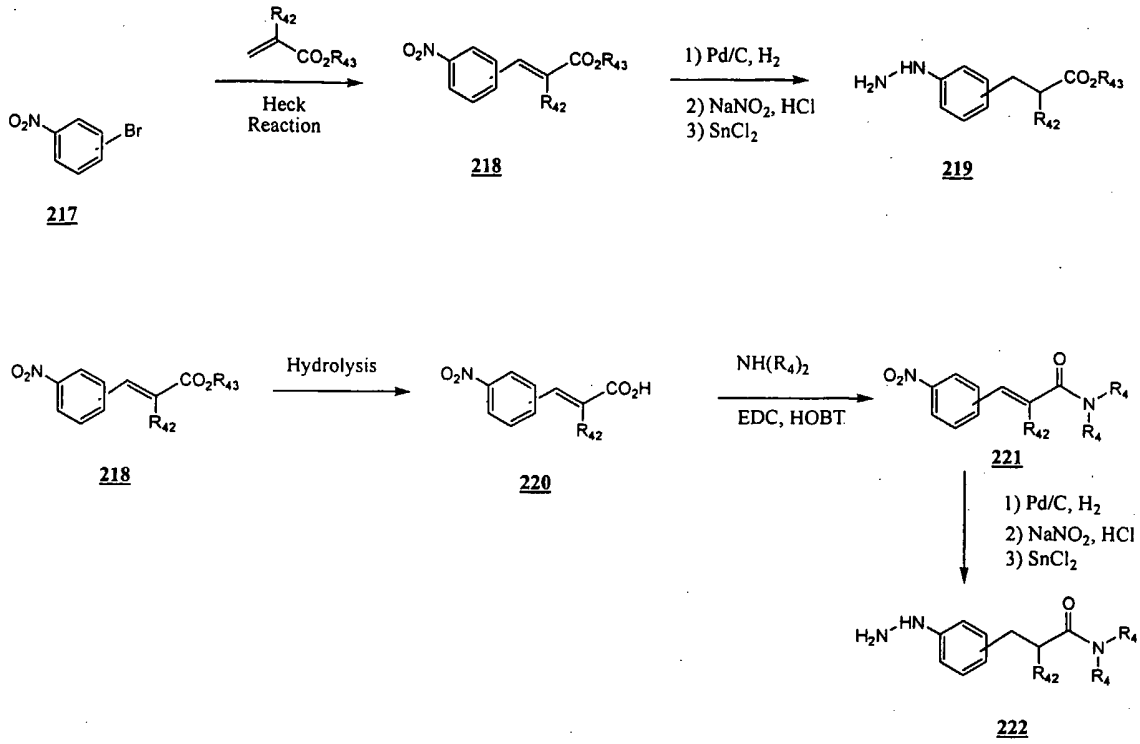
Scheme 39



Alternatively, the ester group of **212** is hydrolyzed to afford carboxylic acid **214**, which is reacted with an amine $NH(R_4)_2$ in the presence of a coupling reagent, preferably EDC/HOBT, to give amide **215**. Conversion of **215** to the substituted hydrazine **216** is accomplished by standard procedures. Hydrazines **213** and **216** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 40 illustrates the synthesis of key substituted hydrazines **219** and **222**, utilized to prepare compounds of formula **I.B** wherein Q is Q-42 and G is methylene. Nitrophenyl bromide **217** is reacted with an *alpha-beta* unsaturated ester using Pd(0) catalyzed Heck reaction conditions, to afford ester **218**. This intermediate is converted to the substituted hydrazine **219** by standard procedures involving concomitant reduction of the *alpha-beta* unsaturated bond. Alternatively, ester **218** is hydrolyzed to the carboxylic acid **220**, which is reacted with an amine $NH(R_4)_2$ in the presence of a coupling reagent, preferably EDC/HOBT, to give amide **221**. Conversion of **221** to the substituted hydrazine **222** is accomplished by standard procedures. Hydrazines **219** and **222** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

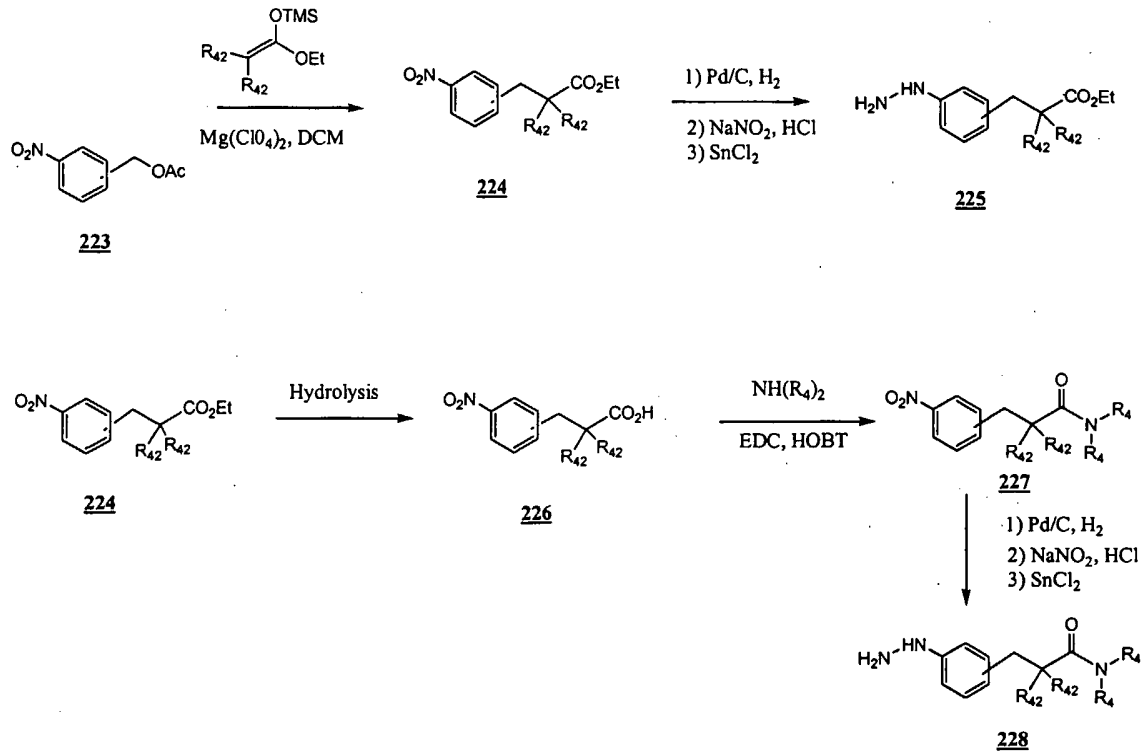
Scheme 40



217 218 219 218 220 221 222

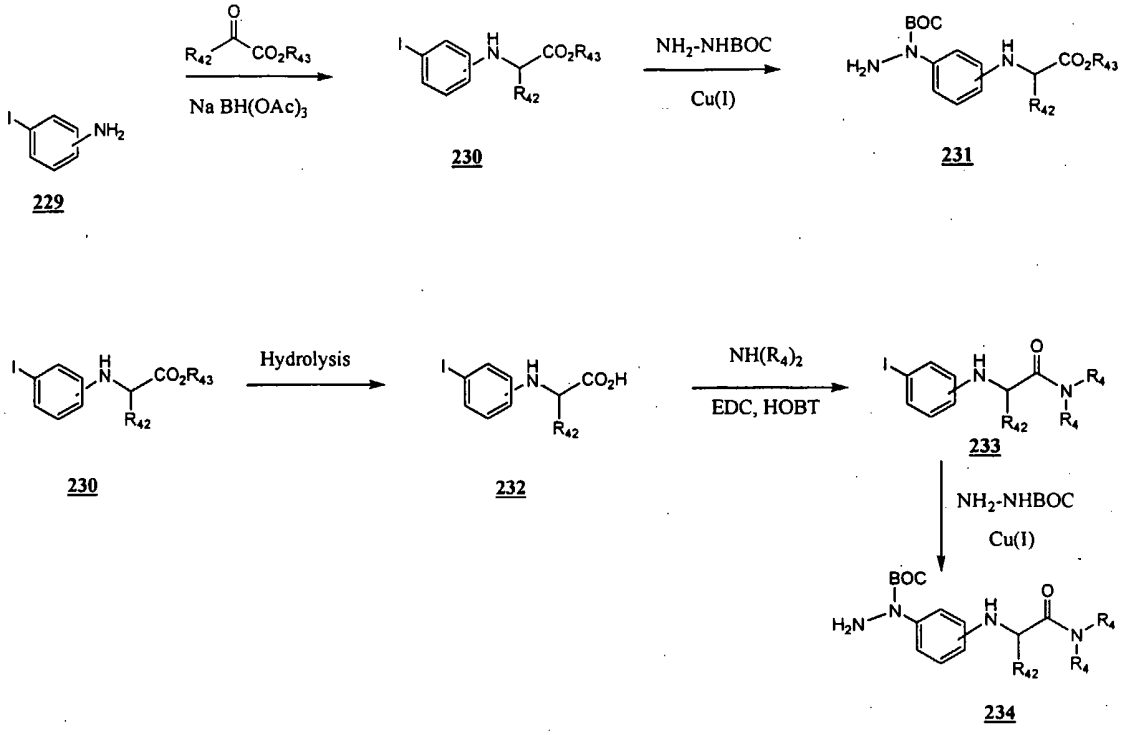
Scheme 41 illustrates an alternative synthesis of key substituted hydrazines **225** and **228**, utilized to prepare compounds of formula **I.B** wherein Q is Q-42, G is methylene, and one or both of R_{42} are carbon-containing substituents. Nitrobenzyl acetate **223** is reacted with a substituted silylketene acetal to afford ester **224**. This intermediate is converted to the substituted hydrazine **225** by standard procedures. Alternatively, ester **223** is hydrolyzed to the carboxylic acid **226**, which is reacted with an amine $NH(R_4)_2$ in the presence of a coupling reagent, preferably EDC/HOBT, to give amide **227**. Conversion of **227** to the substituted hydrazine **228** is accomplished by standard procedures. Hydrazines **225** and **228** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 41



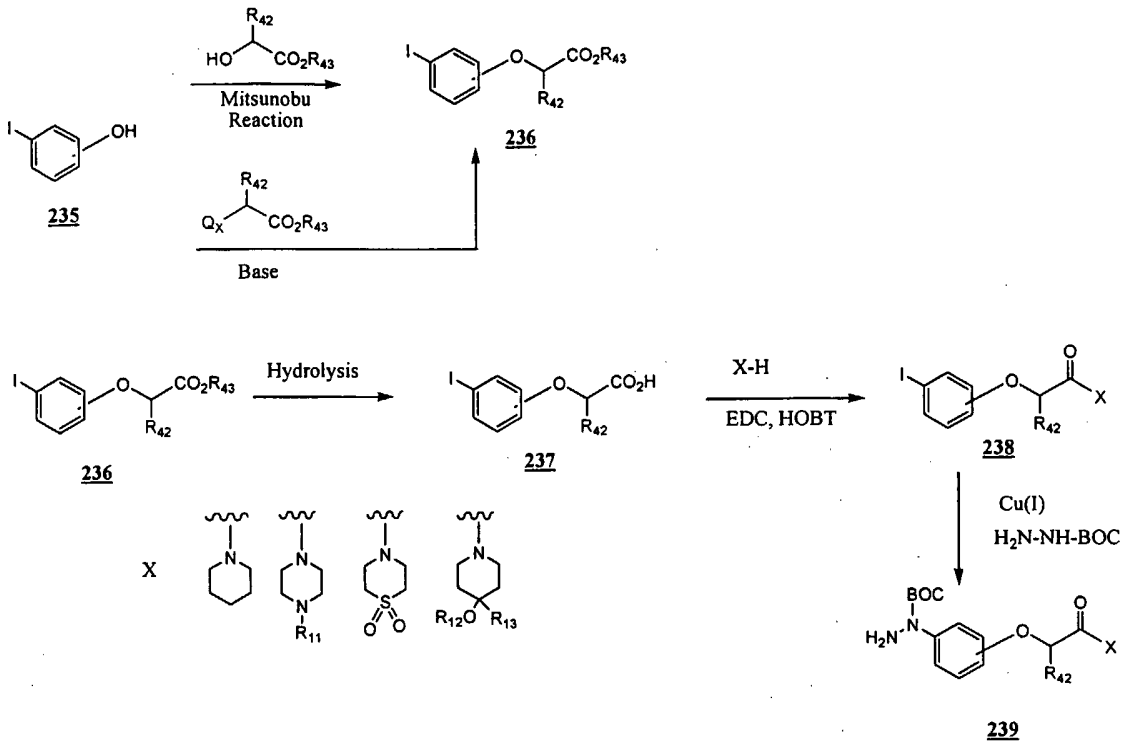
Scheme 42 illustrates an alternative synthesis of key substituted hydrazines **231** and **234**, utilized to prepare compounds of formula **I.B** wherein Q is Q-42 and G is NH. Iodoaniline **229** is reacted with an alpha-keto ester under reductive amination conditions, preferably sodium triacetoxyborohydride, to afford ester **230**. This intermediate is converted to the substituted hydrazine **231** by Cu(I)-catalyzed reaction with N-BOC hydrazine. Alternatively, ester **231** is hydrolyzed to the carboxylic acid **232**, which is reacted with an amine $NH(R_4)_2$ in the presence of a coupling reagent, preferably EDC/HOBT, to give amide **233**. Conversion of **233** to the substituted hydrazine **234** is accomplished by Cu(I)-catalyzed reaction with N-BOC hydrazine. Hydrazines **231** and **234** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36, after acid-catalyzed removal of the hydrazine N-BOC protecting group, preferably with trifluoroacetic acid or HCl-dioxane.

Scheme 42



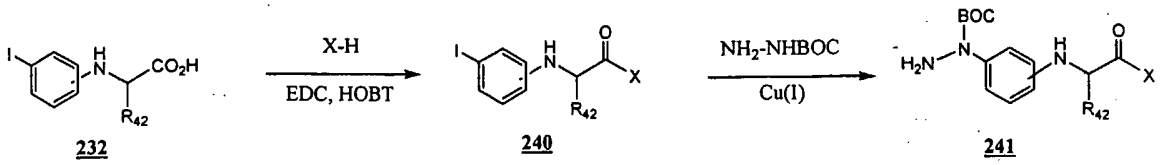
Scheme 43 illustrates an alternative synthesis of key substituted hydrazine **239**, utilized to prepare compounds of formula **I.B** wherein Q is Q-42, G is oxygen, and X is taken from piperidinyl, piperazinyl, thiomorphorlino sulfone, or 4-hydroxypiperinyl. Iodophenol **235** is reacted with an alpha-hydroxy acid under Mitsunobu reaction conditions to give **236**; alternatively **235** is reacted under basic conditions with a carboxylic acid ester containing a displaceable Q_x group to afford **236**. Ester **236** is hydrolyzed to the carboxylic acid **237**, which is reacted with an amine **X-H** in the presence of a coupling reagent, preferably EDC/HOBT, to give amide **238**. Conversion of **238** to the substituted hydrazine **239** is accomplished by Cu(I)-catalyzed reaction with N-BOC hydrazine. Hydrazine **239** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36, after acid-catalyzed removal of the hydrazine N-BOC protecting group, preferably with trifluoroacetic acid or HCl-dioxane.

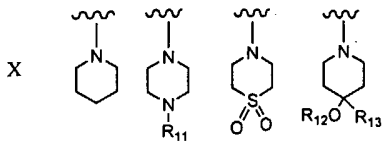
Scheme 43



Scheme 44 illustrates an alternative synthesis of key substituted hydrazine **241**, utilized to prepare compounds of formula **I.B** wherein Q is Q-42, G is NH, and X is taken from piperidinyl, piperazinyl, thiomorphorlino sulfone, or 4-hydroxypiperinyl. Carboxylic acid **237** is reacted with an amine **X-H** in the presence of a coupling reagent, preferably EDC/HOBT, to give amide **240**. Conversion of **240** to the substituted hydrazine **241** is accomplished by Cu(I)-catalyzed reaction with N-BOC hydrazine. Hydrazine **241** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36, after acid-catalyzed removal of the hydrazine N-BOC protecting group, preferably with trifluoroacetic acid or HCl-dioxane.

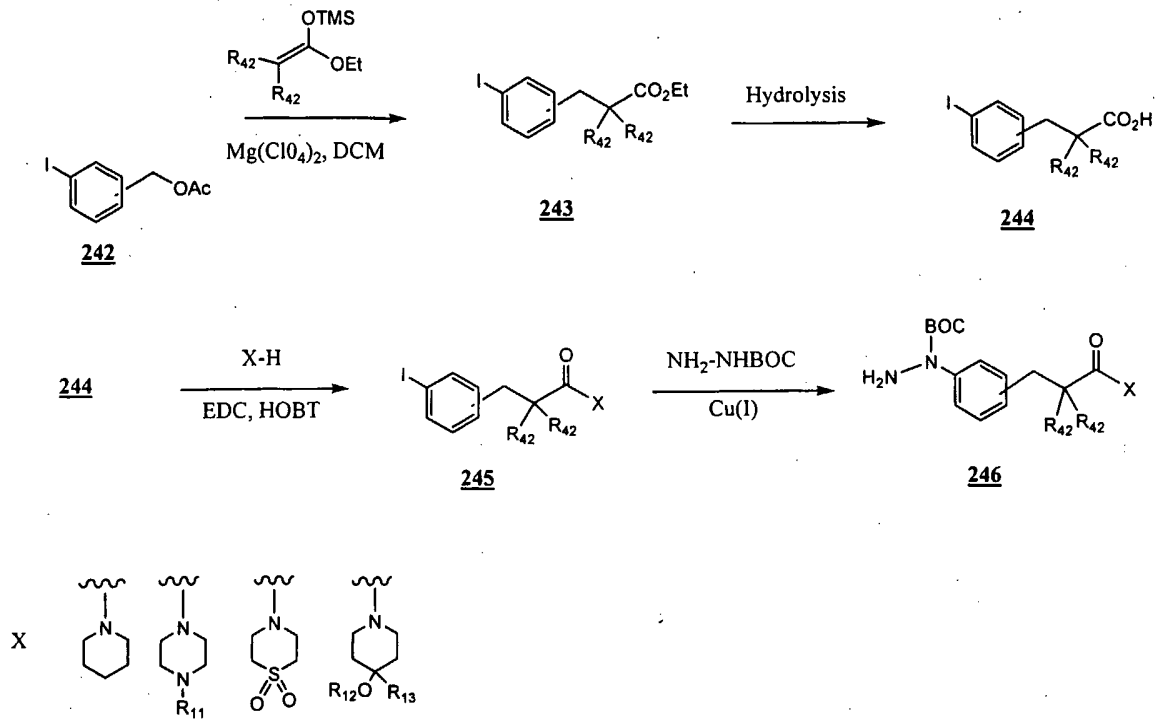
Scheme 44





Scheme 45 illustrates an alternative synthesis of key substituted hydrazine **246**, utilized to prepare compounds of formula **I.B** wherein Q is Q-42, G is methylene, and X is taken from piperidinyl, piperazinyl, thiomorphorlino sulfone, or 4-hydroxypiperinyl. Iodobenzyl acetate **242** is reacted with a substituted silylketene acetal to afford ester **243**. Ester **243** is hydrolyzed to the carboxylic acid **244**, which is reacted with an amine **X-H** in the presence of a coupling reagent, preferably EDC/HOBT, to give amide **245**. Conversion of **245** to the substituted hydrazine **246** is accomplished by Cu(I)-catalyzed reaction with N-BOC hydrazine. Hydrazine **246** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36, after acid-catalyzed removal of the hydrazine N-BOC protecting group, preferably with trifluoroacetic acid or HCl-dioxane.

Scheme 45

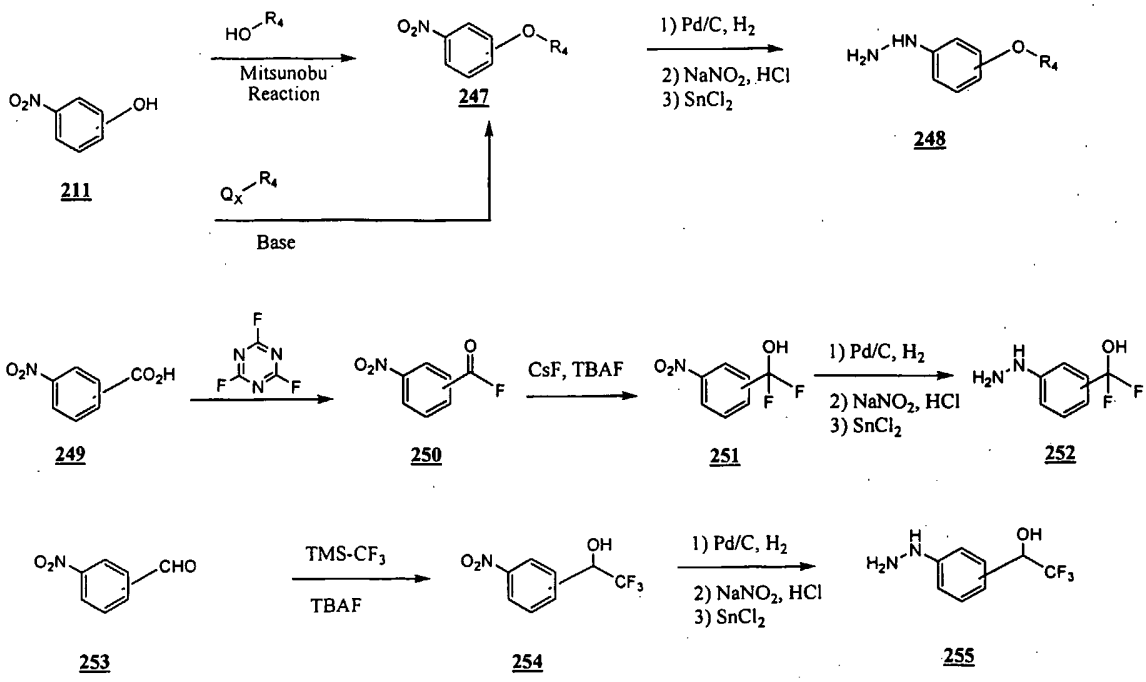


Scheme 46 illustrates an alternative synthesis of key substituted hydrazines **248**, **252**, and **255**, utilized to prepare compounds of formula **I.B** wherein Q is Q-47 or Q-48. Nitrophenol **211** is reacted with a substituted alcohol under Mitsunobu reaction conditions to afford **247**; alternatively **211** is alkylated with R_4-Q_x, wherein Q_x is a suitable leaving group, under basic reaction conditions, to give rise to **247**. Conversion of **247** to the substituted hydrazine **248** is accomplished under standard conditions.

The nitrobenzoic acid **249** is converted to the acid fluoride **250** by reaction with a fluorinating reagent, preferably trifluorotriazine. Treatment of acid fluoride **250** with a nucleophilic fluoride source, preferably cesium fluoride and tetra-*n*-butylammonium fluoride, affords the *alpha-alpha*-difluorosubstituted carbinol **251**. Conversion of **251** to the substituted hydrazine **252** is accomplished under standard conditions.

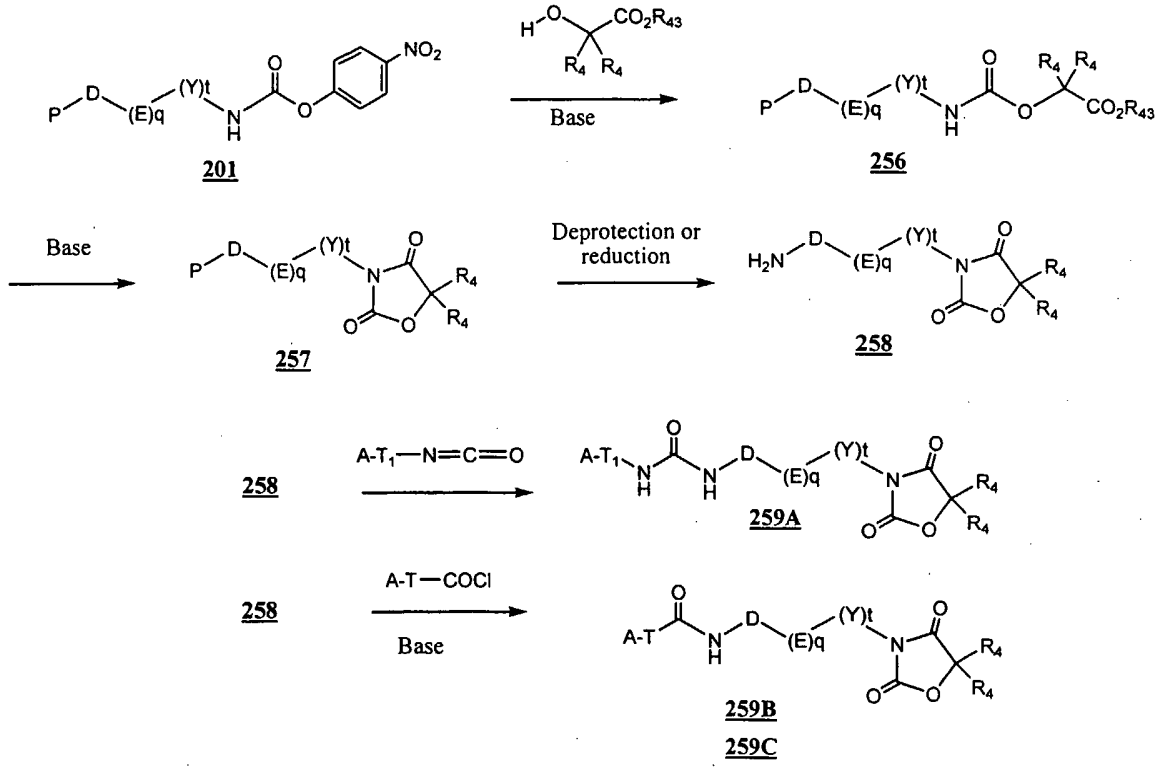
Nitrobenzaldehyde **253** is reacted with trimethylsilyltrifluoromethane (TMS-CF_3) and tetra-*n*-butylammonium fluoride to give rise to trifluoromethyl-substituted carbinol **254**. Conversion of **254** to the substituted hydrazine **255** is accomplished under standard conditions. Hydrazines **248**, **252**, and **255** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 46



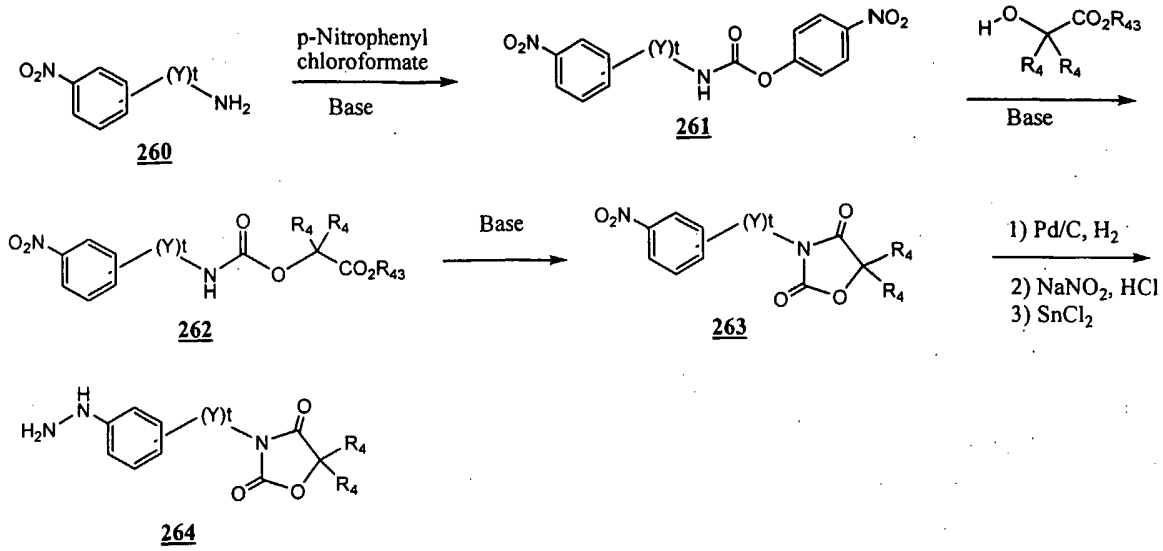
Scheme 47 illustrates the preparation of compounds of formula **I.B** wherein Q is Q-59. p-Nitrophenylcarbamate **201** is reacted with a substituted *alpha*-hydroxy ester with a suitable base to afford carbamate **256**. Further treatment with base results in cyclization to afford oxazolidinedione **257**. The protecting group P is removed to afford the key amine-containing intermediate **258**; alternatively, if P is a nitro group, then **257** is converted to **258** under reducing conditions such as iron/HCl, tin(II) chloride, or catalytic hydrogenation. Amine **258** is converted to **259A** by reaction with an isocyanate wherein T1 is alkylene or a direct bond connecting A and the carbonyl moiety; **258** is converted to amide **259B** by reaction with an acid chloride, acid anhydride, or a suitable activated carboxylic acid in the presence of a suitable base; **258** is converted to carbamate **259C** by reaction with a substituted alkyl or aryl chloroformate in the presence of a suitable base.

Scheme 47



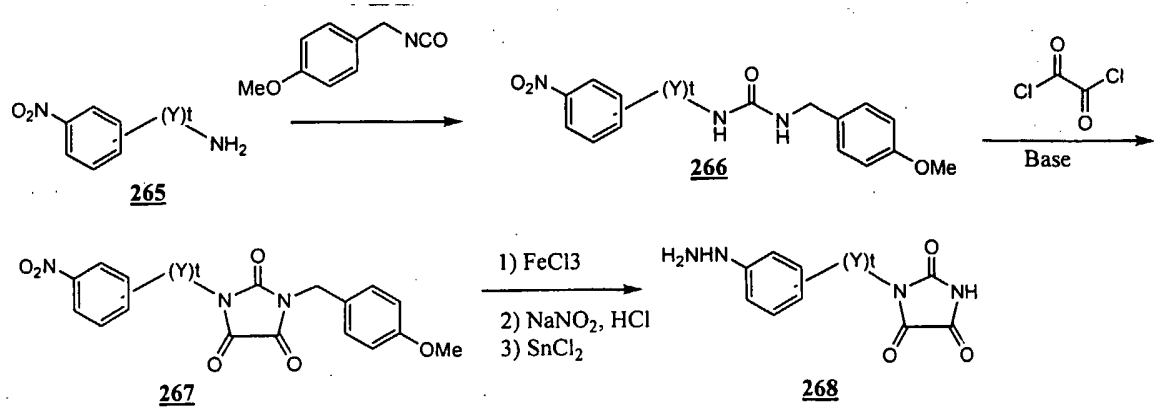
Scheme 48 illustrates an alternative approach to the preparation of compounds of formula **I.B** wherein Q is Q-59. Amine **260** is reacted with p-nitrophenylchloroformate under basic conditions to give rise to carbamate **261**. This intermediate is reacted with an alpha-hydroxy ester in the presence of base to afford carbamate **262**. Further treatment with base converts **262** into the oxazolidinedione **263**. Conversion of **263** to the substituted hydrazine **264** is accomplished by standard procedures. Hydrazine **264** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 48



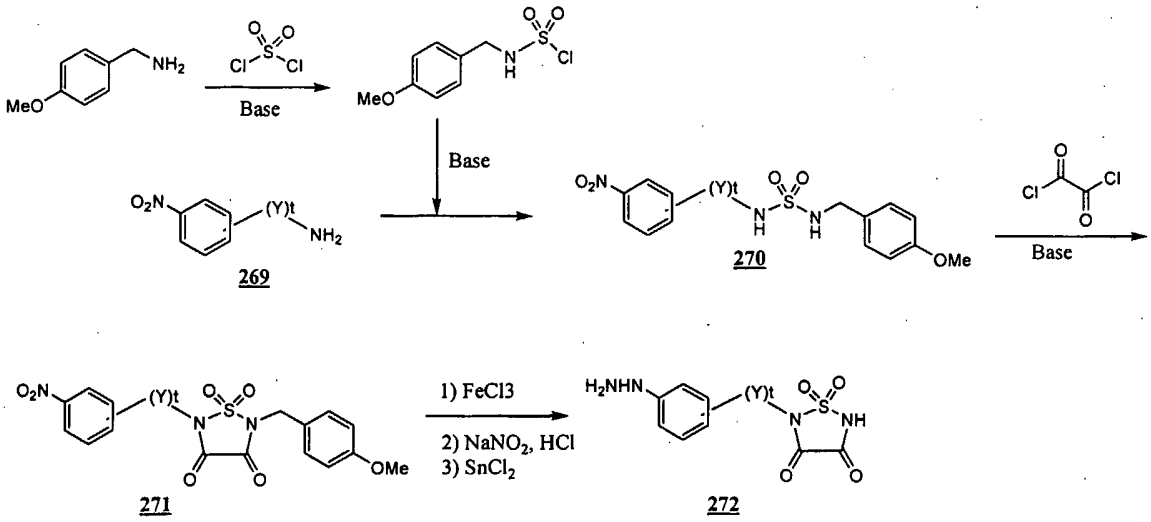
Scheme 49 illustrates thee approach to the preparation of compounds of formula **I.B** wherein Q is Q-57. Amine **265** is reacted with p-methoxybenzylisocyanate under standard conditions to give rise to urea **266**. This intermediate is reacted with an oxalyl chloride in the presence of base to afford trione **267**. Conversion of **267** to the substituted hydrazine **268** and removal of the p-methoxybenzyl protecting group is accomplished by standard procedures. Hydrazine **264** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 49



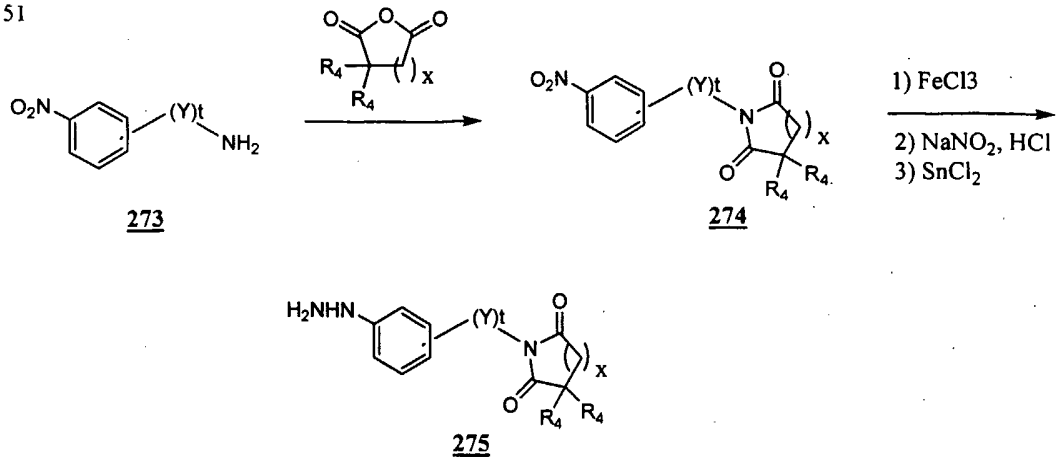
Scheme 50 illustrates an approach to the preparation of compounds of formula **I.B** wherein Q is Q-56. Amine **269** is reacted with p-methoxybenzylsulfonylchloride under standard conditions to give rise to sulfonylurea **270**. This intermediate is reacted with an oxalyl chloride in the presence of base to afford the cyclic sulfonyl urea **271**. Conversion of **271** to the substituted hydrazine **272** and removal of the p-methoxybenzyl protecting group is accomplished by standard procedures. Hydrazine **272** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 50



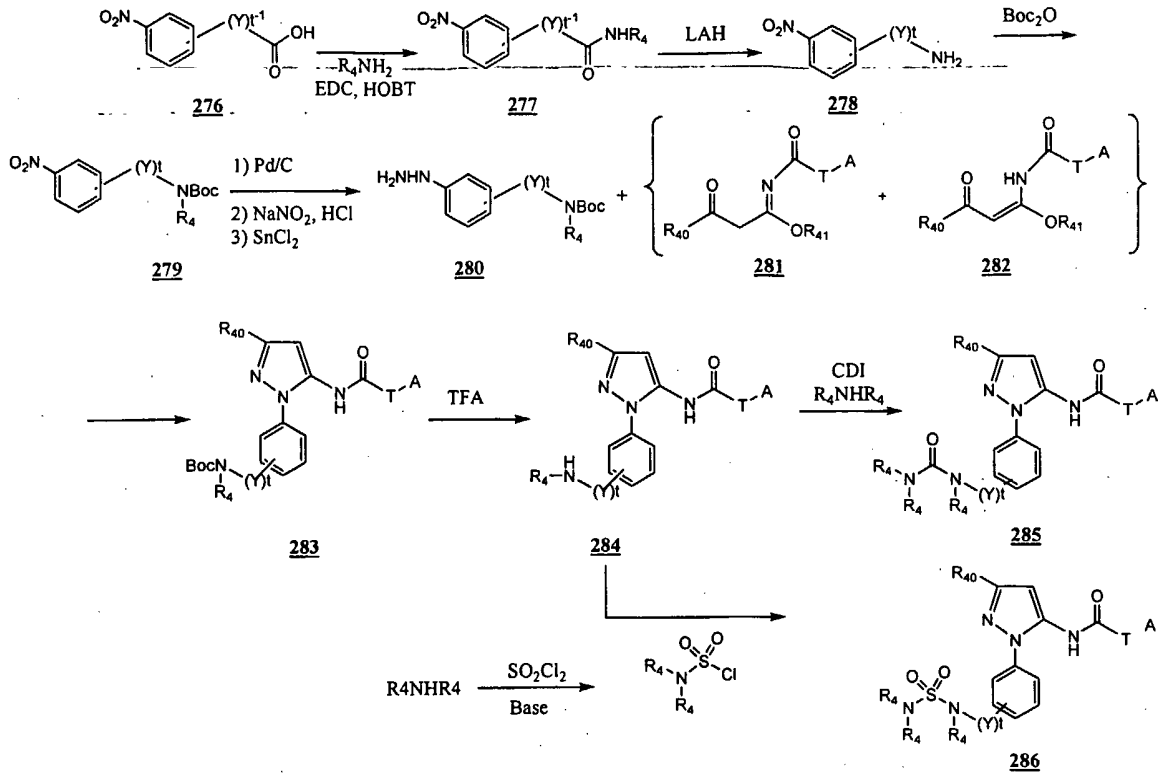
Scheme 51 illustrates an approach to the preparation of compounds of formula **I.B** wherein Q is Q-58. Amine **273** is reacted with a cyclic anhydride e.g. succinic anhydride in the presence of base under standard conditions to give rise to imide **274**. Conversion of **274** to the substituted hydrazine **275** is accomplished by standard procedures. Hydrazine **275** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 51



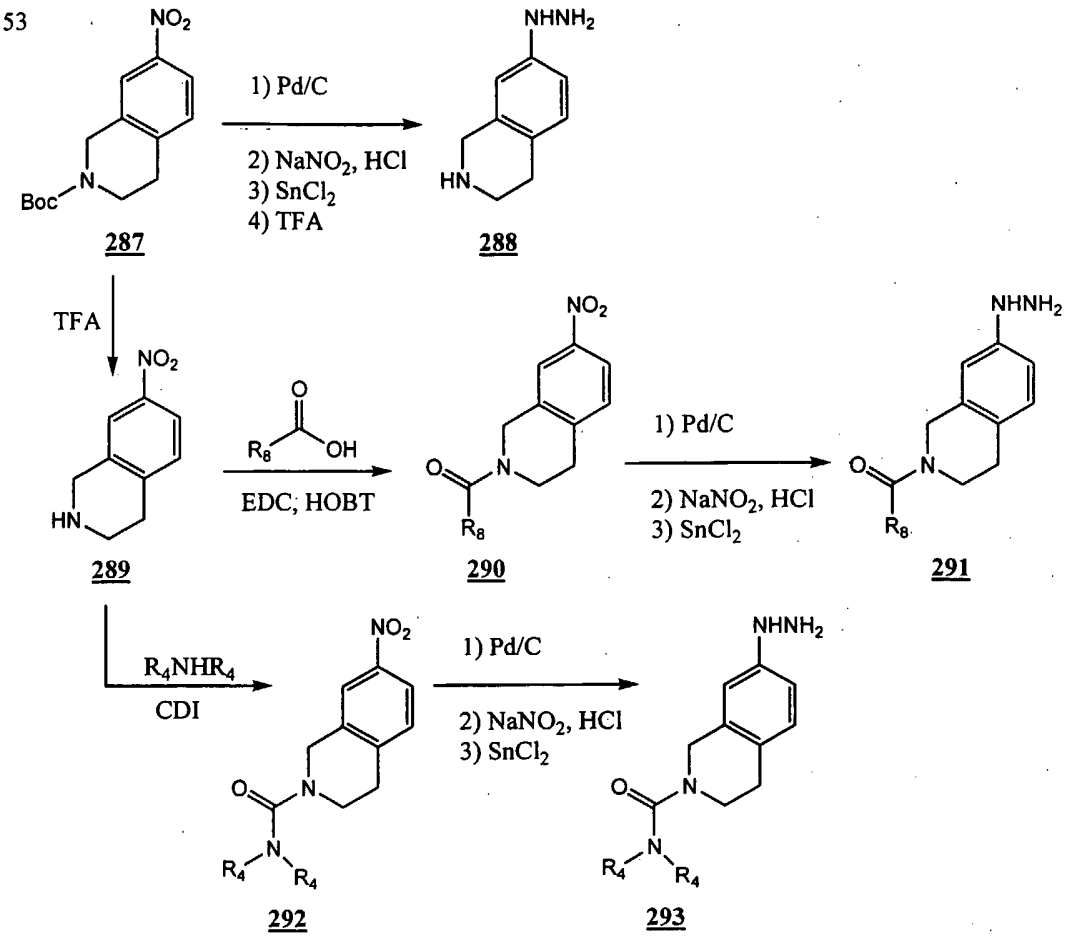
Scheme 52 illustrates an approach to the preparation of compounds of formula **I.B** wherein Q is Q-54 or Q-55. Carboxylic acid **276** is converted to protected amine **279** under standard conditions, which can be subsequently converted to hydrazine **280** by standard procedures. Hydrazine **280** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36 to yield protected amine **283** which is readily deprotected to yield amine **284**. Reaction of amine **284** with CDI and amine $(R_4)_2NH$ yields **285** (Q=Q-54). Reaction of amine **284** with the indicated sulfamoylchloride derivative yields **286** (Q=Q-55).

Scheme 52



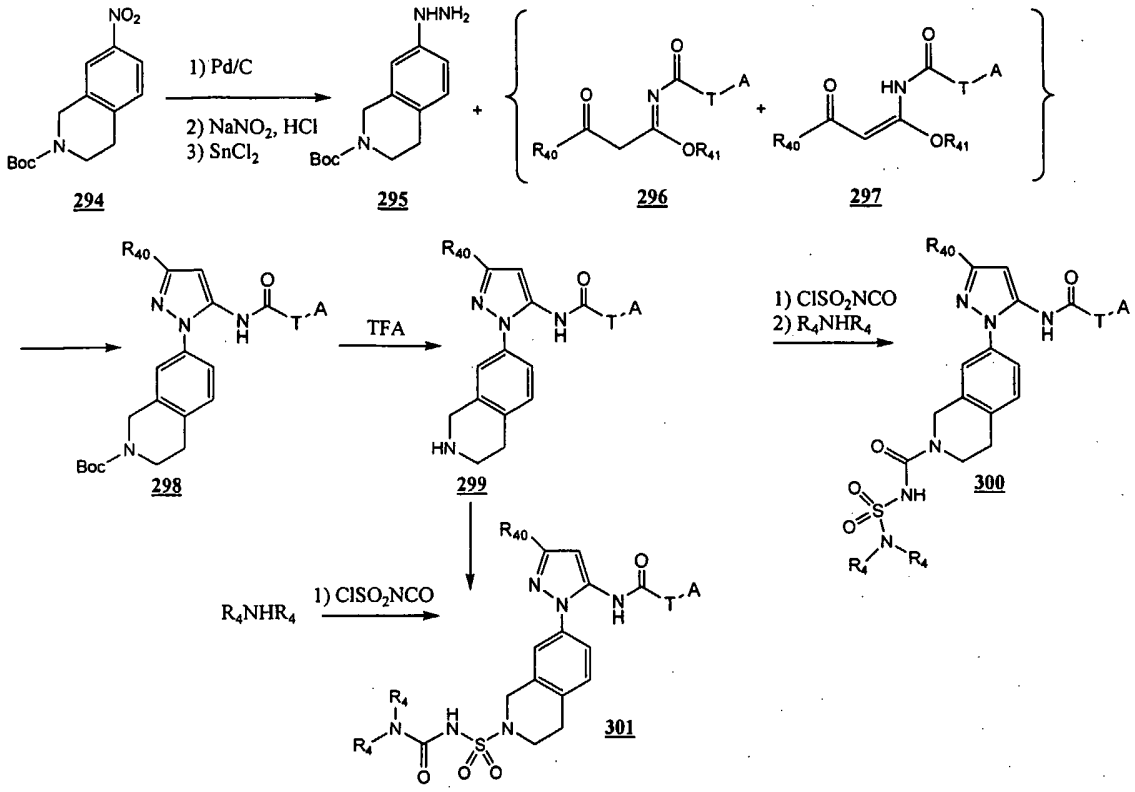
Scheme 53 illustrates an approach to the preparation of compounds of formula **I.B** wherein Q is Q-49, Q-50 or Q-51. Protected amine **287** (available by several literature procedures) is converted to deprotected hydrazine **288** is accomplished by standard procedures. Hydrazine **288** (Q=Q-49) can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36. Amine **287** can be deprotected by TFA to yield amine **289** which can be subsequently converted amide **290**. Amide **290** is converted to hydrazine **291** (Q=Q-50) by standard procedures, which can be subsequently converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36. Alternatively, amine **289** can be reacted with CDI and amine $(R_4)_2NH$ to yield urea **292** (Q=Q-51). Urea **292** is converted to hydrazine **293** (Q=Q-51) by standard procedures, which can be subsequently converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 53



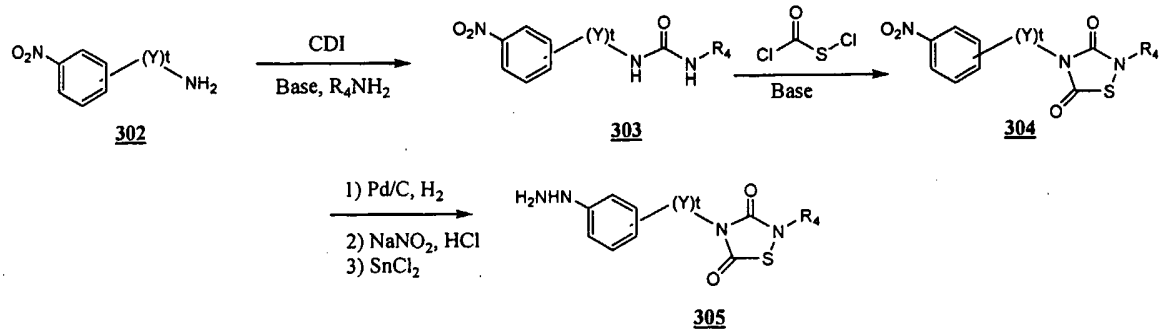
Scheme 54 illustrates an approach to the preparation of compounds of formula **I.B** wherein Q is Q-52 and Q-53. Protected amine **294** (available by several literature procedures) is converted to protected hydrazine **295** is accomplished by standard procedures. Hydrazine **295** (Q=Q-49) can be converted into compounds of formula **I.B** to yield protected amine **298** which is readily deprotected to yield amine **299**. Reaction of amine **299** with chlorosulfonylisocyanate followed by amine $(R_4)_2NH$ yields **300** (Q=Q-52). Alternatively, reaction of chlorosulfonylisocyanate and amine $(R_4)_2NH$ followed by amine **299** yields **301** (Q=Q-53).

Scheme 54



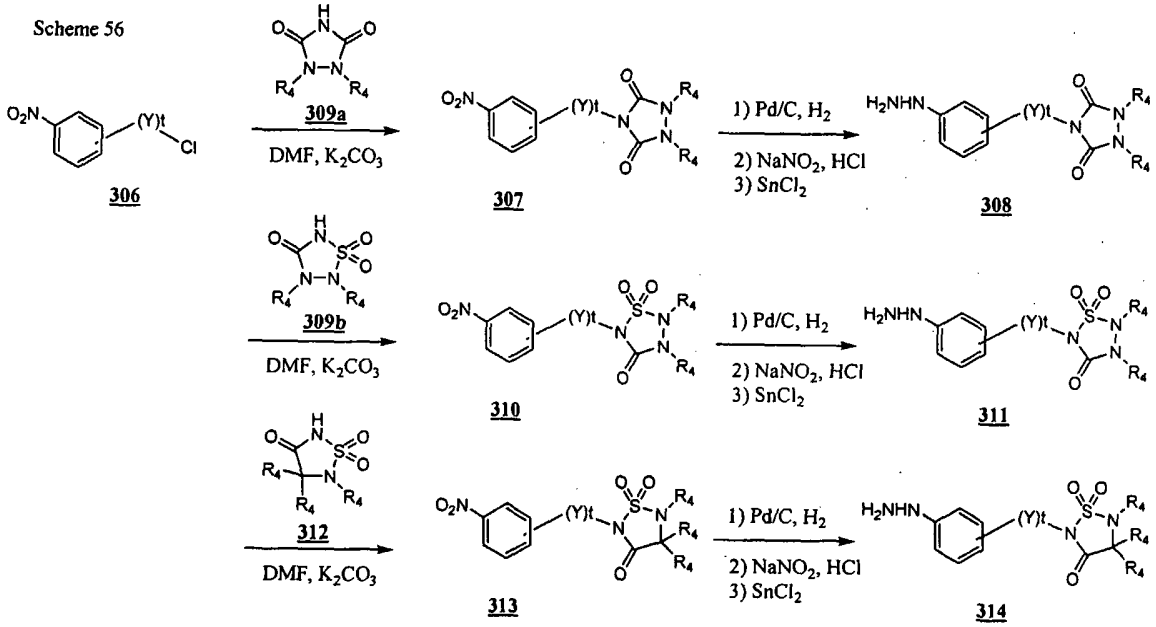
Scheme 55 illustrates an approach to the preparation of compounds of formula **I.B** wherein Q is Q-36. Amine **302** is reacted with CDI and amine R_4NH_2 to yield **303**, which is reacted with chlorocarbonyl sulfenylchloride to yield thiadiazolidinedione **304**. Conversion of **304** to the substituted hydrazine **305** is accomplished by standard procedures. Hydrazine **305** can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 55



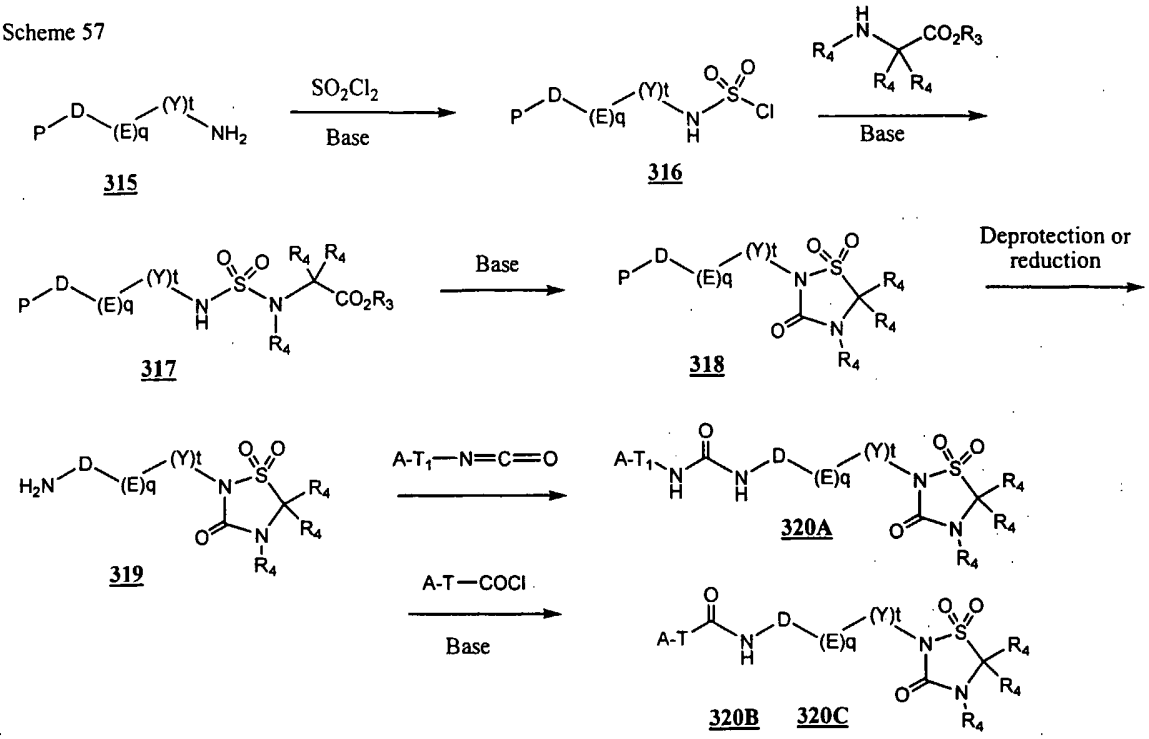
Scheme 56 illustrates an approach to the preparation of compounds of formula **I.B** wherein Q is Q-37, Q-38 or Q-39. Imides **309a**, **309b**, and **312** are all available via several literature methods, and are each able to be alkylated with chloride **306** to yields intermediates **307**, **310** and **313** respectively. Intermediates **307**, **310** and **313** are respectively converted to hydrazines **308** (Q=Q-37), **311** (Q=Q-38), and **314** (Q=Q-39) by standard procedures.

Scheme 56



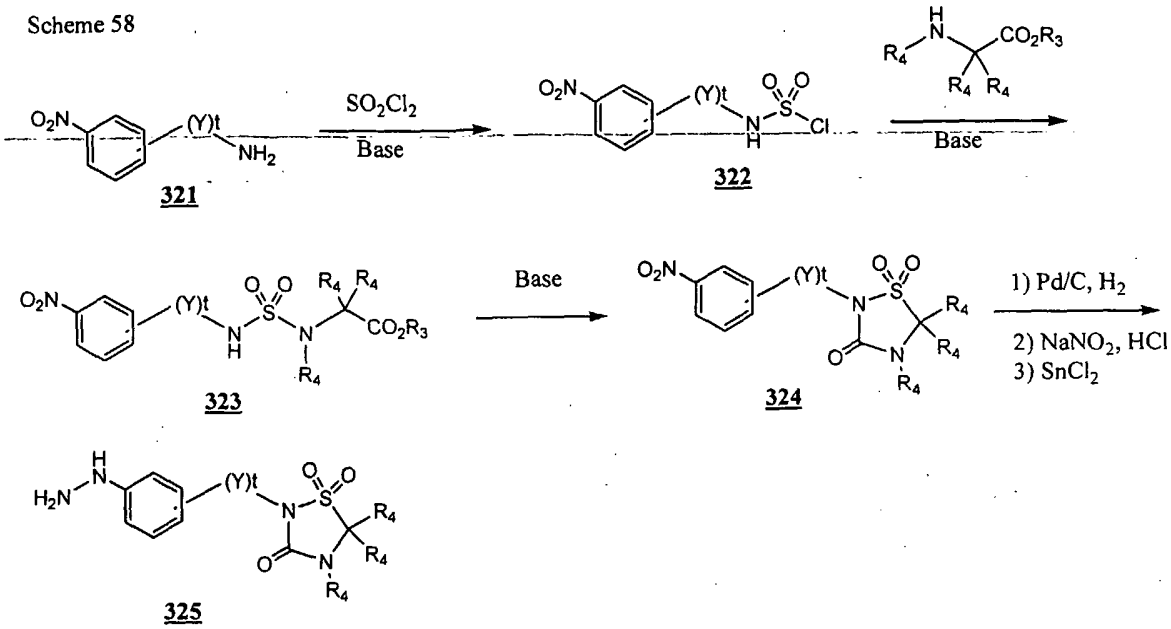
Scheme 57 illustrates an alternative preparation of compounds wherein Q is Q-37. Readily available amine **315**, wherein P is a suitable amine-protecting group or a group convertible to an amine group, is reacted with SO_2Cl_2 to give rise to sulfonyl chloride **316**. Intermediate **316** is reacted with a substituted amino acid ester with a suitable base to afford sulfonylurea **317**. Further treatment with base results in cyclization to afford sulfohydantoin **318**. The protecting group P is removed to afford the key amine-containing intermediate **319**. Alternatively, if P is a nitro group, then **318** is converted to **319** under reducing conditions such as iron/HCl, tin(II) chloride, or catalytic hydrogenation. Amine **319** is converted to **320A** by reaction with an isocyanate; **319** is converted to amide **320B** by reaction with an acid chloride, acid anhydride, or a suitable activated carboxylic acid in the presence of a suitable base; **319** is converted to carbamate **320C** by reaction with a substituted alkyl or aryl chloroformate in the presence of a suitable base.

Scheme 57



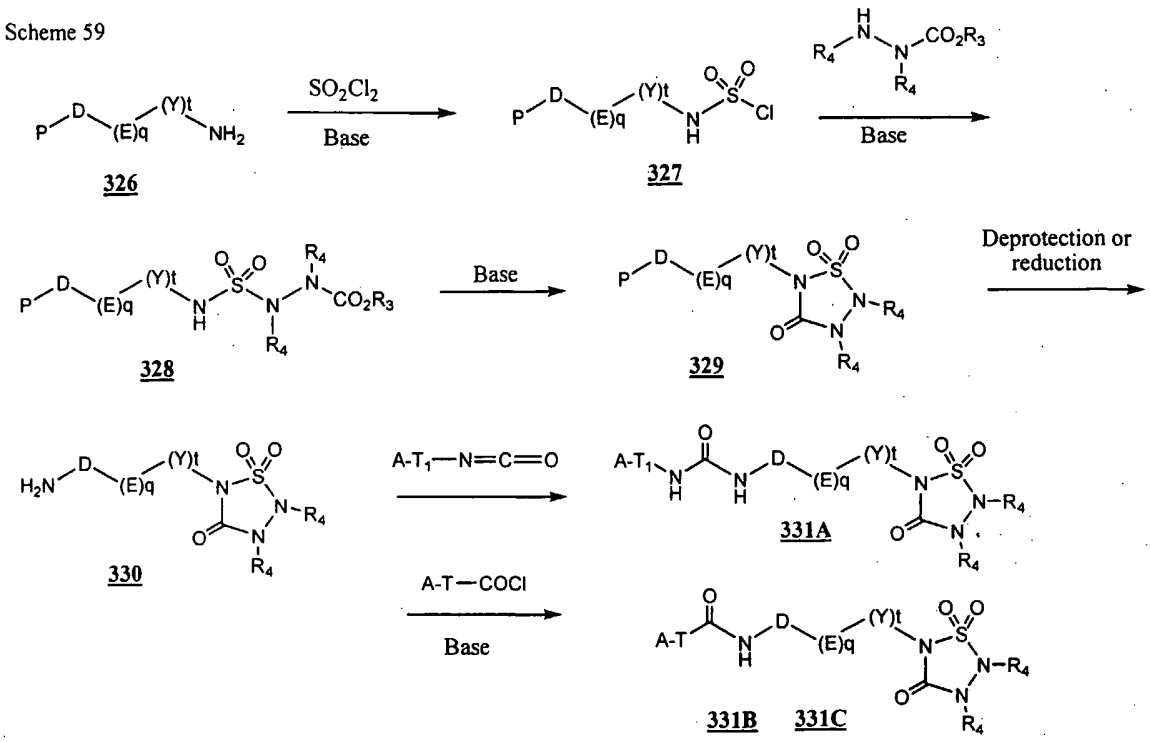
Scheme 58 illustrates an alternative synthesis of key substituted hydrazine **325** of compounds wherein Q is Q-37. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36. The amine **321** is reacted with SO_2Cl_2 to give rise to sulfonyl chloride **322**. Reaction of **322** with a suitable amino acid ester affords sulfonylurea **323**, which is cyclized under basic conditions to give sulfohydantoin **324**. Reduction of the nitro group of **324**, diazotization of the resulting amine, and reduction of the diazonium salt affords key hydrazine **325**.

Scheme 58



Scheme 59 illustrates an alternative preparation of compounds wherein Q is Q-38. Readily available amine **326**, wherein P is a suitable amine-protecting group or a group convertible to an amine group, is reacted with SO_2Cl_2 to give rise to sulfonyl chloride **327**. Intermediate **327** is reacted with a substituted hydrazide ester with a suitable base to afford sulfonylurea **328**. Further treatment with base results in cyclization to afford sulfotriazaolinedione **329**. The protecting group P is removed to afford the key amine-containing intermediate **330**. Alternatively, if P is a nitro group, then **329** is converted to **330** under reducing conditions such as iron/HCl, tin(II) chloride, or catalytic hydrogenation. Amine **330** is converted to **331A** by reaction with an isocyanate; **330** is converted to amide **331B** by reaction with an acid chloride, acid anhydride, or a suitable activated carboxylic acid in the presence of a suitable base; **330** is converted to carbamate **331C** by reaction with a substituted alkyl or aryl chloroformate in the presence of a suitable base.

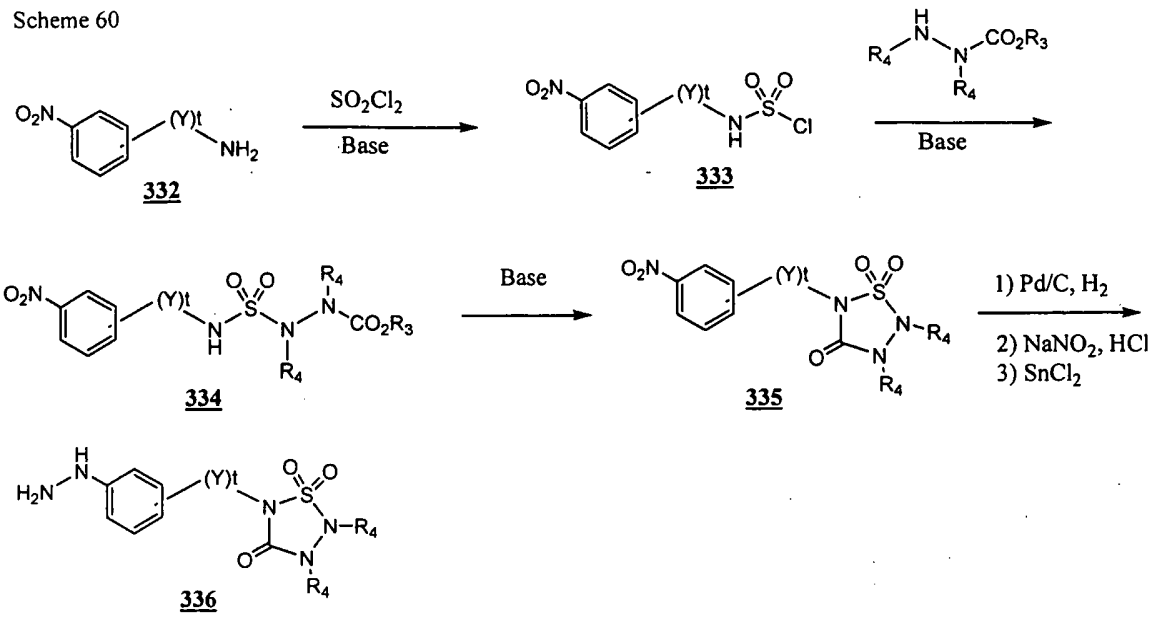
Scheme 59



326 327 328 329 330 331A 331B 331C

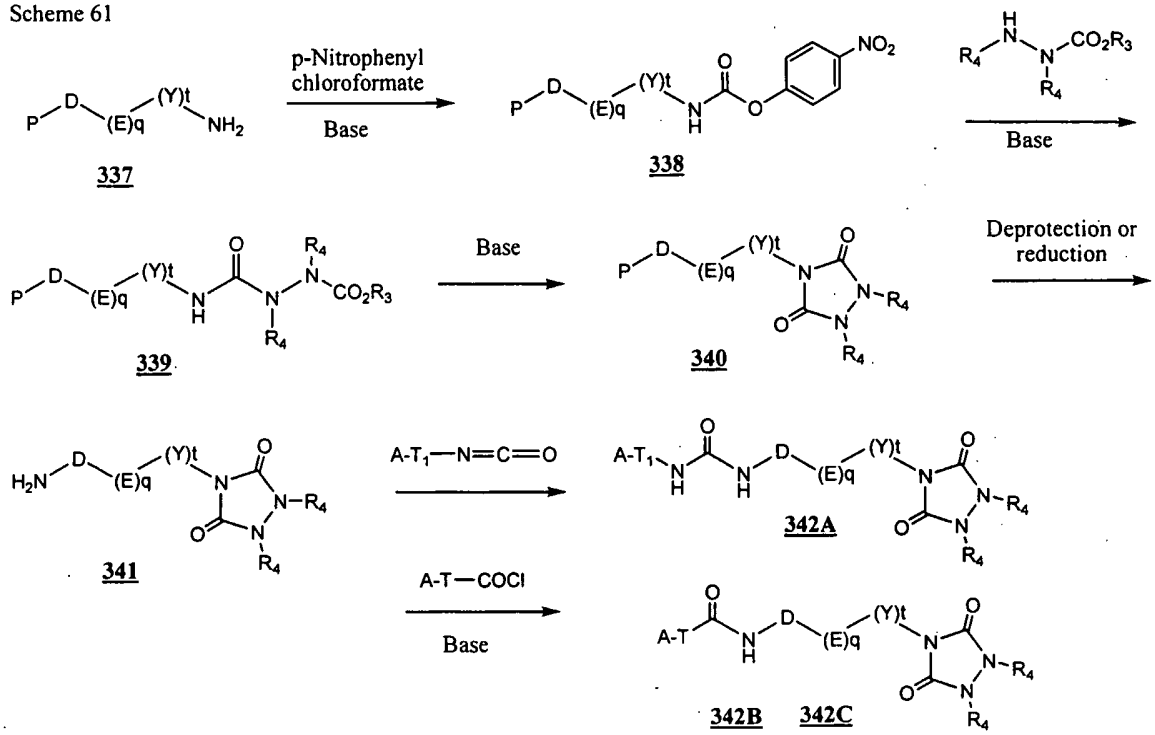
Scheme 60 illustrates an alternative synthesis of key substituted hydrazine **336** of compounds wherein Q is Q-38. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36. The amine **332** is reacted with SO_2Cl_2 to give rise to sulfonyl chloride **333**. Reaction of **333** with a ubstituted hydrazide ester affords sulfonylurea **334**, which is cyclized under basic conditions to give sulfotriazaolinedione **335**. Reduction of the nitro group of **335**, diazotization of the resulting amine, and reduction of the diazonium salt affords key hydrazine **336**.

Scheme 60



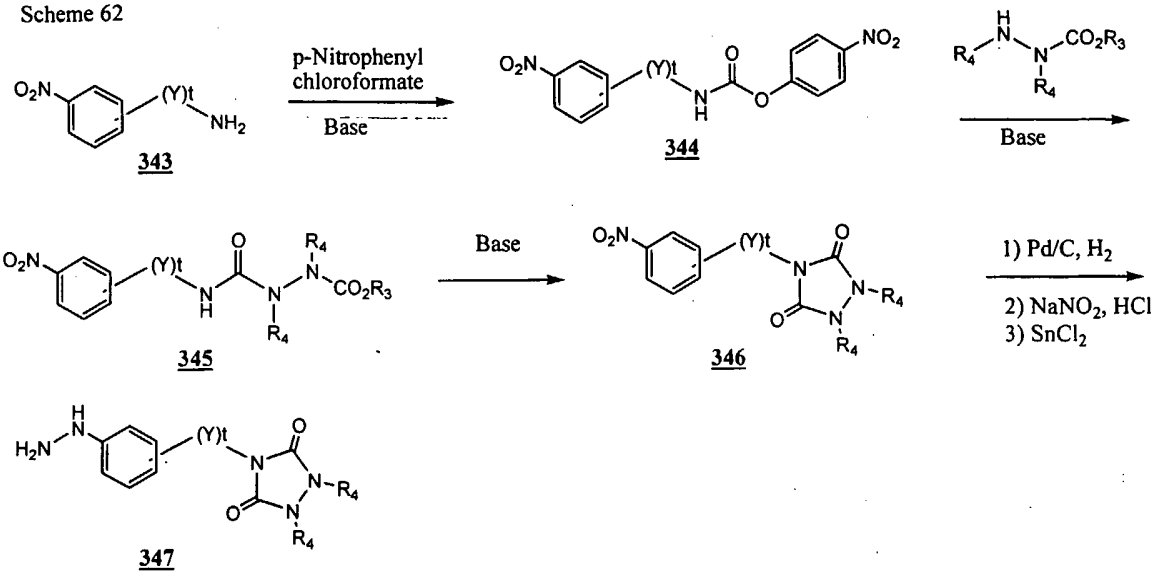
Scheme 61 illustrates the preparation of compounds wherein Q is Q-39. Readily available amine **337**, wherein P is a suitable amine-protecting group or a group convertible to an amine group, is reacted with p-nitrophenyl chloroformate to give rise to carbamate **338**. Intermediate **338** is reacted with a substituted amino acid ester with a suitable base to afford urea **339**. Further treatment with base results in cyclization to afford triazolinedione **340**. The protecting group P is removed to afford the key amine-containing intermediate **341**. Alternatively, if P is a nitro group, then **340** is converted to **341** under reducing conditions such as iron/HCl, tin(II) chloride, or catalytic hydrogenation. Amine **341** is converted to **342A** by reaction with an isocyanate; **341** is converted to amide **342B** by reaction with an acid chloride, acid anhydride, or a suitable activated carboxylic acid in the presence of a suitable base; **341** is converted to carbamate **342C** by reaction with a substituted alkyl or aryl chloroformate in the presence of a suitable base.

Scheme 61



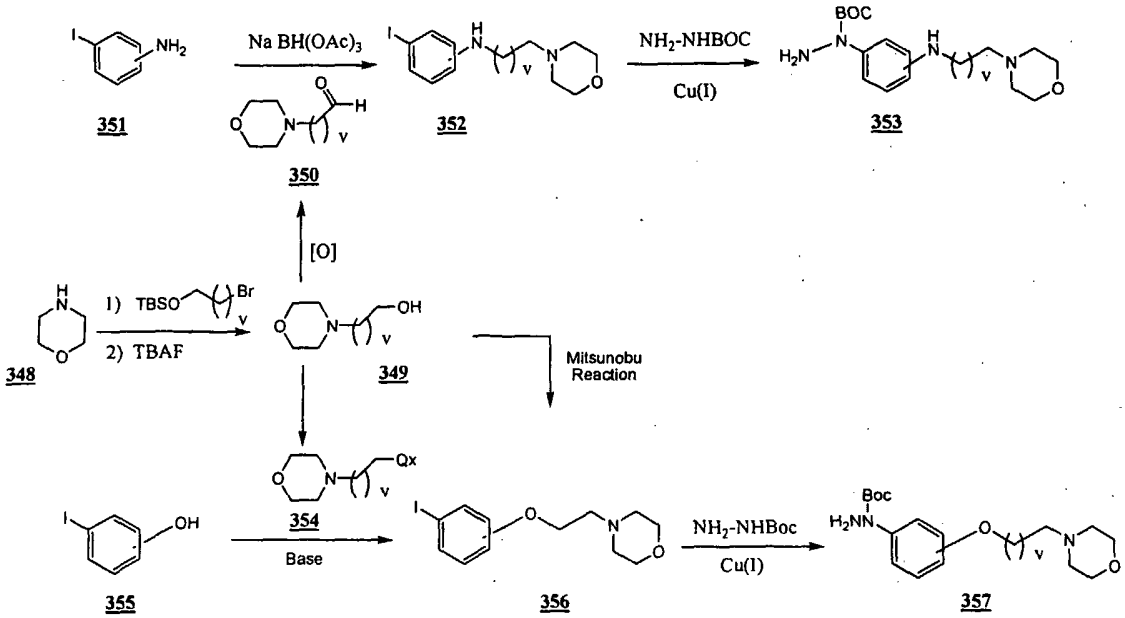
Scheme 62 illustrates an alternative synthesis of key substituted hydrazine **347** of compounds wherein Q is Q-39. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36. The nitrophenyl substituted amine **343** is reacted with *p*-nitrophenyl chloroformate to give rise to carbamate **344**. Reaction of **344** with a suitable amino acid ester affords urea **345**, which is cyclized under basic conditions to give triazolinedione **346**. Reduction of the nitro group of **346**, diazotization of the resulting amine, and reduction of the diazonium salt affords key hydrazine **347**.

Scheme 62



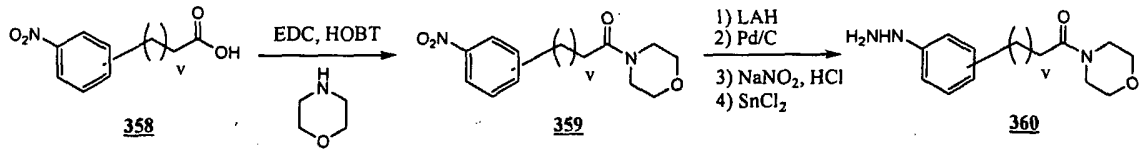
Scheme 63 illustrates the synthesis of compounds wherein Q is Q-43. Morphiline **348** is alkylated with protected bromohydrine. Removal of the alcohol protecting group yields intermediate **349**, which can be oxidized to aldehyde **350**. When G=NH, iodoaniline **351** is reacted with **350** under reductive amination conditions, preferably sodium triacetoxyborohydride, to afford intermediate **352**. This intermediate is converted to the substituted hydrazine **353** by Cu(I)-catalyzed reaction with N-BOC hydrazine. When G=O, iodophenol **355** is either alkylated with **354** or reacted under Mitsunobu conditions with alcohol **349** to yield intermediate **356**. This intermediate is converted to the substituted hydrazine **353** by Cu(I)-catalyzed reaction with N-BOC hydrazine.

Scheme 63



Scheme 64 illustrates the synthesis of compounds wherein Q is Q-43, G=CH_2. Nitroacid **358** (readily available by anyone with normal skills in the art) is reacted with morphiline to yield amide **359**, which upon reduction to the amine and conversion of the nitro group under standard conditions results in hydrazine **360**. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

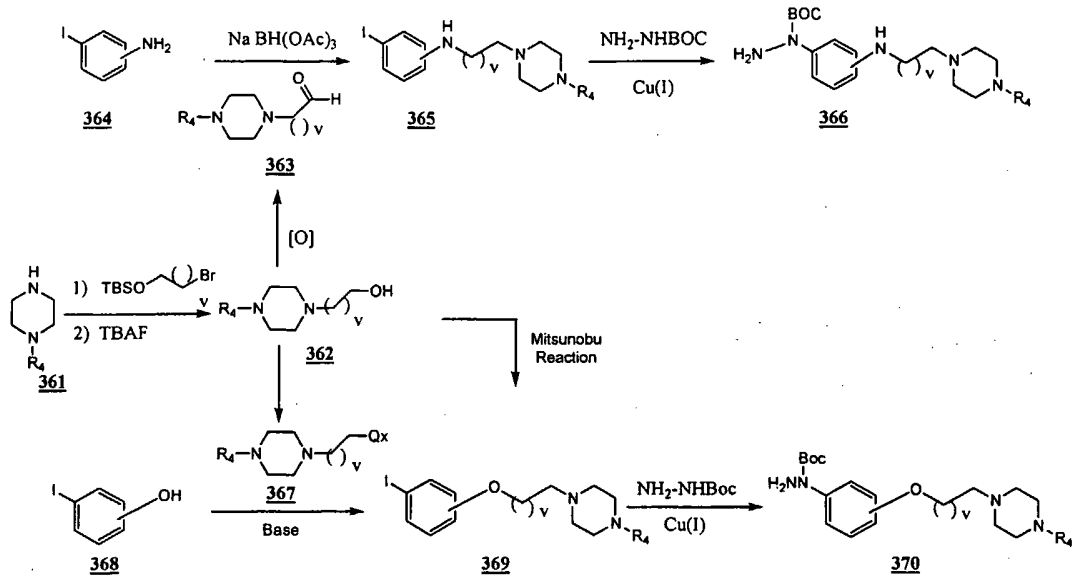
Scheme 64



Scheme 65 illustrates the synthesis of compounds wherein Q is Q-44. N-methyl piperazine **361** is alkylated with protected bromohydrine. Removal of the alcohol protecting group yields intermediate **362**, which can be oxidized to aldehyde **363**. When G=NH, iodoaniline **364** is reacted with **363** under reductive amination conditions, preferably sodium triacetoxyborohydride, to afford intermediate **365**. This intermediate is converted to the substituted hydrazine **366** by Cu(I)-catalyzed reaction with N-BOC hydrazine. When G=O, iodophenol **368** is either alkylated with **367** or reacted under Mitsunobu conditions with

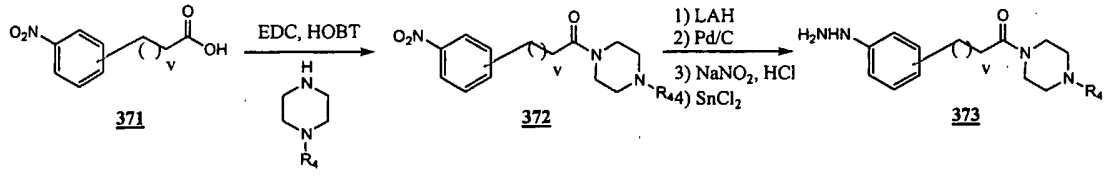
alcohol **362** to yield intermediate **369**. This intermediate is converted to the substituted hydrazine **370** by Cu(I)-catalyzed reaction with N-BOC hydrazine.

Scheme 65



Scheme 66 illustrates the synthesis of compounds wherein Q is Q-44, G=CH_2. Nitroacid **371** (readily available by anyone with normal skills in the art) is reacted with N-methyl piperazine to yield amide **372**, which upon reduction to the amine and conversion of the nitro group under standard conditions results in hydrazine **373**. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

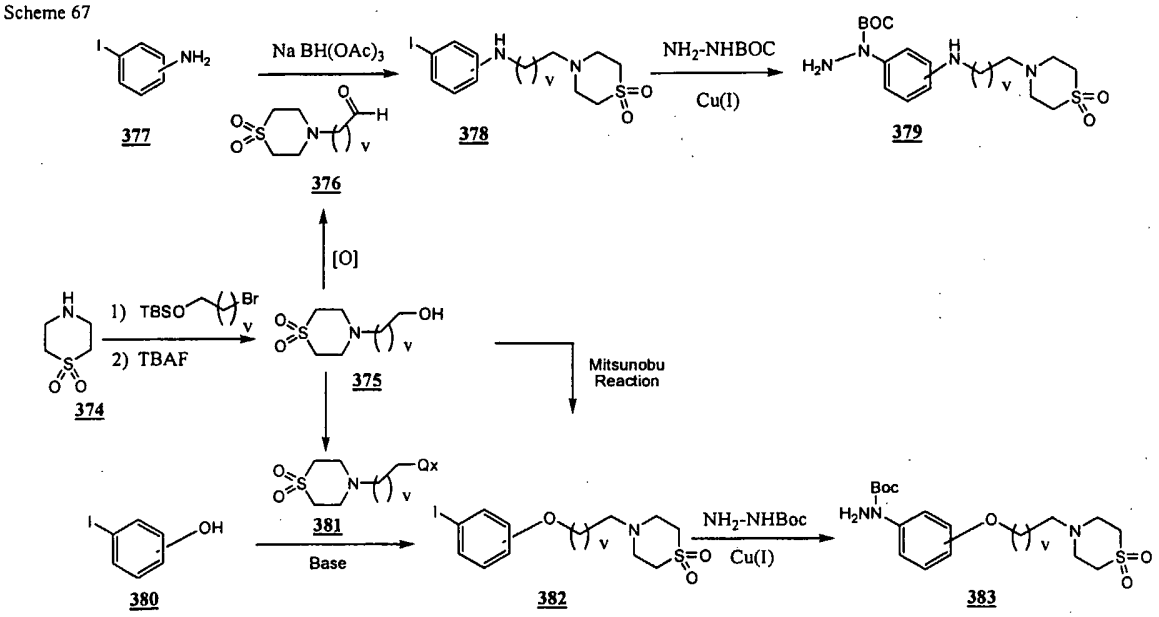
Scheme 66



Scheme 67 illustrates the synthesis of compounds wherein Q is Q-45. Thiomorpholine sulphone **374** is alkylated with protected bromohydrine. Removal of the alcohol protecting group yields intermediate **375**, which can be oxidized to aldehyde **376**. When G=NH, iodoaniline **377** is reacted with **376** under reductive amination conditions, preferably sodium triacetoxyborohydride, to afford intermediate **378**. This intermediate is

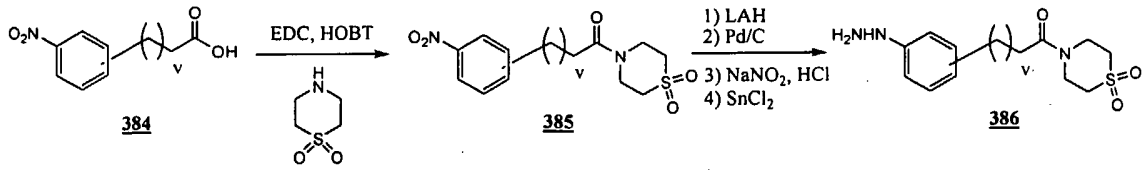
converted to the substituted hydrazine **379** by Cu(I)-catalyzed reaction with N-BOC hydrazine. When G=O, iodophenol **380** is either alkylated with **381** or reacted under Mitsunobu conditions with alcohol **375** to yield intermediate **382**. This intermediate is converted to the substituted hydrazine **383** by Cu(I)-catalyzed reaction with N-BOC hydrazine.

Scheme 67



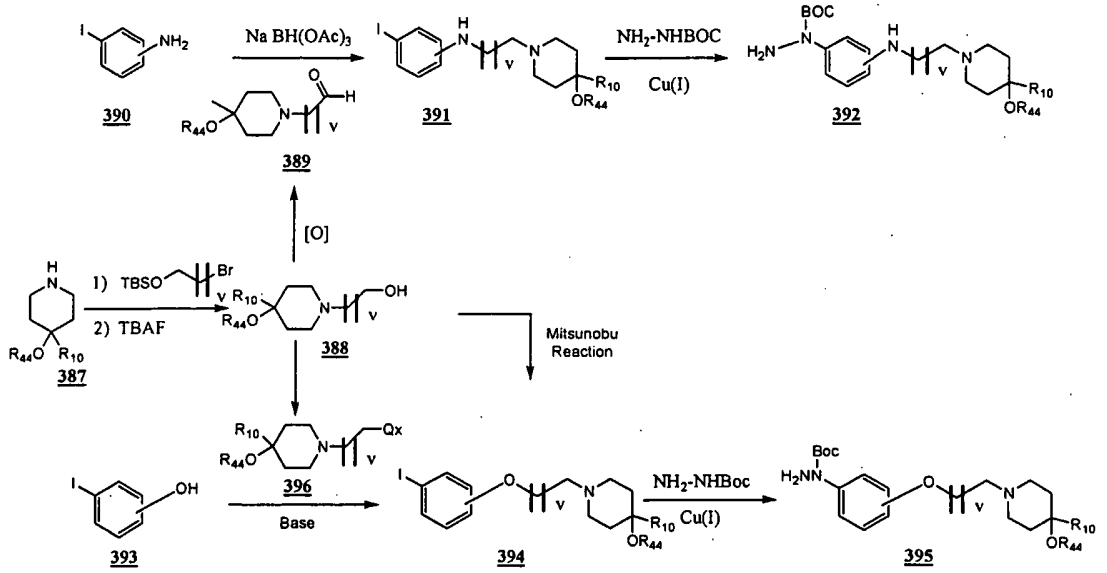
Scheme 68 illustrates the synthesis of compounds wherein Q is Q-44, G=CH_2. Nitroacid **384** (readily available by anyone with normal skills in the art) is reacted with thiomorpholine sulphone to yield amide **385**, which upon reduction to the amine and conversion of the nitro group under standard conditions results in hydrazine **386**. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 68



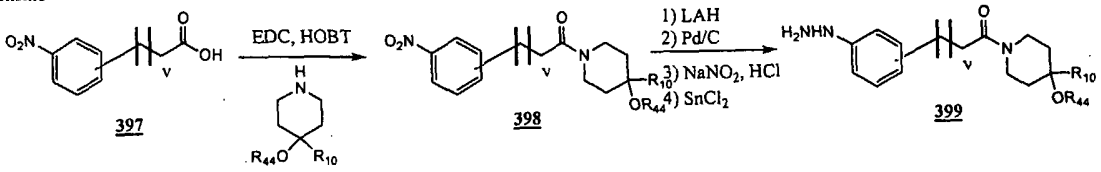
Scheme 69 illustrates the synthesis of compounds wherein Q is Q-46. Piperadine derivative **387** is alkylated with protected bromohydrine. Removal of the alcohol protecting group yields intermediate **388**, which can be oxidized to aldehyde **389**. When G=NH, iodoaniline **390** is reacted with **389** under reductive amination conditions, preferably sodium triacetoxyborohydride, to afford intermediate **391**. This intermediate is converted to the substituted hydrazine **392** by Cu(I)-catalyzed reaction with N-BOC hydrazine. When G=O, iodophenol **393** is either alkylated with **396** or reacted under Mitsunobu conditions with alcohol **388** to yield intermediate **394**. This intermediate is converted to the substituted hydrazine **395** by Cu(I)-catalyzed reaction with N-BOC hydrazine.

Scheme 69



Scheme 70 illustrates the synthesis of compounds wherein Q is Q-44, G=CH_2. Nitroacid **397** (readily available by anyone with normal skills in the art) is reacted with thiomorpholine sulphone to yield amide **398**, which upon reduction to the amine and conversion of the nitro group under standard conditions results in hydrazine **399**. This hydrazine can be converted into compounds of formula **I.B** using the methods previously outlined in Schemes 35 and 36.

Scheme 70



397 398 399

AFFINITY AND BIOLOGICAL ASSESSMENT
OF P38-ALPHA KINASE INHIBITORS

A fluorescence binding assay is used to detect binding of inhibitors of Formula I with unphosphorylated p38-alpha kinase as previously described: see J. Regan et al, *Journal of Medicinal Chemistry* (2002) 45:2994.

1. P38 MAP kinase binding assay

The binding affinities of small molecule modulators for p38 MAP kinase were determined using a competition assay with SKF 86002 as a fluorescent probe, modified based on published methods (C. Pargellis, et al Nature Structural Biology (2002) 9, 268-272. J. Regan, et al J. Med. Chem. (2002) 45, 2994-3008). Briefly, SKF 86002, a potent inhibitor of p38 kinase (K_d = 180 nM), displays an emission fluorescence around 420 nm when excitated at 340 nm upon its binding to the kinase. Thus, the binding affinity of an inhibitor for p38 kinase can be measured by its ability to decrease the fluorescence from SKF 86002. The assay was performed in a 384 plate (Greiner uclear 384 plate) on a Polarstar Optima plate reader (BMG). Typically, the reaction mixture contained 1 μM SKF 86002, 80 nM p38 kinase and various concentrations of an inhibitor in 20 mM Bis-Tris Propane buffer, pH 7, containing 0.15 % (w/v) n-octylglucoside and 2 mM EDTA in a final volume of 65 μl. The reaction was initiated by addition of the enzyme. The plate was incubated at room temperature (~ 25 °C) for 2 hours before reading at emission of 420 nm and excitation at 340 nm. By comparison of rfu (relative fluorescence unit) values with that of a control (in the absence of an inhibitor), the percentage of inhibition at each concentration of the inhibitor was calculated. IC_{50} value for the inhibitor was calculated from the % inhibition values obtained at a range of concentrations of the inhibitor using Prism. When time-dependent inhibition was assessed, the plate was read at multiple reaction times such as 0.5, 1, 2, 3, 4 and 6 hours. The IC_{50} values were calculated at the each time point. An inhibition was assigned as time-dependent if the IC_{50} values decrease with the reaction time (more than two-fold in four hours). This is illustrated below in Table 1.

Table 1

Example #	IC50, nM	Time-dependent
1	292	Yes
2	997	No
2	317	No
3	231	Yes
4	57	Yes
5	1107	No
6	238	Yes
7	80	Yes
8	66	Yes
9	859	No
10	2800	No
11	2153	No
12	~ 10000	No
13	384	Yes
15	949	No
19	~ 10000	No
21	48	Yes
22	666	No
25	151	Yes
26	68	Yes
29	45	Yes
30	87	Yes
31	50	Yes
32	113	Yes
37	497	No
38	508	No
41	75	Yes
42	373	No
43	642	No
45	1855	No
46	1741	No
47	2458	No
48	3300	No
57	239	Yes

IC50 values obtained at 2 hours reaction time

P-38 *alpha* kinase assay (spectrophometric assay)

Activity of phosphorylated p-38 kinase was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, *et al.* Science (2000) *289*, 1938-1942). In this assay, the oxidation of NADH was continuously measured spectrophometrically. The reaction mixture (100 µl) contained phospho p-38 *alpha* kinase (3.3 nM. Panvera), peptide substrate (IPTSPITTTYFFFKKK-OH, 0.2 mM), ATP (0.3 mM), $MgCl_2$ (10 mM), pyruvate kinase (8 units. Sigma), lactate dehydrogenase (13 units. Sigma), phosphoenol pyruvate (1 mM), and NADH (0.28 mM) in 65 mM Tris buffer, pH 7.5, containing 3.5 % DMSO and 150 uM *n*-Dodecyl-B-D-maltopyranoside. The reaction was initiated by adding ATP. The absorption at 340 nm was monitored continuously for up to 4 hours at 30 °C on Polarstar Optima plate reader (BMG). The kinase activity (reaction rate) was calculated from the slope at the time frame from 1.5 h to 2 h. Under these conditions, a turn over number (k_{cat}) of ~1 s^{-1} was obtained. The reaction rates calculated from different time frames such as 0.5 min to 0.5 h, 0.5 h to 1 h, 1.5 h to 2 h or 2.5 h to 3 h were generally constant.

For inhibition determinations, test compounds were incubated with the reaction mixture for ~ 5 min before adding ATP to start the reaction. Percentage of inhibition was obtained by comparison of reaction rate with that of a control well containing no test compound. IC_{50} values were calculated from a series of % inhibition values determined at a range of concentrations of each inhibitor using Prism to process the data and fit inhibition curves. Generally, the rates obtained at the time frame of 1.5 h to 2 h were used for these calculations. In assessing whether inhibition of a test compound was time-dependent (i.e., greater inhibition with a longer incubation time), the values of % inhibition and/or IC50 values obtained from other time frames were also calculated for the inhibitor. The biological activity for compounds of the present invention in the spectrophotometric assay are illustrated in Tables 2 and 3.

TABLE 2

Example #	IC50, uM	% inhibition @ concentration, uM
1	0.067	
2	0.29	
3	0.019	
4	0.609	
5	0.514	
6	0.155	
7	0.165	
9	0.355	
10		83% @ 10
11	0.953	
12		70% @ 10
13	0.269	
14	0.096	
15	0.53	
17		40% @ 10
18		60% @ 10
21	0.171	
22	0.445	
25	0.055	
26	0.19	
29	0.011	
30	0.251	
31	0.056	
32	0.307	
38	0.51	
39	0.012	
40	0.055	
41	0.013	
42	0.425	
43	7.5	
45	0.48	
46	1	
47	0.295	
48	2	
49	0.071	
51	0.033	
52	0.416	
53	0.109	
54		68% @ 1.0
55	0.74	
57	0.782	
58	0.172	
59	0.709	
60	0.264	
D	0.179	
F	0.437	

TABLE 3

Example #	IC50, uM	% Inhibition @ concentration, uM
145	1.3	
146		9% @ 10
147		27% @ 10
150		53% @ 10
154		21% @ 10
155		58% @ 10
160	0.044	
161	0.1	
162	0.65	
163	0.464	
196	0.028	
197	0.243	
198	0.137	
199	0.684	
200		73% @ 1.0
201	0.029	
202	1.9	
203	0.328	
204	0.008	
206	0.013	
207	0.033	
209	0.354	
234	11	
284	1.95	
285	0.102	
286	0.079	
287	0.041	
288	0.104	
289	1.3	
291	5.1	
294	2.1	
295	1.2	
296	0.284	
297	0.34	
298	0.025	
299	2.3	
300	0.251	
301	0.63	
302	0.077	

Human peripheral blood mononuclear leukocyte cell assay.

Human peripheral blood mononuclear leukocytes are challenged with 25ng/mL lipopolysaccharide (LPS) in the absence or presence of Test Compound and incubated for 16 hours as described by Welker P. et al, *International Archives Allergy and Immunology* (1996) 109: 110. The quantity of LPS-induced tumor necrosis factor-alpha (TNF-*alpha*) cytokine release is measured by a commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kit. Test compounds are evaluated for their ability to inhibit TNF-*alpha* release. Table 2 records IC_{50} values for inhibition of TNF-*alpha* release by Test Compounds of the present invention, wherein the IC_{50} value, in micromolar concentration, represents the concentration of Test Compound resulting in a 50% inhibition of TNF-alpha release from human peripheral blood mononuclear leukocytes as compared to control experiments containing no Test Compound. Test compounds evaluated are illustrated in Table 4.

TABLE 4

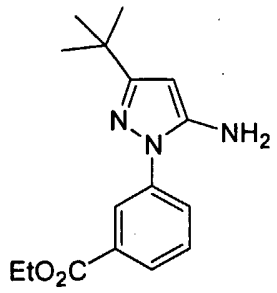
Example Number	IC50, uM
3	6.1
13	6.32
21	3.4
29	2.68
31	4.52
60	2.34
296	3.49
300	4.78
302	5.45

EXAMPLES

The following examples set forth preferred methods in accordance with the invention. It is to be understood, however, that these examples are provided by way of illustration and nothing therein should be taken as a limitation upon the overall scope of the invention.

[Boc-sulfamide] aminoester (Reagent AA), 1,5,7,-trimethyl-2,4-dioxo-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid (Reagent BB), and Kemp acid anhydride (Reagent CC) was prepared according to literature procedures. See Askew et. al *J. Am. Chem. Soc.* **1989**, *111*, 1082 for further details.

EXAMPLE A

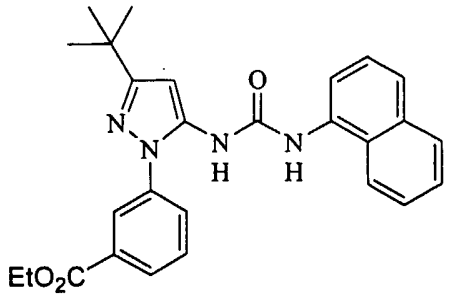


To a solution (200 mL) of *m*-amino benzoic acid (200 g, 1.46 mol) in concentrated HCl was added an aqueous solution (250 mL) of $NaNO_2$ (102 g, 1.46 mol) at 0 °C. The reaction mixture was stirred for 1 h and a solution of $SnCl_2 \cdot 2H_2O$ (662 g, 2.92 mol) in concentrated HCl (2 L) was then added at 0 °C, and the reaction stirred for an additional 2h at RT. The precipitate was filtered and washed with ethanol and ether to yield 3-hydrazino-benzoic acid hydrochloride as a white solid.

The crude material from the previous reaction (200 g, 1.06 mol) and 4,4-dimethyl-3-oxo-pentanenitrile (146 g, 1.167 mol) in ethanol (2 L) were heated to reflux overnight. The reaction solution was evaporated in vacuo and the residue purified by column chromatography to yield ethyl 3-(3-*tert*-butyl-5-amino-1*H*-pyrazol-1-yl)benzoate (Example A, 116 g, 40%) as a white solid together with 3-(5-amino-3-*tert*-butyl-1*H*-pyrazol-1-yl)benzoic acid (93 g, 36%). ^{1}H NMR (DMSO-d_6): 8.09 (s, 1H), 8.05 (brd, J = 8.0 Hz, 1H), 7.87 (brd, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0

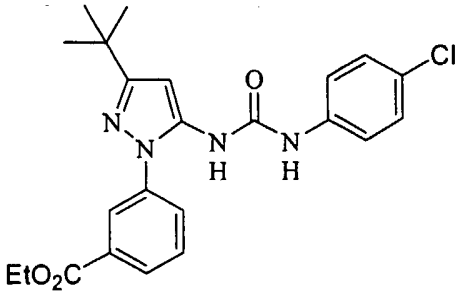
Hz, 1H), 5.64 (s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.28 (s, 9H).

EXAMPLE B



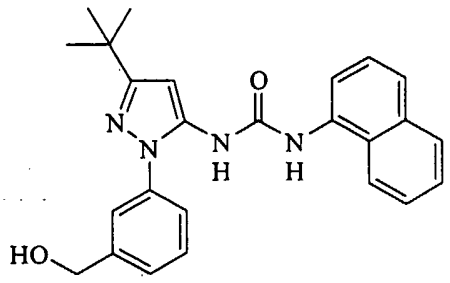
To a solution of 1-naphthyl isocyanate (9.42 g, 55.7 mmol) and pyridine (44 mL) in THF (100 mL) was added a solution of Example A (8.0 g, 27.9 mmol) in THF (200 mL) at 0 °C. The mixture was stirred at RT for 1h, heated until all solids were dissolved, stirred at RT for an additional 3h and quenched with H_2O (200 mL). The precipitate was filtered, washed with dilute HCl and H_2O, and dried in vacuo to yield ethyl 3-[3-*t*-butyl-5-(3-naphthalen-1-yl)ureido)-1*H*-pyrazol-1-yl]benzoate(12.0 g, 95%) as a white power. ^{1}H NMR (DMSO-d_6): 9.00 (s, 1 H), 8.83 (s, 1 H), 8.25 7.42 (m, 11 H), 6.42 (s, 1 H), 4.30 (q, J = 7.2 Hz, 2 H), 1.26 (s, 9 H), 1.06 (t, J = 7.2 Hz, 3 H); MS (ESI) m/z: 457.10 ($M+H^+$).

EXAMPLE C



To a solution of Example A (10.7 g, 70.0 mmol) in a mixture of pyridine (56 mL) and THF (30 mL) was added a solution of 4-nitrophenyl 4-chlorophenylcarbamate (10 g, 34.8 mmol) in THF (150 mL) at 0 °C. The mixture was stirred at RT for 1 h and heated until all solids were dissolved, and stirred at RT for an additional 3 h. H_2O (200 mL) and CH_2Cl_2 (200 mL) were added, the aqueous phase separated and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with 1N NaOH, and 0.1N HCl, saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to yield ethyl 3-{3-*tert*-butyl-5-[3-(4-chlorophenyl)ureido]-1*H*-pyrazol-1-yl}benzoate (8.0 g, 52%). ^{1}H NMR (DMSO-d_6): δ 9.11 (s, 1H), 8.47 (s, 1H), 8.06 (m, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 8.0, 7.6 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.34 (s, 1H), 4.30 (q, J = 6.8 Hz, 2H), 1.27 (s, 9H), 1.25 (t, J = 6.8 Hz, 3H); MS (ESI) m/z: 441 (M^++H).

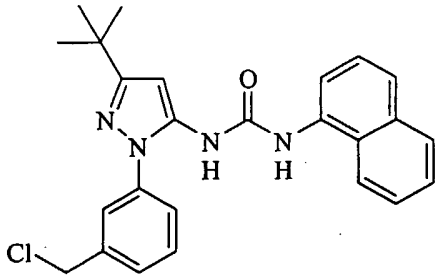
EXAMPLE D



To a stirred solution of Example B (8.20 g, 18.0 mmol) in THF (500 mL) was added $LiAlH_4$ powder (2.66 g, 70.0 mmol) at -10 °C under N_2. The mixture was stirred for 2 h at RT

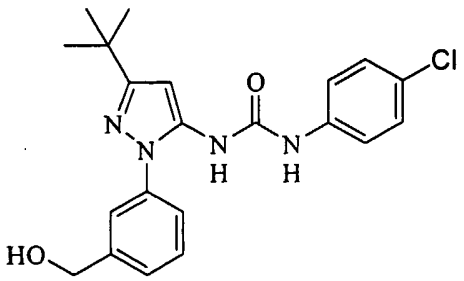
and excess $LiAlH_4$ destroyed by slow addition of ice. The reaction mixture was acidified to pH = 7 with dilute HCl, concentrated in vacuo and the residue extracted with EtOAc. The combined organic layers were concentrated in vacuo to yield 1-{3-*tert*-butyl-1-[3-(hydroxymethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(naphthalen-1-yl)urea (7.40 g, 99%) as a white powder. ^{1}H NMR (DMSO-d_6): 9.19 (s, 1 H), 9.04 (s, 1 H), 8.80 (s, 1 H), 8.26-7.35 (m, 11 H), 6.41 (s, 1 H), 4.60 (s, 2 H), 1.28 (s, 9 H); MS (ESI) m/z: 415 ($M+H^+$).

EXAMPLE E



A solution of Example C (1.66 g, 4.0 mmol) and $SOCl_2$ (0.60 mL, 8.0 mmol) in CH_3Cl (100 mL) was refluxed for 3 h and concentrated in vacuo to yield 1-{3-*tert*-butyl-1-[3-chloromethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(naphthalen-1-yl)urea (1.68 g, 97%) was obtained as white powder. ^{1}H NMR (DMSO-*d*6): δ 9.26 (s, 1 H), 9.15 (s, 1 H), 8.42 - 7.41 (m, 11 H), 6.40 (s, 1 H), 4.85 (s, 2 H), 1.28 (s, 9 H). MS (ESI) m/z: 433 ($M+H^+$).

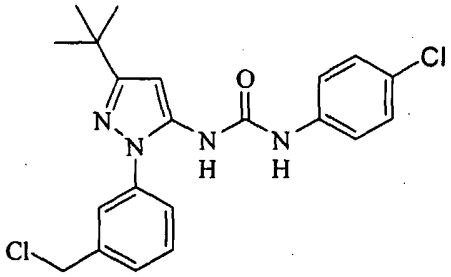
EXAMPLE F



To a stirred solution of Example C (1.60 g, 3.63 mmol) in THF (200 mL) was added $LiAlH_4$ powder (413 mg, 10.9 mmol) at -10 °C under N_2. The mixture was stirred for 2h and

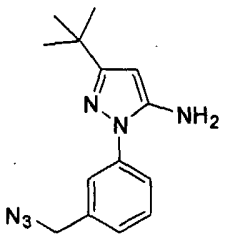
excess $LiAlH_4$ was quenched by adding ice. The solution was acidified to pH = 7 with dilute HCl. Solvents were slowly removed and the solid was filtered and washed with EtOAc (200 + 100 mL). The filtrate was concentrated to yield 1-{3-*tert*-butyl-1-[3-hydroxymethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea (1.40 g, 97%). ^{1}H NMR (DMSO- d_6): δ 9.11 (s, 1H), 8.47 (s, 1H), 7.47-7.27 (m, 8H), 6.35 (s, 1H), 5.30 (t, J = 5.6 Hz, 1H), 4.55 (d, J = 5.6 Hz, 2H), 1.26 (s, 9H); MS (ESI) m/z: 399 ($M+H^+$).

EXAMPLE G



A solution of Example F (800 mg, 2.0 mmol) and $SOCl_2$ (0.30 mL, 4 mmol) in $CHCl_3$ (30 mL) was refluxed gently for 3h. The solvent was evaporated in vacuo and the residue was taken up to in CH_2Cl_2 (2 × 20 mL). After removal of the solvent, 1-{3-*tert*-butyl-1-[3-(chloromethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea (812 mg, 97%) was obtained as white powder. ^{1}H NMR (DMSO- d_6): δ 9.57 (s, 1H), 8.75 (s, 1H), 7.63 (s, 1H), 7.50 - 7.26 (m, 7H), 6.35 (s, 1H), 4.83 (s, 2H), 1.27 (s, 9H); MS (ESI) m/z: 417 ($M+H^+$).

EXAMPLE H

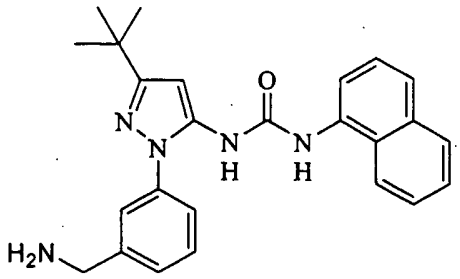


To a suspension of $LiAlH_4$ (5.28 g, 139.2 mmol) in THF (1000 mL) was added Example

A (20.0 g, 69.6 mmol) in portions at 0 °C under N_2. The reaction mixture was stirred for 5 h, quenched with 1 N HCl at 0 °C and the precipitate was filtered, washed by EtOAc and the filtrate evaporated to yield [3-(5-amino-3-*tert*-butyl-1*H*-pyrazol-1-yl)phenyl]methanol (15.2 g, 89%). ^{1}H NMR (DMSO-d_6): 7.49 (s, 1H), 7.37 (m, 2H), 7.19 (d, J = 7.2 Hz, 1H), 5.35 (s, 1H), 5.25 (t, J =5.6 Hz, 1H), 5.14 (s, 2H), 4.53 (d, J = 5.6 Hz, 2H), 1.19 (s, 9H); MS (ESI) m/z: 246.19 ($M+H^+$).

The crude material from the previous reaction (5.0 g, 20.4 mmol) was dissolved in dry THF (50 mL) and $SOCl_2$ (4.85 g, 40.8 mmol), stirred for 2h at RT, concentrated in vacuo to yield 3-*tert*-butyl-1-(3-chloromethylphenyl)-1*H*-pyrazol-5-amine (5.4 g), which was added to N_3 (3.93 g, 60.5 mmol) in DMF (50 mL). The reaction mixture was heated at 30 °C for 2 h, poured into H_2O (50 mL), and extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo to yield crude 3-*tert*-butyl-1-[3-(azidomethyl)phenyl]-1*H*-pyrazol-5-amine (1.50 g, 5.55 mmol).

EXAMPLE I

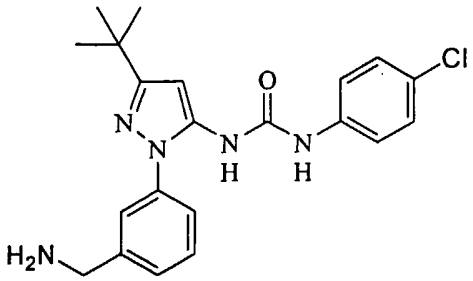


Example H was dissolved in dry THF (10 mL) and added a THF solution (10 mL) of 1-isocyano naphthalene (1.13 g, 6.66 mmol) and pyridine (5.27 g, 66.6 mmol) at RT. The reaction mixture was stirred for 3h, quenched with H_2O (30 mL), the resulting precipitate filtered and washed with 1N HCl and ether to yield 1-[2-(3-azidomethyl-phenyl)-5-t-butyl-2H-pyrazol-3-yl]-3-naphthalen-1-yl-urea (2.4 g, 98%) as a white solid.

The crude material from the previous reaction and Pd/C (0.4 g) in THF (30 mL) was hydrogenated under 1 atm at RT for 2 h. The catalyst was removed by filtration and the filtrate concentrated in vacuo to yield 1-{3-*tert*-butyl-1-[3-(amonomethyl)phenyl}-1*H*-pyrazol-5yl)-3-(naphthalene-1-yl)urea (2.2 g, 96%) as a yellow solid. ^{1}H NMR (DMSO-d_6): 9.02 (s, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 7.6 Hz, 2H), 7.67-7.33 (m, 9H), 6.40 (s, 1H), 3.81 (s, 2H), 1.27

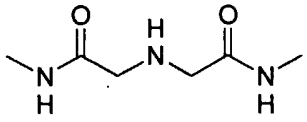
(s, 9H); MS (ESI) m/z: 414 ($M+H^+$).

EXAMPLE J



To a solution of Example H (1.50 g, 5.55 mmol) in dry THF (10 mL) was added a THF solution (10 mL) of 4-chlorophenyl isocyanate (1.02 g, 6.66 mmol) and pyridine (5.27 g, 66.6 mmol) at RT. The reaction mixture was stirred for 3 h and then H_2O (30 mL) was added. The precipitate was filtered and washed with 1N HCl and ether to give 1-{3-*tert*-butyl-1-[3-(amonomethyl)phenyl}-1*H*-pyrazol-5yl)-3-(4-chlorophenyl)urea (2.28 g, 97%) as a white solid, which was used for next step without further purification. MS (ESI) m/z: 424 ($M+H^+$).

EXAMPLE K



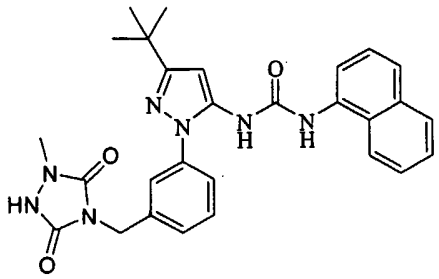
To a solution of benzyl amine (16.5g, 154 mmol) and ethyl bromoacetate (51.5g, 308 mmol) in ethanol (500 mL) was added K_2CO_3 (127.5g, 924 mmol). The mixture was stirred at RT for 3h, was filtered, washed with EtOH, concentrated in vacuo and chromatographed to yield N-(2-ethoxy-2-oxoethyl)-N-(phenylmethyl)-glycine ethyl ester (29g, 67%). ^1H NMR ($CDCl_3$): δ 7.39-7.23 (m, 5H), 4.16 (q, J = 7.2 Hz, 4H), 3.91(s, 2H), 3.54 (s, 4H), 1.26 (t, J = 7.2 Hz, 6H); MS (ESI): m/e: 280 (M^++H).

A solution of N-(2-ethoxy-2-oxoethyl)-N-(phenylmethyl)-glycine ethyl ester (7.70g, 27.6 mmol) in methylamine alcohol solution (25-30%, 50 mL) was heated to 50°C in a sealed tube for 3h, cooled to RT and concentrated in vacuo to yield N-(2-methylamino-2-oxoethyl)-N-

(phenylmethyl)-glycine methylamide in quantitative yield (7.63g). ^{1}H NMR ($CDCl_3$): δ 7.35-7.28 (m, 5H), 6.75 (br s, 2H), 3.71(s, 2H), 3.20 (s, 4H), 2.81 (d, J = 5.6 Hz, 6H); MS (ESI) m/e 250($M+H^+$).

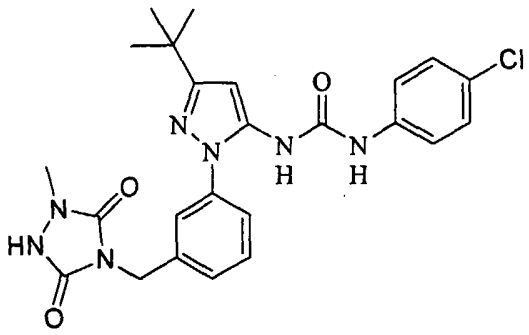
The mixture of N-(2-methylamino-2-oxoethyl)-N-(phenylmethyl)-glycine methylamide (3.09g, 11.2 mmol) in MeOH (30 mL) was added 10% Pd/C (0.15g). The mixture was stirred and heated to 40°C under 40 psi H_2 for 10h, filtered and concentrated in vacuo to yield N-(2-methylamino-2-oxoethyl)-glycine methylamide in quantitative yield (1.76g). ^{1}H NMR ($CDCl_3$): δ 6.95(br s, 2H), 3.23 (s, 4H), 2.79 (d, J=6.0, 4.8 Hz), 2.25(br s 1H); MS (ESI) m/e 160($M+H^+$)

EXAMPLE 1



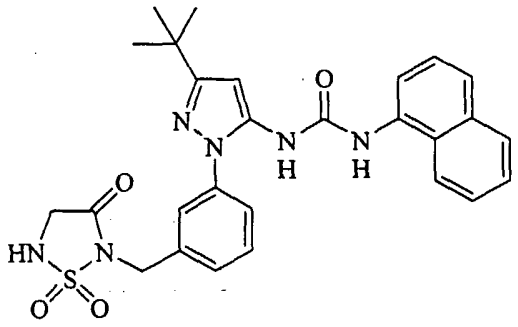
To a solution of 1-methyl-[1,2,4]triazolidine-3, 5-dione (188 mg, 16.4 mmol) and sodium hydride (20 mg, 0.52 mmol) in DMSO (1 mL) was added Example E (86 mg, 0.2 mmol). The reaction was stirred at RT overnight, quenched with H_2O (10 mL), extracted with CH_2Cl_2, and the organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative HPLC to yield 1-(3-*tert*-butyl-1-{3-[(1-methyl-3,5-dioxo-1,2,4-triazolidin-4-yl)methyl]phenyl}-1*H*-pyrazol-5-yl)-3-(naphthalene-1-yl)urea (Example 1, 14 mg). ^{1}H NMR (CD_3OD): δ7.88-7.86 (m, 2H), 7.71-7.68 (m, 2H), 7.58 (m, 2H), 7.60-7.42 (m, 5H), 6.49 (s, 1H), 4.85 (s, 1H), 1.34 (s, 9H), 1.27 (s, 6H); MS (ESI) m/z: 525 ($M+H^+$).

EXAMPLE 2



The title compound was synthesized in a manner analogous to Example 1, utilizing Example G to yield 1-(3-*tert*-butyl-1-{3-[(1-methyl-3,5-dioxo-1,2,4-triazolidin-4-yl)methyl]phenyl}-1*H*-pyrazol-5-yl)-3-(4-chlorophenyl)urea ^{1}H NMR (CD_3OD): δ 7.2~7.5 (m, 7H), 6.40 (s 1H), 4.70 (s, 2H), 2.60 (d, J = 14 Hz, 2H), 1.90 (m, 1H), 1.50 (m, 1H), 1.45 (s, 9H), 1.30 (m, 2H), 1.21 (s, 3H), 1.18 (s, 6H); MS (ESI) m/z: 620 ($M+H^+$).

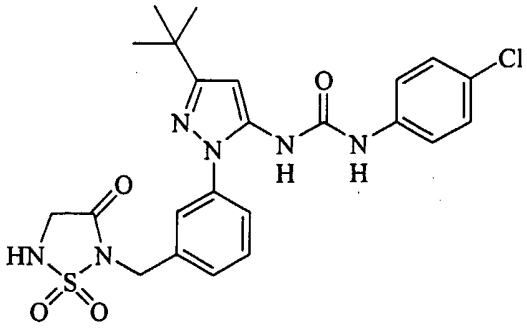
EXAMPLE 3



A mixture of compound 1,1-Dioxo-[1,2,5]thiadiazolidin-3-one (94 mg, 0.69 mmol) and NaH (5.5 mg, 0.23 mmol) in THF (2 mL) was stirred at -10 °C under N_2 for 1h until all NaH was dissolved. Example E (100 mg, 0.23 mmol) was added and the reaction was allowed to stir at RT overnight, quenched with H_2O, and extracted with CH_2Cl_2. The combined organic layers were concentrated in vacuo and the residue was purified by preparative HPLC to yield 1-(3-*tert*-butyl-1-{[3-(1,1,3-trioxo-[1,2,5]thiadiazolidin-2-yl)methyl]phenyl}-1*H*-pyrazol-5-yl)-3-(naphthalen-1-yl)urea (18 mg) as a white powder. ^{1}H NMR (CD_3OD): δ 7.71 - 7.44 (m, 11 H), 6.45 (s, 1 H),

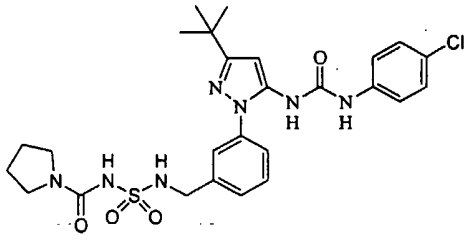
4.83 (s, 2 H), 4.00 (s, 2 H), 1.30 (s, 9 H). MS (ESI) m/z: 533.40 ($M+H^+$).

EXAMPLE 4



The title compound was obtained in a manner analogous to Example 3 utilizing Example G. to yield 1-(3-*tert*-butyl-1-{[3-(1,1,3-trioxo-[1,2,5]thiadiazolidin-2-yl)methyl]phenyl}-1*H*-pyrazol-5-yl)-3-(4-chlorophenyl)urea. ^{1}H NMR (CD_3OD): δ 7.38 - 7.24 (m, 8 H), 6.42 (s, 1 H), 4.83 (s, 2 H), 4.02 (s, 2 H), 1.34 (s, 9 H); MS (ESI) m/z: 517 ($M+H^+$).

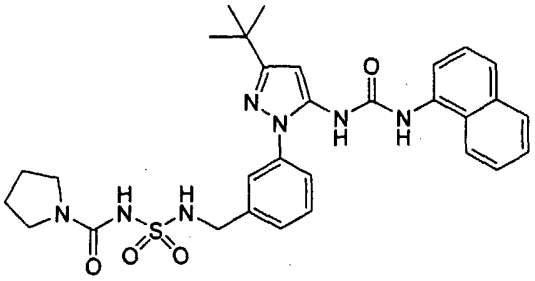
EXAMPLE 5



To a stirred solution of chlorosulfonyl isocyanate (19.8 μL, 0.227 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was added pyrrolidine (18.8 μL, 0.227 mmol) at such a rate that the reaction solution temperature did not rise above 5 °C. After stirring for 1.5 h, a solution of Example J (97.3 mg, 0.25 mmol) and Et_3N (95 μL, 0.678 mmol) in CH_2Cl_2 (1.5 mL) was added at such a rate that the reaction temperature didn rise above 5 °C. When the addition was completed, the reaction solution was warmed to RT and stirred overnight. The reaction mixture was poured into 10%

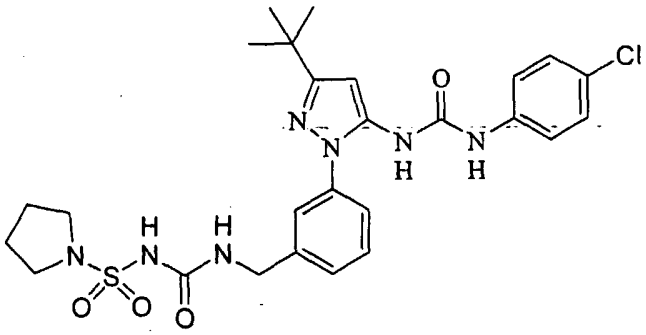
HCl, extracted with CH_2Cl_2, the organic layer washed with saturated NaCl, dried over $MgSO_4$, and filtered. After removal of the solvents, the crude product was purified by preparative HPLC to yield 1-(3-*tert*-butyl-1-[[3-N-[[(1-pyrrolidinylcarbonyl)amino]sulphonyl]aminomethyl]phenyl]-1*H*-pyrazol-5-yl)-3-(4-chlorophenyl)urea. ^{1}H NMR(CD_3OD): δ 7.61 (s, 1 H), 7.43 -7.47 (m, 3 H), 7.23 - 7.25 (dd, *J* =6.8 Hz, 2 H), 7.44 (dd, *J* =6.8 Hz, 2 H), 6.52 (s, 1 H), 4.05 (s, 2 H), 3.02 (m, 4 H), 1.75 (m, 4 H), 1.34 (s, 9 H); MS (ESI) m/z: 574.00 ($M+H^+$).

EXAMPLE 6



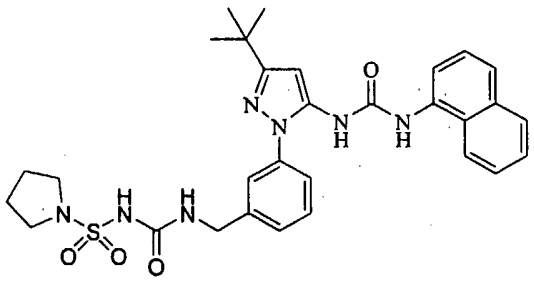
The title compound was made in a manner analogous to Example 5 utilizing Example I to yield 1-(3-*tert*-butyl-1-[[3-N-[[(1-pyrrolidinylcarbonyl)amino]sulphonyl]aminomethyl]-phenyl]-1*H*-pyrazol-5-yl)-3-(naphthalen-1-yl)urea. ^{1}HNMR ($CDCl_3$): δ 7.88 (m, 2 H), 7.02 - 7.39 (m, 2 H), 7.43 - 7.50 (m, 7 H), 6.48 (s, 1 H), 4.45 (s, 1 H), 3.32 - 3.36 (m, 4 H), 1.77 - 1.81 (m, 4 H), 1.34 (s,9 H); MS (ESI) m/z: 590.03 ($M+H^+$).

EXAMPLE 7



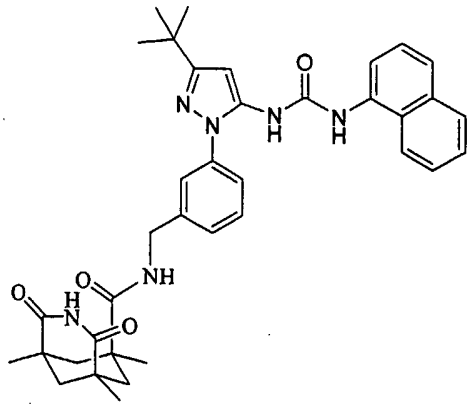
To a stirred solution of chlorosulfonyl isocyanate (19.8 μΛ, 0.227 μμολ) ιν $XH_lX\lambda_l$ (0.5 μΛ) ατ 0°C, was added Example J (97.3 mg, 0.25 mmol) at such a rate that the reaction solution temperature did not rise above 5 °C. After being stirred for 1.5 h, a solution of pyrrolidine (18.8 μL, 0.227 mmol) and Et_3N (95 μL, 0.678 mmol) in CH_2Cl_2 (1.5 mL) was added at such a rate that the reaction temperature didn rise above 5 °C. When addition was completed, the reaction solution was warmed to RT and stirred overnight. The reaction mixture was poured into 10% HCl, extracted with CH_2Cl_2, the organic layer was washed with saturated NaCl, dried over Mg_2SO_4, and filtered. After removal of the solvents, the crude product was purified by preparative HPLC to yield 1-(3-*tert*-butyl-1-[[3-N-[[(1-pyrrolidinylsulphonyl)amino]carbonyl]aminomethyl]phenyl]-1*H*-pyrazol-5-yl)-3-(4-chlorophenyl)urea. ^{1}HNMR ($CDCl_3$): δ 7.38 (m, 1 H), 7.36 - 7.42 (m, 3 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 6.43 (s, 1 H), 4.59 (s, 1 H), 4.43 (s, 2 H), 1.81 (s, 2 H), 1.33 (s, 9 H); MS (ESI) m/z: 574.10 ($M+H^+$).

EXAMPLE 8



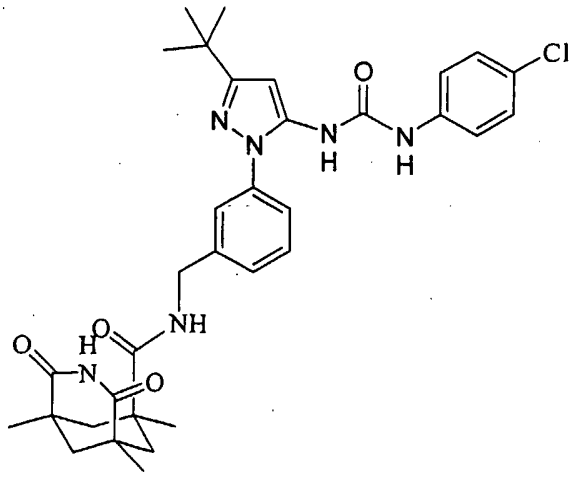
The title compound was made in a manner analogous to Example 7 utilizing Example I to yield 1-(3-*tert*-butyl-1-[[3-N-[[(1-pyrrolidinylsulphonyl)amino]carbonyl]aminomethyl]-phenyl]-1*H*-pyrazol-5-yl)-3-(naphthalen-1-yl)urea. ^{1}HNMR ($CDCl_3$): δ 7.88 (m, 2 H), 7.02 - 7.39 (m, 2 H), 7.43 - 7.50 (m, 7 H), 6.48 (s, 1 H), 4.45 (s, 1 H), 3.32 - 3.36 (m, 4 H), 1.77 - 1.81 (m, 4 H), 1.34 (s,9 H); MS (ESI) m/z: 590.03 ($M+H^+$).

EXAMPLE 9



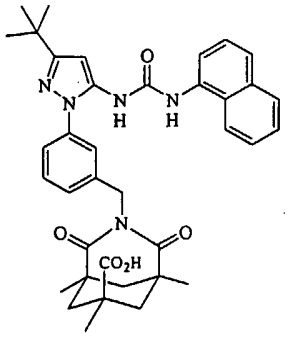
To a solution of Reagent BB (36 mg, 0.15 mmol), Example I (62 mg, 0.15 mmol), HOBt (40 mg, 0.4 mmol) and NMM (0.1 mL, 0.9 mmol) in DMF (10 mL) was added EDCI (58 mg, 0.3 mmol). After being stirred overnight, the mixture was poured into water (15 mL) and extracted with EtOAc (3 5 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC to yield 1,5,7-trimethyl-2,4-dioxo-3-azabicyclo[3.3.1]nonane-7-carboxylic acid 3-[3-t-butyl-5-(3-naphthalen-1-yl-ureido)-pyrazol-1-yl]benzylamide (22 mg). ^{1}H NMR ($CDCl_3$): δ 8.40 (s, 1H), 8.14 (d, J = 8.0 Hz, 2H), 7.91 (s, 1H), 7.87 (s, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.57-7.40 (m, 4H), 7.34 (d, J = 7.6 Hz, 1H), 6.69 (s, 1H), 6.32 (t, J = 5.6 Hz, 1H), 5.92 (brs, 1H), 4.31 (d, J = 5.6 Hz, 2H), 2.37 (d, J = 14.8 Hz, 2H), 1.80 (d, J = 13.2 Hz, 1H), 1.35 (s, 9H), 1.21 (d, J = 13.2 Hz, 1H), 1.15 (s, 3H), 1.12 (d, J = 12.8 Hz, 2H), 1.04 (s, 6H); MS (ESI) m/z: 635 ($M+H^+$).

EXAMPLE 10



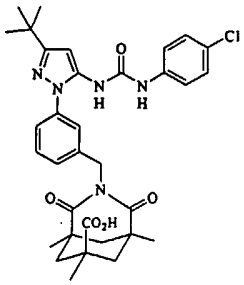
The title compound, was synthesized in a manner analogous to Example 9 utilizing Example J to yield 1,5,7-trimethyl-2,4-dioxo-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid 3-{3-t-butyl-5-[3-(4-chloro-phenyl)-ureido]-pyrazol-1-yl}benzylamide. ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H), 7.78 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.26 (m, 3H), 6.62 (s, 1H), 6.35(t, J = 6.0 Hz, 1H), 5.69 (brs, 1H), 4.26 (d, J = 6.0 Hz, 2H), 2.48 (d, J = 14.0 Hz, 2H), 1.87 (d, J = 13.6 Hz,1H), 1.35 (s, 9H), 1.25 (m, 6H), 1.15 (s, 6H); MS (ESI) m/z: 619 ($M+H^+$).

EXAMPLE 11



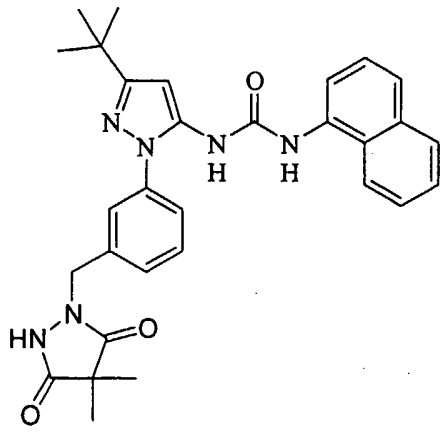
A mixture of Example I (41 mg, 0.1 mmol), Kemp acid anhydride (24 mg, 0.1 mmol) and Et_3N (100 mg, 1 mmol) in anhydrous CH_2Cl_2 (2 mL) were stirred overnight at RT, and concentrated in vacuo. Anhydrous benzene (20 mL) was added to the residue, the mixture was refluxed for 3h, concentrated in vacuo and purified by preparative HPLC to yield 3-{3-[3-t-butyl-5-(3-naphthalen-1-yl-ureido)-pyrazol-1-yl]-benzyl}-1,5-di-methyl-2,4-dioxo-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid (8.8 mg, 14%). ^{1}H NMR (CD_3OD): δ 7.3 - 7.4 (m, 2H), 7.20 (m, 2H), 7.4 - 7.6 (m, 7H), 6.50 (m, 1H), 4.80 (s, 2H), 2.60 (d, J = 14 Hz, 2H), 1.90 (m, 1H), 1.40 (m, 1H), 1.30 (m, 2H), 1.20 (s, 3H), 1.15 (s, 6H); MS (ESI) m/z: 636 ($M+H^+$).

EXAMPLE 12



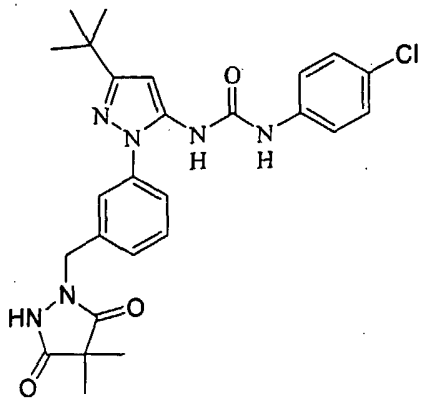
The title compound, was synthesized in a manner analogous to Example 11 utilizing Example J to yield 3-{3-[3-t-butyl-5-(3-naphthalen-1-yl-ureido)-pyrazol-1-yl]-benzyl}-1,5-dimethyl-2,4-dioxo-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid. ^{1}H NMR (CD_3OD): δ 7.2 - 7.5 (m, 7H), 6.40 (s 1H), 4.70 (s, 2H), 2.60 (d, J = 14 Hz, 2H), 1.90 (m, 1H), 1.50 (m, 1H), 1.45 (s, 9H), 1.30 (m, 2H), 1.21 (s, 3H), 1.18 (s, 6H); MS (ESI) m/z: 620 ($M+H^+$).

EXAMPLE 13



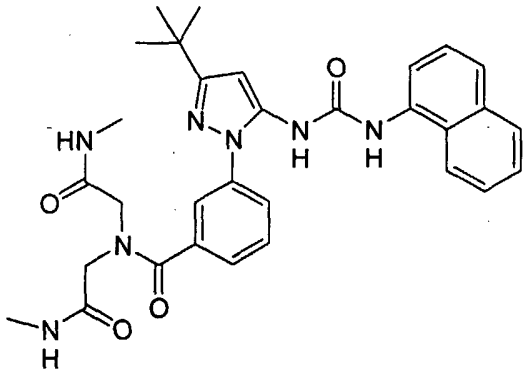
The title compound was synthesized in a manner analogous to Example 1 utilizing Example E and 4,4-dimethyl-3,5-dioxo-pyrazolidine to yield 1-(3-*tert*-butyl-1-{3-[(4,4-dimethyl-3,5-dioxopyrazolidin-1-yl)methyl]phenyl}-1*H*-pyrazol-5-yl)-3-(naphthalen-1-yl)urea. ^{1}H NMR (CD_3OD): δ 7.88 - 7.86 (m, 2H), 7.71-7.68 (m, 2H), 7.58 (m, 2H), 7.60-7.42 (m, 5H), 6.49 (s, 1H), 4.85 (s, 1H), 1.34 (s, 9H), 1.27 (s, 6H); MS (ESI) m/z: 525 ($M+H^+$).

EXAMPLE 14



The title compound was synthesized in a manner analogous to Example 1 utilizing Example G and 4,4-dimethyl-3,5-dioxo-pyrazolidine to yield 1-(3-*tert*-butyl-1-{3-[(4,4-dimethyl-3,5-dioxopyrazolidin-1-yl)methyl]phenyl}-1*H*-pyrazol-5-yl)-3-(4-chlorophenyl)urea. ^{1}H NMR (CD_3OD): δ 7.60 - 7.20 (m, 8H), 6.43 (s, 1H), 4.70 (s, 1H), 1.34 (s, 9H), 1.26 (s, 6H); MS (ESI) m/z: 509, 511 ($M+H^+$).

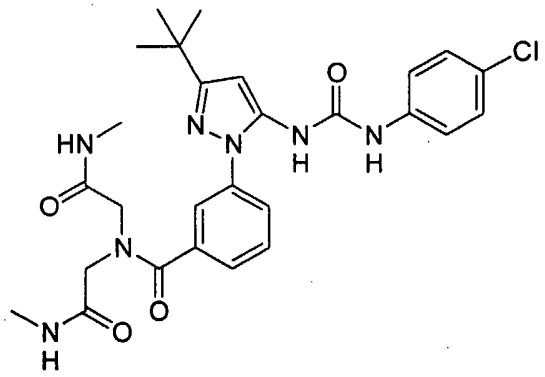
EXAMPLE 15



Example B was saponified with 2N LiOH in MeOH, and to the resulting acid (64.2 mg, 0.15 mmol) were added HOBt (30 mg, 0.225 mmol), Example K (24 mg, 0.15 mmol) and 4-methylmorpholine (60 mg, 0.60 mmol 4.0 equiv), DMF (3 mL) and EDCI (43 mg, 0.225 mmol). The reaction mixture was stirred at RT overnight and poured into H_2O (3mL), and a white

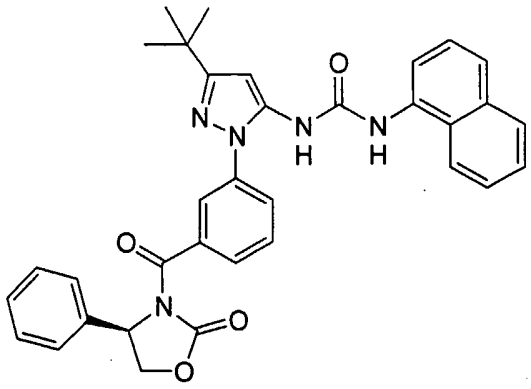
precipitate collected and further purified by preparative HPLC to yield 1-[1-(3-{bis[(methylcarbamoyl)methyl]carbamoyl}phenyl)-3-*tert*-butyl-1*H*-pyrazol-5-yl]-3-(naphthalen-1-yl)urea (40 mg). ^{1}H NMR ($CDCl_3$): δ 8.45 (brs, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.86-7.80 (m, 2H), 7.63-7.56 (m, 2H), 7.52 (s, 1H), 7.47-7.38 (m, 3H), 7.36-7.34 (m, 1H), 7.26 (s, 1H), 7.19-7.17 (m, 2H), 6.60 (s, 1H), 3.98 (s, 2H), 3.81 (s, 3H), 2.87 (s, 3H), 2.63 (s, 3H), 1.34 (s, 9H); MS (ESI) m/z: 570 ($M+H^+$).

EXAMPLE 16



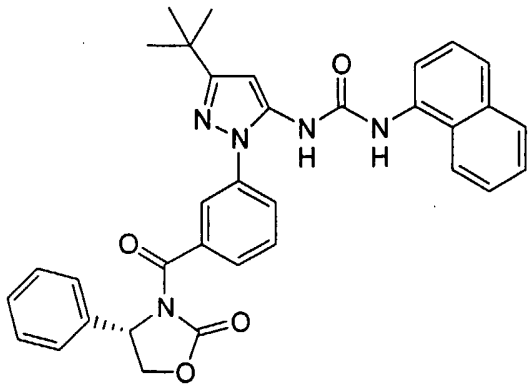
The title compound was synthesized in a manner analogous to Example 15 utilizing Example C (37 mg) and Example K to yield 1-[1-(3-{bis[(methylcarbamoyl)methyl]carbamoyl}phenyl)-3-*tert*-butyl-1*H*-pyrazol-5-yl]-3-(4-chlorophenyl)urea. ^{1}H NMR (CD_3OD): δ 8.58 (brs, 1H), 8.39 (brs, 1H), 7.64 - 7.62 (m, 3H), 7.53-7.51 (m,1H), 7.38 (d, J = 9.2 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.44 (s, 1H), 4.17 (s, 2H), 4.11 (s, 2H), 2.79 (s, 3H), 2.69 (s, 3H), 1.34-1.28 (m, 12H); MS (ESI) m/z: 554 ($M+H^+$).

EXAMPLE 17



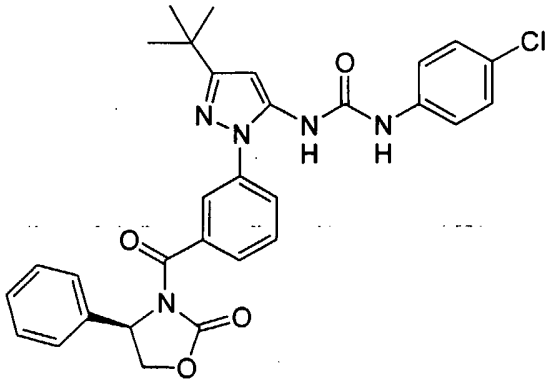
Example B was saponified with 2N LiOH in MeOH, and to the resulting acid (0.642 g, 1.5 mmol) in dry THF (25 mL) at -78 °C were added freshly distilled triethylamine (0.202 g, 2.0 mmol) and pivaloyl chloride (0.216 g,1.80 mmol) with vigorous stirring. After stirring at -78 °C for 15 min and at 0 °C for 45 min, the mixture was again cooled to -78 °C and then transferred into the THF solution of lithium salt of D-4-phenyl-oxazolidin-2-one [*: The lithium salt of the oxazolidinone regeant was previously prepared by the slow addition of n-BuLi (2.50M in hexane, 1.20 mL, 3.0 mmol) into THF solution of D- 4-phenyl-oxazoldin-2-one at -78 °C]. The reaction solution was stirred at -78 °C for 2 h and RT overnight, and then quenched with aq. ammonium chloride and extracted with dichloromethane (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative HPLC to yield D-1-{5-*tert*-butyl-2-[3-(2-oxo-4-phenyl-oxazolidinyl-3-carbonyl)phenyl]-2*H*-pyrazol-3-yl}-3-(naphthalen-1-yl)urea (207 mg, 24%). ^{1}H NMR ($CDCl_3$): δ 8.14 - 8.09 (m, 2H), 8.06 (s,1H), 7.86 - 7.81 (m, 4H), 7.79 (s, 1H), 7.68 - 7.61 (m, 2H), 7.51 - 7.40 (m, 9H), 6.75 (s, 1H), 5.80 (t, *J*=9.2, 7.6 Hz, 1H), 4.89 (t, *J* = 9.2 Hz, 1H), 4.42 (dd, *J*=9.2, 7.6 Hz, 1H), 1.37 (s, 9H); MS (ESI) m/z: 574 ($M+H^+$).

EXAMPLE 18



The title compound was synthesized in a manner analogous to Example 17 utilizing Example B and L-4-phenyl-oxazolidin-2-one to yield L-1-{5-*tert*-butyl-2-[3-(2-oxo-4-phenyl-oxazolidinyl-3-carbonyl)phenyl]-2*H*-pyrazol-3-yl}-3-(naphthalen-1-yl)urea ^{1}H NMR ($CDCl_3$): δ 8.14 - 8.09 (m, 2H), 8.06 (s,1H), 7.86 - 7.81 (m, 4H), 7.79 (s, 1H), 7.68 - 7.61 (m, 2H), 7.51 - 7.40 (m, 9H), 6.75 (s, 1H), 5.80 (t, *J*=9.2, 7.6 Hz, 1H), 4.89 (t, *J* = 9.2 Hz, 1H), 4.42 (dd, *J*=9.2, 7.6 Hz, 1H), 1.37 (s, 9H); MS (ESI) m/z: 574 ($M+H^+$)

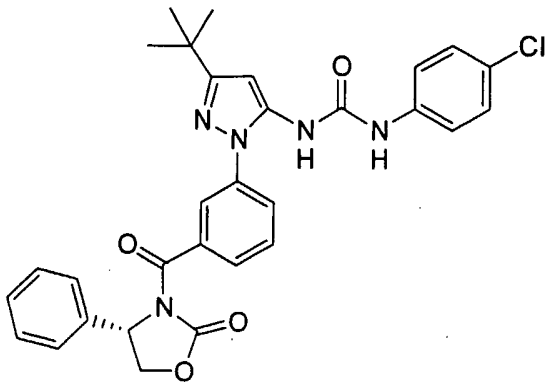
EXAMPLE 19



The title compound was synthesized in a manner analogous to Example 17 utilizing Example C and D-4-phenyl-oxazolidin-2-one to yield D-1-{5-*tert*-butyl-2-[3-(2-oxo-4-phenyl-oxazolidinyl-3-carbonyl)phenyl]-2*H*-pyrazol-3-yl}-3-(4-chlorophenyl)urea. ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.71 (m, 1H), 7.65 (m, 1H),

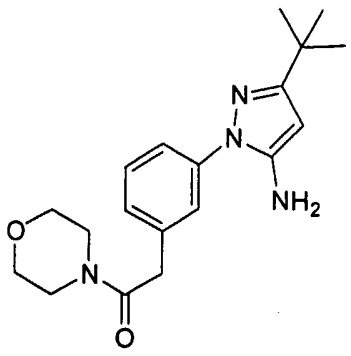
7.49 - 7.40 (m, 8H), 7.26 - 7.24 (m, 2H), 6.68 (s, 1H), 5.77 (dd, J = 8.8, 8.0 Hz, 1H), 4.96 (t, 8.8 Hz, 1H), 4.44 (dd, J = 8.8, 8.0 Hz, 1H), 1.36 (s, 9H); MS (ESI) m/z: 558 ($M+H^+$)

EXAMPLE 20



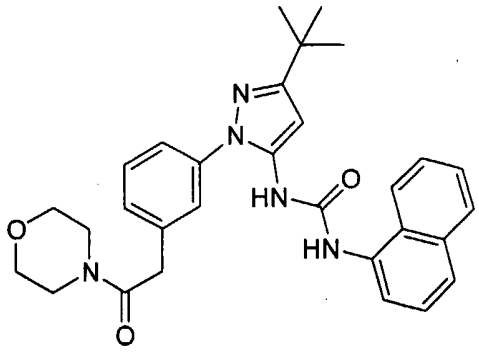
The title compound was synthesized in a manner analogous to Example 17 utilizing Example C and L-4-phenyl-oxazolidin-2-one to yield L-1-{5-*tert*-butyl-2-[3-(2-oxo-4-phenyl-oxazolidinyl-3-carbonyl)phenyl]-2*H*-pyrazol-3-yl}-3-(4-chlorophenyl)urea. ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.71 (m, 1H), 7.65 (m, 1H), 7.49 - 7.40 (m, 8H), 7.26 - 7.24 (m, 2H), 6.68 (s, 1H), 5.77 (dd, J = 8.8, 8.0 Hz, 1H), 4.96 (t, 8.8 Hz, 1H), 4.44 (dd, J = 8.8, 8.0 Hz, 1H), 1.36 (s, 9H); MS (ESI) m/z: 558 ($M+H^+$)

EXAMPLE L



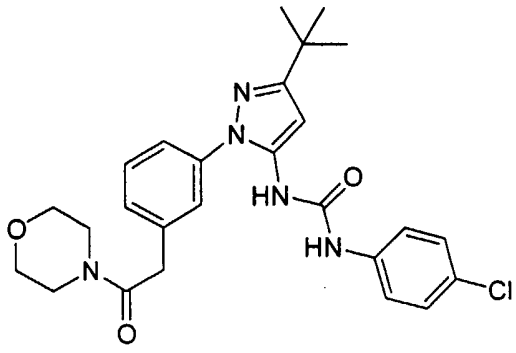
To a stirred suspension of (3-nitro-phenyl)-acetic acid (2 g) in CH_2Cl_2 (40 ml, with a catalytic amount of DMF) at 0 °C under N_2 was added oxalyl chloride (1.1 ml) drop wise. The reaction mixture was stirred for 40 min morpholine (2.5 g) was added. After stirring for 20 min, the reaction mixture was filtered. The filtrate was concentrated in vacuo to yield 1-morpholin-4-yl-2-(3-nitro-pheny)-ethanone as a solid (2 g). A mixture of 1-morpholin-4-yl-2-(3-nitro-pheny)-ethanone (2 g) and 10 % Pd on activated carbon (0.2 g) in ethanol (30 ml) was hydrogenated at 30 psi for 3h and filtered over Celite. Removal of the volatiles in vacuo provided 2-(3-amino-phenyl)-1-morpholin-4-yl-ethanone (1.7 g). A solution of 2-(3-amino-phenyl)-1-morpholin-4-yl-ethanone (1.7 g, 7.7 mmol) was dissolved in 6 N HCl (15 ml), cooled to 0 °C, and vigorously stirred. Sodium nitrite (0.54 g) in water (8 ml) was added. After 30 min, tin (II) chloride dihydrate (10 g) in 6 N HCl (30 ml) was added. The reaction mixture was stirred at 0 °C for 3 h. The pH was adjusted to pH 14 with solid potassium hydroxide and extracted with EtOAc. The combined organic extracts were concentrated in vacuo provided 2-(3-hydrazin-phenyl)-1-morpholin-4-yl-ethanone (1.5 g). 2-(3-Hydrazinophenyl)-1-morpholin-4-yl-ethanone (3 g) and 4,4-dimethyl-3-oxopentanenitrile (1.9 g, 15 mmol) in ethanol (60 ml) and 6 N HCl (1 ml) were refluxed for 1h and cooled to RT. The reaction mixture was neutralized by adding solid sodium hydrogen carbonate. The slurry was filtered and removal of the volatiles in vacuo provided a residue that was extracted with ethyl acetate. The volatiles were removed in vacuo to provide 2-[3-(3-*tert*-butyl-5-amino-1*H*-pyrazol-1-yl)phenyl]-1-morpholinoethanone (4 g), which was used without further purification.

EXAMPLE 21



A mixture of Example L (0.2 g, 0.58 mmol) and 1-naphthylisocyanate (0.10 g, 0.6 mmol) in dry CH_2Cl_2 (4 ml) was stirred at RT under N_2 for 18 h. The solvent was removed in vacuo and the crude product was purified by column chromatography using ethyl acetate/hexane/CH_2Cl_2 (3/1/0.7) as the eluent (0.11 g, off-white solid) to yield 1-{3-*tert*-butyl-1-[3-(2-morpholino-2-oxoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(naphthalene-1-yl)urea. mp: 194 - 196 ; ^{1}H NMR (200MHz, DMSO-d_6): δ 9.07 (1H, s), 8.45 (s, 1H), 8.06 - 7.93 (m, 3H), 7.69 - 7.44 (m, 7H), 7.33 - 7.29 (d, 6.9 Hz, 1H), 6.44 (s, 1H), 3.85 (m, 2H), 3.54 - 3.45 (m, 8H), 1.31 (s, 9H); MS:

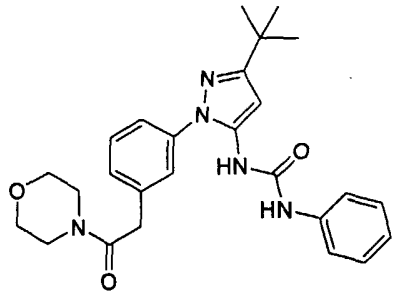
EXAMPLE 22



The title compound was synthesized in a manner analogous to Example 21 utilizing Example L (0.2 g, 0.58 mmol) and 4-chlorophenylisocyanate (0.09 g, 0.6 mmol) to yield 1-{3-*tert*-butyl-1-[3-(2-morpholino-2-oxoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea.

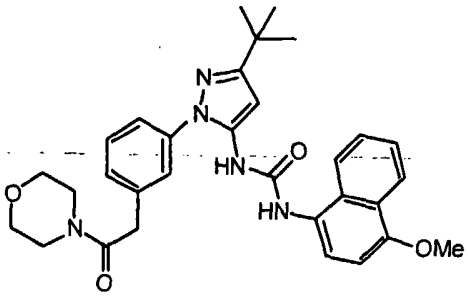
mp: 100 104 ; ^{1}H NMR (200MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.45 (s, 1H), 7.52-7.30 (m, 8H), 6.38 (s, 1H), 3.83 (m, 1H), 3.53 - 3.46 (m, 8H), 1.30 (s, 9H); MS:

EXAMPLE 23



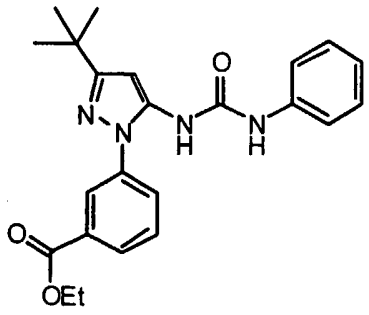
The title compound is synthesized in a manner analogous to Example 21 utilizing Example L (0.2 g, 0.58 mmol) and phenylisocyanate (0.09 g, 0.6 mmol) to yield 1-{3-*tert*-butyl-1-[3-(2-morpholino-2-oxoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-phenylurea.

EXAMPLE 24



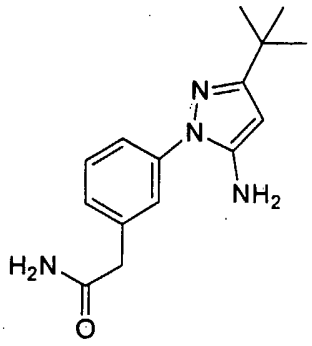
The title compound is synthesized in a manner analogous to Example 21 utilizing Example L (0.2 g, 0.58 mmol) and 1-isocyanato-4-methoxy-naphthalene to yield 1-{3-*tert*-butyl-1-[3-(2-morpholino-2-oxoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(1-methoxynaphthalen-4-yl)urea.

EXAMPLE M



The title compound is synthesized in a manner analogous to Example C utilizing Example A and phenylisocyanate to yield ethyl 3-(3-tert-butyl-5-(3-phenylureido)-1H-pyrazol-1-yl)benzoate.

EXAMPLE N

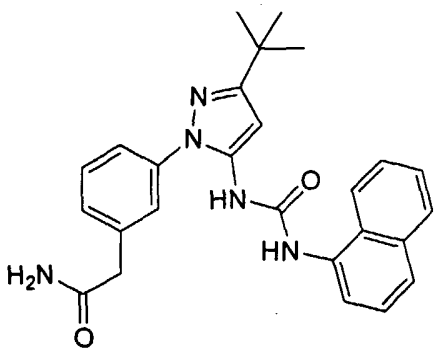


A solution of (3-nitrophenyl)acetic acid (23 g, 127 mmol) in methanol (250 ml) and a catalytic amount of concentrated in vacuo H_2SO_4 was heated to reflux for 18 h. The reaction mixture was concentrated in vacuo to a yellow oil. This was dissolved in methanol (250 ml) and stirred for 18 h in an ice bath, whereupon a slow flow of ammonia was charged into the solution. The volatiles were removed in vacuo. The residue was washed with diethyl ether and dried to afford 2-(3-nitrophenyl)acetamide (14 g, off-white solid). ^{1}H NMR ($CDCl_3$): δ 8.1 (s, 1H), 8.0 (d, 1H), 7.7 (d, 1H), 7.5 (m, 1H), 7.1 (bd s, 1H), 6.2 (brs, 1H), 3.6 (s, 2H).

The crude material from the previous reaction (8 g) and 10 % Pd on activated carbon (1 g) in ethanol (100 ml) was hydrogenated at 30 psi for 18 h and filtered over Celite. Removal of the volatiles in vacuo provided 2-(3-aminophenyl)acetamide (5.7 g). A solution of this material (7 g, 46.7 mmol) was dissolved in 6 N HCl (100 ml), cooled to 0 °C, and vigorously stirred. Sodium nitrite (3.22 g, 46.7 mmol) in water (50 ml) was added. After 30 min, tin (II) chloride dihydrate (26 g) in 6 N HCl (100 ml) was added. The reaction mixture was stirred at 0 °C for 3 h. The pH was adjusted to pH 14 with 50 % aqueous NaOH solution and extracted with ethyl acetate. The combined organic extracts were concentrated in vacuo provided 2-(3-hydrazinophenyl)acetamide.

The crude material from the previous reaction (ca. 15 mmol) and 4,4-dimethyl-3-oxopentanenitrile (1.85 g, 15 mmol) in ethanol (60 ml) and 6 N HCl (1.5 ml) was refluxed for 1 h and cooled to RT. The reaction mixture was neutralized by adding solid sodium hydrogen carbonate. The slurry was filtered and removal of the volatiles in vacuo provided a residue, which was extracted with ethyl acetate. The solvent was removed in vacuo to provide 2-[3-(3-*tert*-butyl-5-amino-1*H*-pyrazol-1-yl)phenyl]acetamide as a white solid (3.2 g), which was used without further purification.

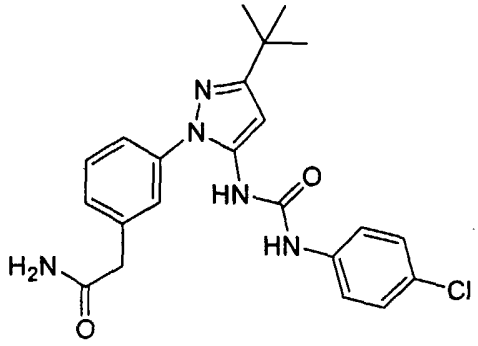
EXAMPLE 25



A mixture of Example N (2 g, 0.73 mmol) and 1-naphthylisocyanate (0.124 g, 0.73

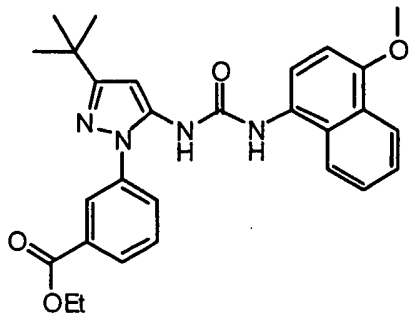
mmol) in dry CH_2Cl_2 (4 ml) was stirred at RT under N_2 for 18 h. The solvent was removed in vacuo and the crude product was washed with ethyl acetate (8 ml) and dried in vacuo to yield 1-{3-*tert*-butyl-1-[3-(carbamoylmethyl)phenyl)-1*H*-pyrazol-5-yl}-3-(naphthalene-1-yl)urea as a white solid (0.22 g). mp: 230 (dec.); ^{1}H NMR (200MHz, DMSO- d_6): δ 9.12 (s, 1H), 8.92 (s, 1H), 8.32 - 8.08 (m, 3H), 7.94 - 7.44 (m, 8H), 6.44 (s, 1H), 3.51 (s, 2H), 1.31 (s, 9H); MS:

EXAMPLE 26



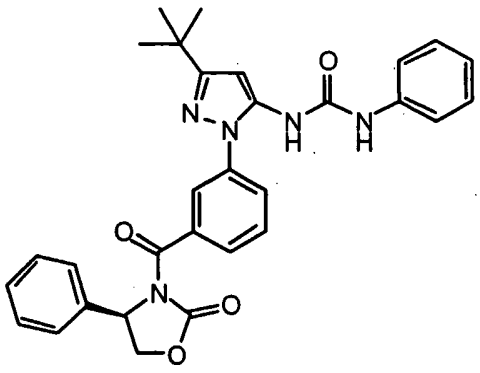
The title compound was synthesized in a manner analogous to Example 23 utilizing Example N (0.2 g, 0.73 mmol) and 4-chlorophenylisocyanate (0.112 g, 0.73 mmol) to yield 1-{3-*tert*-butyl-1-[3-(carbamoylmethyl)phenyl)-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea as a white solid (0.28 g). mp: 222 224 . (dec.); ^{1}H NMR (200MHz, DMSO- d_6); δ 9.15 (s, 1H), 8.46 (s, 1H), 7.55 - 7.31 (m, 8H), 6.39 (s, 1H), 3.48 (s, 2H), 1.30 (s, 9H); MS:

EXAMPLE O



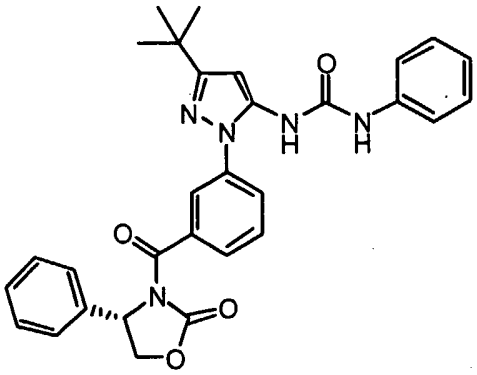
The title compound is synthesized in a manner analogous to Example C utilizing Example A and 1-isocyanato-4-methoxy-naphthaleneto yield ethyl 3-(3-tert-butyl-5-(3-(1-methoxynaphthalen-4-yl)ureido)-1H-pyrazol-1-yl)benzoate.

EXAMPLE 27



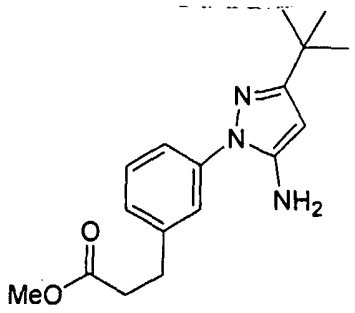
The title compound is synthesized in a manner analogous to Example 17 utilizing Example M and D-4-phenyl-oxazolidin-2-one to yield D-1-{5-*tert*-butyl-2-[3-(2-oxo-4-phenyl-oxazolidinyl-3-carbonyl)phenyl]-2*H*-pyrazol-3-yl}-3-phenylurea.

EXAMPLE 28



The title compound is synthesized in a manner analogous to Example 17 utilizing Example M and and L-4-phenyl-oxazolidin-2-one to yield L-1-{5-*tert*-butyl-2-[3-(2-oxo-4-phenyl-oxazolidinyl-3-carbonyl)phenyl]-2*H*-pyrazol-3-yl}-3-phenylurea.

EXAMPLE P

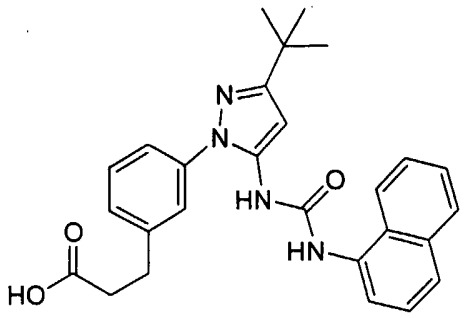


A mixture of 3-(3-amino-phenyl)-acrylic acid methyl ester (6 g) and 10 % Pd on activated carbon (1 g) in ethanol (50 ml) was hydrogenated at 30 psi for 18*h* and filtered over Celite. Removal of the volatiles in vacuo provided 3-(3-amino-phenyl)propionic acid methyl ester (6 g).

A vigorously stirred solution of the crude material from the previous reaction (5.7 g, 31.8 mmol) dissolved in 6 N HCl (35 ml) was cooled to 0 °C, and sodium nitrite (2.2 g) in water (20 ml) was added. After 1h, tin (II) chloride dihydrate (18 g) in 6 N HCl (35 ml) was added. And the mixture was stirred at 0 °C for 3 h. The pH was adjusted to pH 14 with solid KOH and extracted with EtOAc. The combined organic extracts were concentrated in vacuo provided methyl 3-(3-hydrazino-phenyl)propionate (1.7 g).

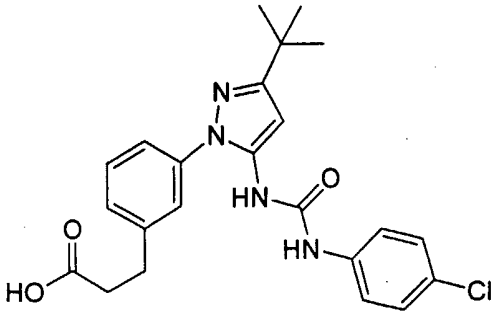
A stirred solution of the crude material from the previous reaction (1.7 g, 8.8 mmol) and 4,4-dimethyl-3-oxopentanenitrile (1.2 g, 9.7 mmol) in ethanol (30 ml) and 6 N HCl (2 ml) was refluxed for 18 h and cooled to RT. The volatiles were removed in vacuo and the residue dissolved in EtOAc and washed with 1 N aqueous NaOH. The organic layer was dried (Na_2SO_4) and concentrated in vacuo and the residue was purified by column chromatography using 30 % ethyl acetate in hexane as the eluent to provide methyl 3-[3-(3-*tert*-butyl-5-amino-1*H*-pyrazol -1-yl)phenyl]propionate (3.2 g), which was used without further purification

EXAMPLE 29



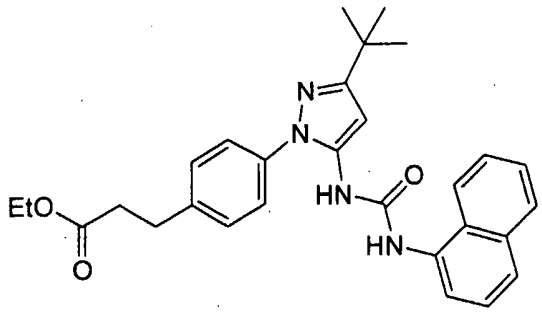
A mixture of Example P (0.35 g, 1.1 mmol) and 1-naphthylisocyanate (0.19 g, 1.05 mmol) in dry CH_2Cl_2 (5 ml) was stirred at RT under N_2 for 20 h. The solvent was removed in vacuo and the residue was stirred in a solution of THF (3 ml)/MeOH (2 ml)/water (1.5 ml) containing lithium hydroxide (0.1 g) for 3 h at RT, and subsequently diluted with EtOAc and dilute citric acid solution. The organic layer was dried (Na_2SO_4), and the volatiles removed in vacuo. The residue was purified by column chromatography using 3 % methanol in CH_2Cl_2 as the eluent to yield 3-(3-{3-*tert*-butyl-5-[3-(naphthalen-1-yl)ureido]-1*H*-pyrazol-1-yl)phenylpropionic acid (0.22 g, brownish solid). mp: 105-107 ; ^{1}H NMR (200MHz, $CDCl_3$): δ 7.87 - 7.36 (m, 10H), 7.18 - 7.16 (m, 1H), 6.52 (s, 1H), 2.93 (t, J = 6.9 Hz, 2H), 2.65 (t, J = 7.1 Hz, 2H), 1.37 (s, 9H); MS

EXAMPLE 30



The title compound was synthesized in a manner analogous to Example 29 utilizing Example P (0.30g, 0.95 mmol) and 4-chlorophenylisocyanate (0.146 g, 0.95 mmol) to yield 3-(3-{3-*tert*-butyl-5-[3-(4-chloropnehyl)ureido]-1*H*-pyrazol-1-yl)phenyl)propionic acid (0.05 g, white solid). mp:85 87 ; ^{1}H NMR (200MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.44 - 7.14 (m, 7H), 6.98 (s, 1H), 6.55 (s, 1H), 2.98 (t, J = 5.2 Hz, 2H), 2.66 (t, J = 5.6 Hz, 2H), 1.40 (s, 9H); MS

EXAMPLE Q



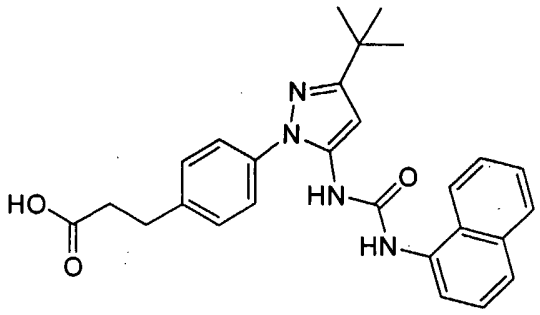
A mixture of ethyl 3-(4-aminophenyl)acrylate(1.5 g) and 10 % Pd on activated carbon (0.3 g) in ethanol (20 ml) was hydrogenated at 30 psi for 18h and filtered over Celite. Removal of the volatiles in vacuo provided ethyl 3-(4-aminophenyl)propionate (1.5 g).

A solution of the crude material from the previous reaction (1.5 g, 8.4 mmol) was dissolved in 6 N HCl (9 ml), cooled to 0 °C, and vigorously stirred. Sodium nitrite (0.58 g) in water (7 ml) was added. After 1h, tin (II) chloride dihydrate (5 g) in 6 N HCl (10 ml) was added.

The reaction mixture was stirred at 0 °C for 3h. The pH was adjusted to pH 14 with solid KOH and extracted with EtOAc. The combined organic extracts were concentrated in vacuo provided ethyl 3-(4-hydrazino-phenyl)-propionate(1 g).

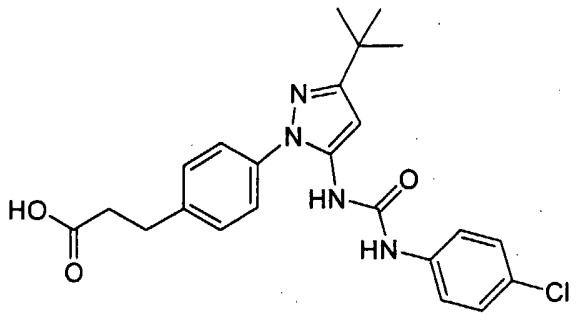
The crude material from the previous reaction (1 g, 8.8 mmol) and 4,4-dimethyl-3-oxopentanenitrile (0.7 g) in ethanol (8 ml) and 6 N HCl (1 ml) was refluxed for 18h and cooled to RT. The volatiles were removed in vacuo. The residue was dissolved in ethyl acetate and washed with 1 N aqueous sodium hydroxide solution. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography using 0.7 % methanol in CH_2Cl_2 as the eluent to provide ethyl 3-{4-[3-*tert*-butyl-5-(3-(naphthalene-1-yl)ureido]-1*H*-pyrazol-1-yl}phenyl)prpanoate (0.57 g).

EXAMPLE 31



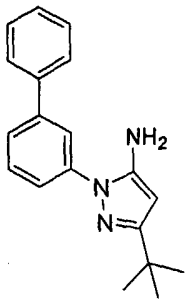
A mixture of Example Q (0.25 g, 0.8 mmol) and 1-naphthylisocyanate (0.13 g, 0.8 mmol) in dry CH_2Cl_2 (5 ml) was stirred at RT under N_2 for 20 h. The solvent was removed in vacuo and the residue was stirred in a solution of THF (3 ml)/MeOH (2 ml)/water (1.5 ml) containing lithium hydroxide (0.1 g) for 3h at RT and diluted with EtOAc and diluted citric acid solution. The organic layer was dried (Na_2SO_4), and the volatiles removed in vacuo. The residue was purified by column chromatography using 4 % methanol in CH_2Cl_2as the eluent to yield 3-{4-[3-*tert*-butyl-5-(3-(naphthalene-1-yl)ureido]-1*H*-pyrazol-1-yl}phenyl)propanonic acid (0.18 g, off-white solid). mp: 120 122 ; ^{1}H NMR (200MHz, $CDCl_3$): δ 7.89 - 7.06 (m, 11H), 6.5 (s, 1H), 2.89 (m, 2H), 2.61 (m, 2H), 1.37 (s, 9H); MS

EXAMPLE 32



The title compound was synthesized in a manner analogous to Example 31 utilizing Example Q (0.16 g, 0.5 mmol) and 4-chlorophenylisocyanate (0.077 g, 0.5 mmol) to yield 3-{4-[3-*tert*-butyl-5-(3-(4-chlorphenyl)ureido]-1*H*-pyrazol-1-yl}phenyl)propanonic acid acid (0.16 g, off-white solid). mp: 112 - 114 ; ^{1}H NMR (200MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.56 (s, 1H), 7.21 (s, 2H), 7.09 (s, 2H), 6.42 (s, 1H), 2.80 (m, 2H), 2.56 (m, 2H), 1.32 (s, 9H); MS

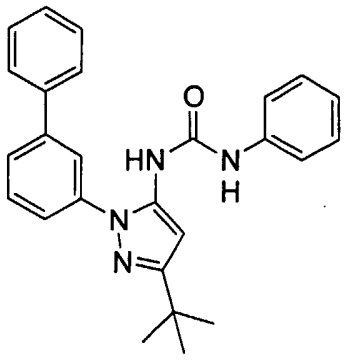
EXAMPLE R



A 250 mL pressure vessel (ACE Glass Teflon screw cap) was charged with 3-nitrobiphenyl (20 g, 0.10 mol) dissolved in THF (~100 mL) and 10% Pd/C (3 g). The reaction vessel was charged with H_2 (g) and purged three times. The reaction was charged with 40 psi H_2 (g) and placed on a Parr shaker hydrogenation apparatus and allowed to shake overnight at RT. HPLC showed that the reaction was complete thus the reaction mixture was filtered through a bed of Celite and evaporated to yield the amine: 16.7g (98% yield)

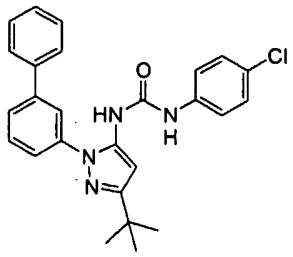
In a 250 mL Erlenmeyer flask with a magnetic stir bar, the crude material from the previous reaction (4.40 g, 0.026 mol) was added to 6 N HCl (40 mL) and cooled with an ice bath to ~ 0 °C. A solution of $NaNO_2$ (2.11 g, 0.0306 mol, 1.18 eq.) in water (5 mL) was added drop wise. After 30 min, $SnCl_2 2H_2O$ (52.0 g, 0.23 mol, 8.86 eq.) in 6N HCl (100 mL) was added and the reaction mixture was allowed to stir for 3h, then subsequently transferred to a 500 mL round bottom flask. To this, 4,4-dimethyl-3-oxopentanenitrile (3.25 g, 0.026 mol) and EtOH (100 ml) were added and the mixture refluxed for 4h, concentrated in vacuo and the residue extracted with EtOAc (2x100 mL). The residue was purified by column chromatograph using hexane/ EtOAc/Et_3N (8:2:0.2) to yield 0.53g of Example R. ^1H NMR ($CDCl_3$): δ 7.5 (m, 18H), 5.8 (s, 1H), 1.3 (s, 9H).

EXAMPLE 33



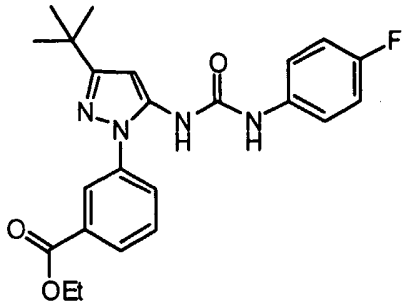
In a dry vial with a magnetic stir bar, Example R (0.145 g; 0.50 mmol) was dissolved in 2 mL CH_2Cl_2 (anhydrous) followed by the addition of phenylisocyanate (0.0544 mL; 0.50 mmol; 1 eq.). The reaction was kept under argon and stirred for 17h. Evaporation of solvent gave a crystalline mass that was triturated with hexane/EtOAc (4:1) and filtered to yield 1-(3-*tert*-butyl-1-(3-phenylphenyl)-1*H*-pyrazol-5-yl)-3-phenylurea (0.185 g, 90%). HPLC purity: 96%; mp: 80 84 ; ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 16 H), 6.3 (s, 1H), 1.4 (s, 9H).

EXAMPLE 34



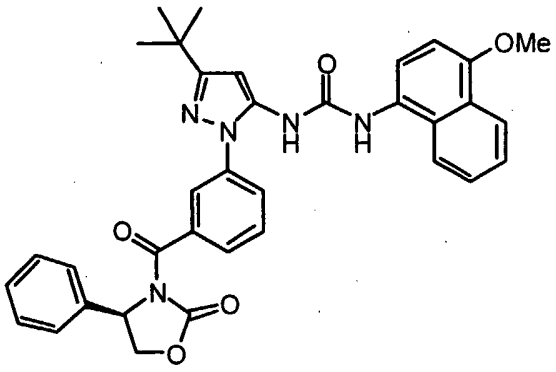
The title compound was synthesized in a manner analogous to Example 33 utilizing Example R (0.145 g; 0.50 mmol) and *p*-chlorophenylisocyanate (0.0768 g, 0.50 mmol, 1 eq.) to yield 1-(3-*tert*-butyl-1-(3-phenylphenyl)-1*H*-pyrazol-5-yl)-3-(4-chlorophenyl)urea (0.205 g, 92%). HPLC purity: 96.5%; mp: 134 136 ; ^{1}H NMR ($CDCl_3$): δ 7.5 (m, 14H), 7.0 (s, 1H), 6.6 (s, 1H), 6.4 (s, 1H), 1.4 (s, 9H).

EXAMPLE S



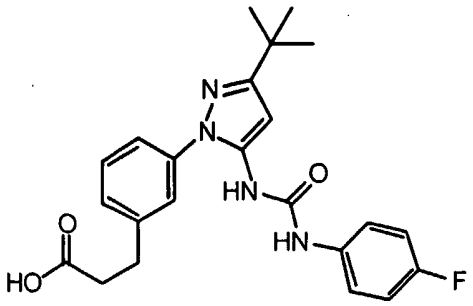
The title compound is synthesized in a manner analogous to Example C utilizing Example A and 4-fluorophenyl isocyanate yield ethyl 3-(3-tert-butyl-5-(3-(4-flurophenyl)ureido)-1H-pyrazol-1-yl)benzoate.

EXAMPLE 35



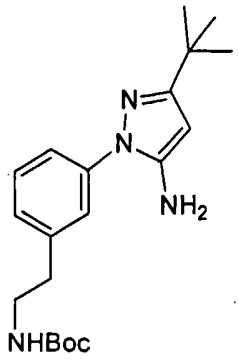
The title compound is synthesized in a manner analogous to Example 17 utilizing Example M and D-4-phenyl-oxazolidin-2-one to yield D-1-{5-*tert*-butyl-2-[3-(2-oxo-4-phenyl-oxazolidinyl-3-carbonyl)phenyl]-2*H*-pyrazol-3-yl}-3--(naphthalen-1-yl)urea.

EXAMPLE 36



The title compound is synthesized in a manner analogous to Example 29 utilizing Example P (0.30g, 0.95 mmol) and 4-flu0rophenylisocyanate (0.146 g, 0.95 mmol) to yield 3-(3-(3-tert-butyl-5-(3-(4-fluorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)propanoic acid.

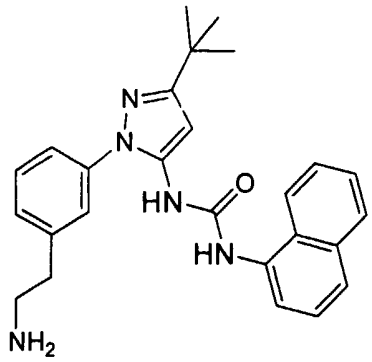
EXAMPLE T



To a stirred solution of Example N (2 g, 7.35 mmol) in THF (6 ml) was added borane-methylsulfide (18 mmol). The mixture was heated to reflux for 90 min and cooled to RT, after which 6 N HCl was added and heated to reflux for 10 min. The mixture was basified with NaOH and extracted with EtOAc. The organic layer was dried (Na_2SO_4) filtered and concentrated in vacuo to yield 3-*tert*-butyl-1-[3-(2-aminoethyl)phenyl]-1*H*-pyrazol-5 amine (0.9 g).

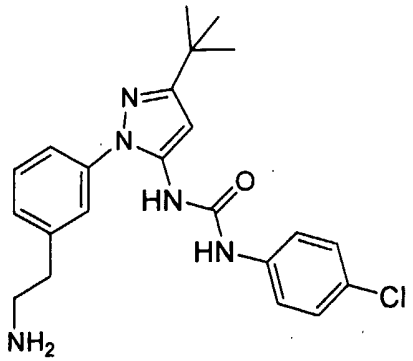
A mixture of the crude material from the previous reaction (0.8 g, 3.1 mmol) and di-*tert*-butylcarbonate (0.7 g, 3.5 mmol) and catalytically amount of DMAP in dry CH_2Cl_2 (5 ml) was stirred at RT under N_2 for 18 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography using 1% methanol in CH_2Cl_2 as the eluent to yield *tert*-butyl 3-(3-*tert*-butyl-5-amino-1*H*-pyrazol-1-yl)phenylcarbamate (0.5 g).

EXAMPLE 37



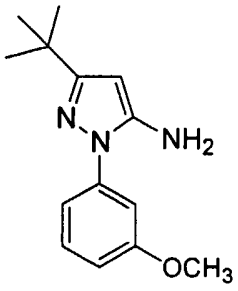
A mixture of Example T (0.26 g, 0.73 mmol) and 1-naphthylisocyanate (0.123 g, 0.73 mmol) in dry CH_2Cl_2 (5 ml) was stirred at RT under N_2 for 48 h. The solvent was removed in vacuo and the residue was purified by column chromatography using 1% methanol in CH_2Cl_2as the eluent (0.15 g, off-white solid). The solid was then treated with TFA (0.2ml) for 5 min and diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered and concentrated in vacuo to yield 1-{3-*tert*-butyl-1-[3-(2-Aminoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(naphthalen-1-yl)urea as a solid (80 mg). mp: 110 - 112 ; ^{1}H NMR (200MHz, DMSO-d_6): δ 9.09 (s, 1H), 8.90 (s, 1H), 8.01 - 7.34 (m, 11H), 6.43 (s, 1H), 3.11 (m, 2H), 2.96 (m, 2H), 1.29 (s, 9H); MS

EXAMPLE 38



The title compound was synthesized in a manner analogous to Example 37 utilizing Example T (0.15 g, 0.42 mmol) and 4-chlorophenylisocyanate (0.065 g, 0.42 mmol) to yield 1-{3-*tert*-butyl-1-[3-(2-Aminoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea as an off-white solid (20 mg). mp:125-127 ; ^{1}H NMR (200MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.66 (s, 1H), 7.36 - 7.13 (m, 8H), 6.54 (s, 1H), 3.15 (brs, 2H), 2.97 (brs, 2H), 1.32 (s, 9H); MS

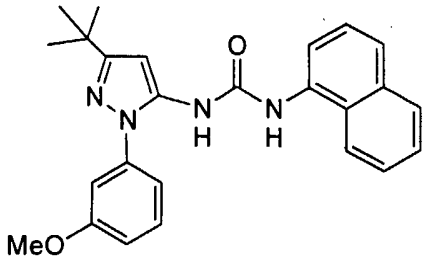
EXAMPLE U



In a 250 mL Erlenmeyer flask with a magnetic stir bar, *m*-anisidine (9.84 g, 0.052 mol) was added to 6 N HCl (80 mL) and cooled with an ice bath to 0 °C. A solution of $NaNO_2$ (4.22 g, 0.0612 mol, 1.18 eq.) in water (10 mL) was added drop wise. After 30 min, $SnCl_2 2H_2O$ (104.0 g, 0.46 mol, 8.86 eq.) in 6 N HCl (200 mL) was added and the reaction mixture was allowed to stir for 3 h., and then subsequently transferred to a 1000 mL round bottom flask. To this, 4,4-dimethyl-3-oxopentanenitrile (8.00 g, 0.064 mol) and EtOH (200 mL) were added and the mixture refluxed for 4 h, concentrated in vacuo and the residue recrystallized from CH_2Cl_2 to yield 3-*tert*-butyl-1-(3-methoxyphenyl)-1*H*-pyrazol-5-amine as the HCl salt (13.9 g).

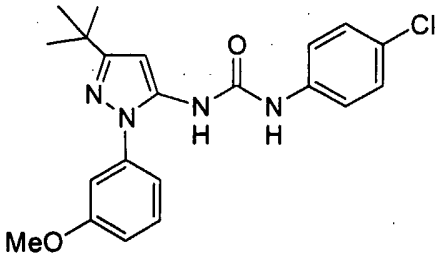
The crude material from the previous reaction (4.65 g, 0.165 mol) was dissolved in 30 mL of CH_2Cl_2 with Et_3N (2.30 mL, 0.0165 mol, 1 eq.) and stirred for 30 min Extraction with water followed by drying of the organic phase with Na_2SO_4 and concentration in vacuo yielded a brown syrup that was the free base, 3-*tert*-butyl-1-(3-methoxyphenyl)-1*H*-pyrazol-5-amine (3.82 g, 94.5%), which was used without further purification.

EXAMPLE 39



In a dry vial with a magnetic stir bar, Example U (2.62 g, 0.0107 mol) was dissolved in CH_2Cl_2 (5 mL, anhydrous) followed by the addition of 1-naphthylisocyanate (1.53 mL, 0.0107 mol, 1 eq.). The reaction was kept under Ar and stirred for 18 h. Evaporation of solvent followed by column chromatography with EtOAc/hexane/Et_3N (7:2:0.5) as the eluent yielded 1-[3-*tert*-butyl-1-(3-methoxyphenyl)-1*H*-pyrazol-5-yl]-3-(naphthalen-1-yl)urea (3.4g, 77%). HPLC: 97%; mp: 78 - 80; ^1H NMR ($CDCl_3$): δ 7.9 - 6.8 (m, 15H), 6.4 (s, 1H), 3.7 (s, 3H), 1.4 (s, 9H).

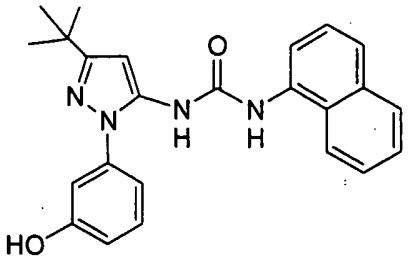
EXAMPLE 40



The title compound was synthesized in a manner analogous to Example 39 utilizing Example U (3.82 g; 0.0156 mol) and *p*-chlorophenylisocyanate (2.39 g, 0.0156 mol, 1 eq.), purified by trituration with hexane/EtOAc (4:1) and filtered to yield 1-[3-*tert*-butyl-1-(3-methoxyphenyl)-1*H*-pyrazol-5-yl]-3-(4-chlorophenyl)urea (6.1g, 98%). HPLC purity: 95%; mp:

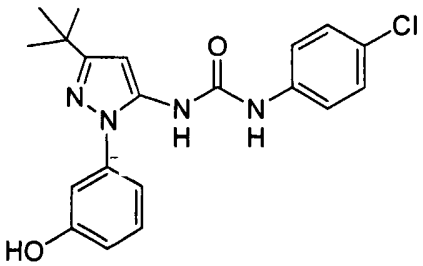
158 - 160 ; ^{1}H NMR ($CDCl_3$): δ 7.7 (s, 1H); δ 7.2 6.8 (m, 8H), 6.4 (s, 1H), 3.7 (s, 3H), 1.3 (s, 9H).

EXAMPLE 41



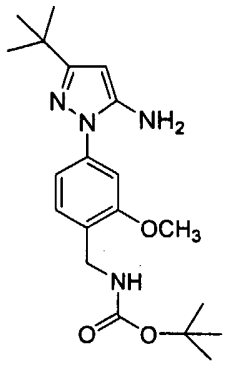
In a 100 ml round bottom flask equipped with a magnetic stir bar, Example 39 (2.07 g) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C with an ice bath. BBr_3 (1 M in CH_2Cl_2; 7.5 mL) was added slowly. The reaction mixture was allowed to warm warm to RT overnight. Additional BBr_3 (1 M in CH_2Cl_2, 2 X 1 mL, 9.5 mmol total added) was added and the reaction was quenched by the addition of MeOH. Evaporation of solvent led to a crystalline material that was chromatographed on silica gel (30 g) using CH_2Cl_2/MeOH (9.6:0.4) as the eluent to yield 1-[3-*tert*-butyl-1-(3-hydroxyphenyl)-1*H*-pyrazol-5-yl]-3-(naphthalene-1-yl)urea (0.40g, 20%). ^{1}H NMR (DMSO-d_6): δ 9.0 (s, 1H), 8.8 (s, 1H), 8.1 - 6.8 (m, 11H), 6.4 (s, 1H), 1.3 (s, 9H). MS (ESI) m/z: 401 ($M+H^+$).

EXAMPLE 42



The title compound was synthesized in a manner analogous to Example 41 utilizing Example 40 (2.00 g, 5 mmol) that resulted in a crystalline material that was filtered and washed with MeOH to yield 1-[3-*tert*-butyl-1-(3-hydroxyphenyl)-1*H*-pyrazol-5-yl]-3-(4-chlorophenyl)urea (1.14 g, 60%). HPLC purity: 96%; mp: 214 - 216 ; ^{1}H NMR ($CDCl_3$): δ 8.4 (s, 1H), 7.7 (s, 1H), 7.4 - 6.6 (m, 9H), 1.3 (s, 9H).

EXAMPLE V



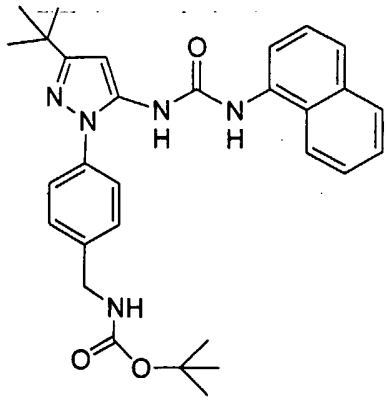
The starting material, 1-[4-(aminomethyl)phenyl]-3-*tert*-butyl-N-nitroso-1*H*-pyrazol-5-amine, was synthesized in a manner analogous to Example A utilizing 4-aminobenzamide and 4,4-dimethyl-3-oxopentanenitrile.

A 1 L four-necked round bottom flask was equipped with a stir bar, a source of dry Ar, a heating mantle, and a reflux condenser. The flask was flushed with Ar and charged with the crude material from the previous reaction (12 g, 46.5 mmol; 258.1 g/mol) and anhydrous THF (500 ml). This solution was treated cautiously with $LiAlH_4$ (2.65 g, 69.8 mmol) and the reaction was stirred overnight. The reaction was heated to reflux and additional $LiAlH_4$ was added complete (a total of 8.35 g added). The reaction was cooled to 0 and H_2O (8.4 ml), 15% NaOH (8.4 ml) and H_2O (24 ml) were added sequentially; The mixture was stirred for 2h, the solids filtered through Celite, and washed extensively with THF, the solution was concentrated in vacuo to yield 1-(4-(aminomethyl-3-methoxy)phenyl)-3-*tert*-butyl-1*H*-pyrazol-5-amine (6.8 g) as an oil.

A 40 mL vial was equipped with a stir bar, a septum, and a source of Ar. The vial was charged with the crude material from the previous reaction (2 g, 8.2 mmol, 244.17 g/mol) and

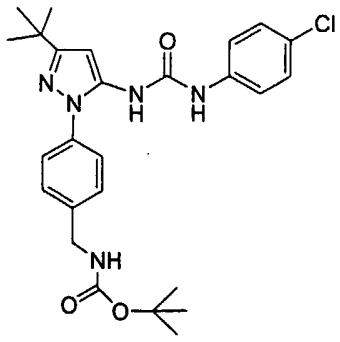
$CHCl_3$ (15 mL) were cooled to 0 under Ar and di-*tert*-butylcarbonate (1.9 g, 9.0 mmol) dissolved in $CHCl_3$ (5 mL) was added drop wise over a 2 min period. The mixture was treated with 1N KOH (2 mL), added over a 2h period. The resulting emulsion was broken with the addition of saturated NaCl solution, the layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 1.5 ml). The combined organic phases were dried over Na_2SO4, filtered, concentrated in vacuo to yield *tert*-butyl [4-(3-*tert*-butyl-5-amino-1*H*-pyrazol-1-yl)-2-methoxybenzylcarbamate (2.23 g, 79%) as a light yellow solid. ^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.6 (s, 1H), 4.4 (d, 2H), 1.5 (s, 9H), 1.3 (s, 9H).

EXAMPLE 43



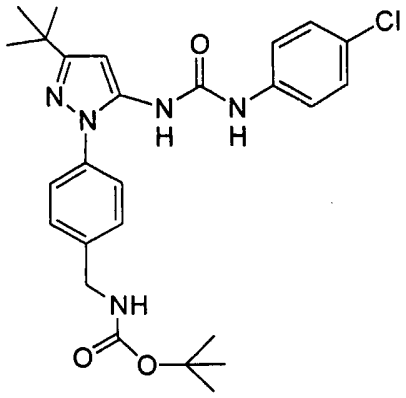
A 40 mL vial was equipped with a septum, a stir bar and a source of Ar, and charged with Example V (2 g, 5.81 mmol), flushed with Ar and dissolved in $CHCl_3$ (20 mL). The solution was treated with 2-naphthylisocyanate (984 mg, 5.81 mmol) in $CHCl_3$ (5 mL) and added over 1 min The reaction was stirred for 8h, and additional 1-naphthylisocyanate (81 mg) was added and the reaction stirred overnight. The solid was filtered and washed with CH_2Cl_2 to yield *tert*-butyl 4-[3-*tert*-butyl-5-(3-naphthalen-1-yl)ureido)-1*H*-pyrazol-1-yl]benzylcarbamate (1.2 g). HPLC purity: 94.4 %; ^{1}H NMR (DMSO-d_6): δ 9.1 (s, 1H), 8.8 (s, 1H), 8.0 (m, 3H), 7.6 (m, 9H), 6.4 (s, 1H), 4.2 (d, 2H), 1.4 (s, 9H), 1.3 (s, 9H).

EXAMPLE 44



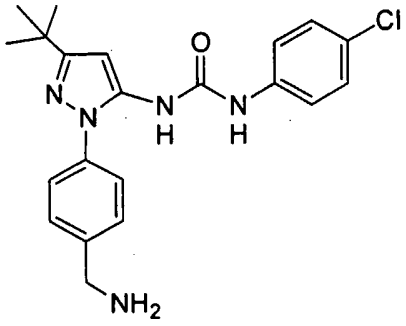
The title compound was synthesized in a manner analogous to Example 43 utilizing Example V (2.0 g, 5.81 mmol) and p-chlorophenylisocyanate (892 mg) to yield *tert*-butyl 4-[3-*tert*-butyl-5-(3-(4-chloropnehyl)ureido)-1*H*-pyrazol-1-yl]benzylcarbamate (1.5 g). HPLC purity: 97%; ^{1}H NMR (DMSO-d_6): δ 9.2 (s, 1H), 8.4 (s, 1H), 7.4 (m, 8H), 6.4 (s, 1H), 4.2 (d, 2H), 1.4 (s, 9H), 1.3 (s, 9H).

EXAMPLE 45



A 10 mL flask equipped with a stir bar was flushed with Ar and charged with Example 43 (770 mg, 1.5 mmol) and CH_2Cl_2 (1 ml) and 1:1 CH_2Cl_2:TFA (2.5 mL). After 1.5 h, reaction mixture was concentrated in vacuo, the residue was dissolved in EtOAc (15 mL), washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL). The organic layers was dried, filtered and concentrated in vacuo to yield 1-{3-*tert*-butyl-1-[4-(aminomethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(naphthalen-1-yl)urea (710 mg). ^{1}H NMR (DMSO-d_6): δ 7.4 (m, 11H), 6.4 (s, 1H), 3.7 (s, 2H), 1.3 (s, 9H).

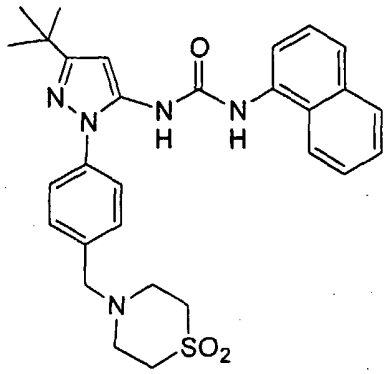
EXAMPLE 46



The title compound was synthesized in a manner analogous to Example 45 utilizing Example 44 (1.5g, 1.5 mmol) to yield 1-{3-*tert*-butyl-1-[4-(aminomethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea (1.0 g). HPLC purity: 93.6%; mp: 100 - 102 ; ^{1}H NMR ($CDCl_3$): δ

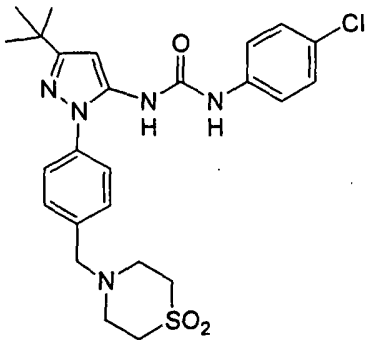
8.6 (s, 1H), 7.3 (m, 8H), 6.3 (s, 1H), 3.7 (brs, 2H), 1.3 (s, 9H).

EXAMPLE 47



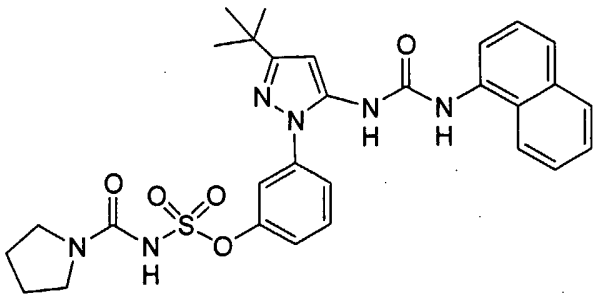
A 10 ml vial was charged with Example 45 (260 mg, 63 mmol) and absolute EtOH (3 mL) under Ar. Divinylsulfone (63 uL, 74 mg, .63 mmol) was added drop wise over 3 min and the reaction was stirred at RT for 1.5 h. and concentrated in vacuo to yield a yellow solid, which was purified via preparative TLC, developed in 5% MeOH:CH_2Cl_2. The predominant band was cut and eluted off the silica with 1:1 EtOAc:MeOH, filtered and concentrated in vacuo to yield 1-{3-*tert*-butyl-1-[4-(1,1-dioxothiomorpholin-4-yl)methylphenyl]-1*H*-pyrazol-5-yl}-3-(naphthalen-1-yl)urea (150 mg). HPLC purity: 96%; ^{1}H NMR (DMSO-d_6): δ 9.1 (s, 1H), 9.0 (s, 1H), 7.9 (m, 3H), 7.5 (m, 8H), 6.4 (s, 1H), 3.1 (brs, 4H), 2.9 (brs, 4H), 1.3 (s, 9H).

EXAMPLE 48



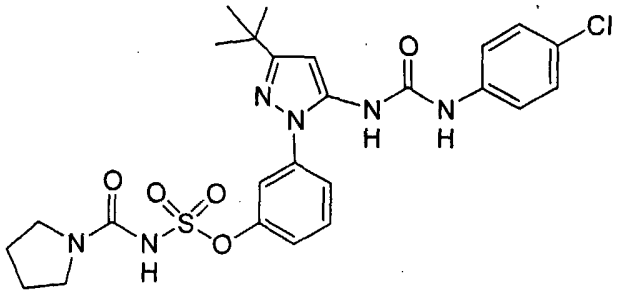
The title compound was synthesized in a manner analogous to Example 47 utilizing Example 46 (260mg, 0.66 mmol) to yield 1-{3-tert-butyl-1-[4-(1,1-dioxothiomorpholin-4-yl)methylphenyl]-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea (180 mg). HPLC purity: 93%; mp: 136 - 138 ; ^{1}H NMR (DMSO-d_6): δ 9.2 (s, 1H), 8.5 (s, 1H), 7.4 (m, 9H), 6.4 (s, 1H), 3.1 (brs, 4H), 3.0 (brs, 4H), 1.3 (s, 9H).

EXAMPLE 49



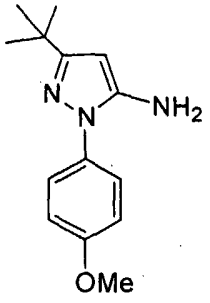
To a stirring solution of chlorosulfonyl isocyanate (0.35g , 5 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added pyrrolidine (0.18 g, 5 mmol) at such a rate that the reaction temperature did not rise above 5 °C. After stirring for 2h, a solution of Example 41 (1.10 g, 6.5 mmol) and triethylmine (0.46 g, 9 mmol) in CH_2Cl_2 (20 mL) was added. When the addition was complete, the mixture was allowed to warm to RT and stirred overnight. The reaction mixture was poured into 10% HCl (10 mL) saturated with NaCl , the organic layer was separated and the aqueous layer extracted with ether (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, purified by preparative HPLC to yield (pyrrolidine-1-carbonyl)sulfamic acid 3-[3-*tert*-butyl-5-(3-naphthalen-1-yl-ureido)-pyrazol-1-yl]phenyl ester (40 mg). ^1H NMR ($CDCl_3$): δ 9.12 (brs, 1H), 8.61 (brs, 1H), 7.85 - 7.80 (m, 3H), 7.65 (d, J = *8.0* Hz, 2H), 7.53 - 7.51 (m, 1H), 7.45 - 7.25 (m, 5H), 6.89 (s, 4H), 3.36 - 3.34 (brs, 1H), 3.14 - 3.13 (brs, 2H), 1.69 (brs, 2H), 1.62 (brs, 2H), 1.39 (s, 9H); MS (ESI) m/z: 577 ($M+H^+$).

EXAMPLE 50



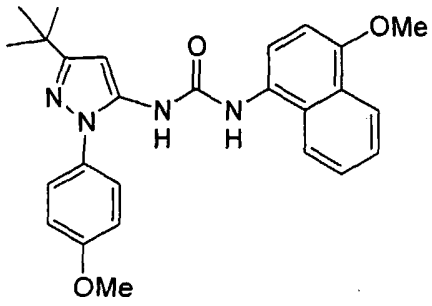
The title compound was synthesized in a manner analogous to Example 49 utilizing Example 42 to yield (pyrrolidine-1-carbonyl)sulfamic acid 3-[3-*tert*-butyl-5-(4-chlorophenyl-1-yl-ureido)pyrazol-1-yl]phenyl ester. MS (ESI) m/z: 561 ($M+H^+$).

EXAMPLE W



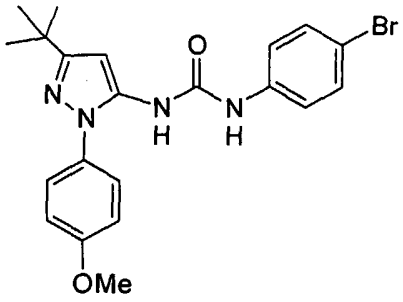
Solid 4-methoxyphenylhydrazine hydrochloride (25.3 g) was suspended in toluene (100 mL) and treated with triethylamine (20.2 g). The mixture was stirred at RT for 30 min and treated with pivaloylacetonitrile (18 g). The reaction was heated to reflux and stirred overnight. The hot mixture was filtered, the solids washed with hexane and dried *in vacuo* to afford 3-*tert*-butyl-1-(4-methoxyphenyl)-1*H*-pyrazol-5-amine (25 g, 70%). ^{1}H NMR (DMSO-d_6): δ 7.5 (d, 2H), 7.0 (d, 1H), 6.4 (s, 1H), 6.1 (s, 2H), 3.9 (s, 3H), 1.3 (s, 9H).

EXAMPLE 51



To a solution of 1-isocyanato-4-methoxy-naphthalene (996 mg) in anhydrous CH_2Cl_2 (20 mL) of was added Example W (1.23 g). The reaction solution was stirred for 3 h, the resulting white precipitate filtered, treated with 10% HCl and recrystallized from MeOH, and dried *in* vacuo to yield 1-[3-*tert*-butyl-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-3-(1-methoxynaphthalen-4-yl-urea as white crystals (900 mg, 40%). HPLC purity: 96%; mp: 143 - 144 ; ^{1}H NMR (DMSO-d_6): δ 8.8 (s, 1H), 8.5 (s, 1H), 8.2 (d, 1H), 8.0 (d, 1H), 7.6 (m, 5H), 7.1 (d, 2H), 7.0 (d, 1H), 6.3 (s, 1H), 4.0 (s, 3H), 3.9 (s, 3H); 1.3 (s, 9H).

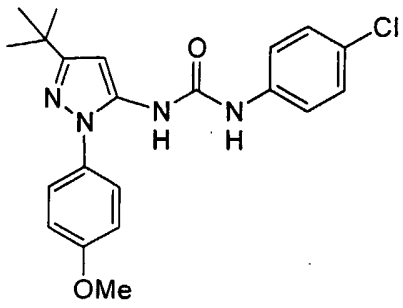
EXAMPLE 52



The title compound was synthesized in a manner analogous to Example 51 utilizing Example W and *p*-bromophenylisocyanate (990mg) to yield 1-{3-*tert*-butyl-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl}-3-(4-bromophenyl)urea as off-white crystals (1.5g, 68%).

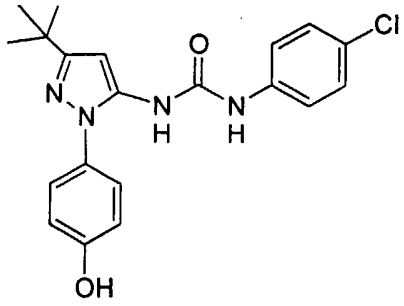
HPLC purity: 98%; mp: 200 - 201 ; ^{1}H NMR (DMSO-d_6): δ 9.3 (s, 1H), 8.3 (s, 1H), 7.4 (m, 6H), 7.0 (d, 2H), 6.3 (s, 1H), 3.8 (s, 3H), 1.3 (s, 9H).

EXAMPLE 53



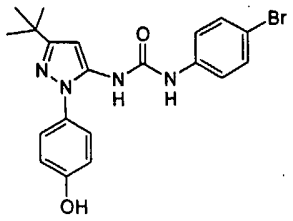
The title compound was synthesized in a manner analogous to Example 51 utilizing Example W and *p*-chlorophenylisocyanate (768 mg) into yield 1-{3-*tert*-butyl-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea as white crystals (1.3g, 65%). HPLC purity: 98%; mp: 209 - 210 ; ^{1}H NMR (DMSO-d_6): δ 9.1 (s, 1H), 8.3 (s, 1H), 7.4 (m, 4H), 7.3 (d, 2H), 7.1 (d, 2H), 6.3 (s, 1H), 3.8 (s, 3H), 1.3 (s, 9H).

EXAMPLE 54



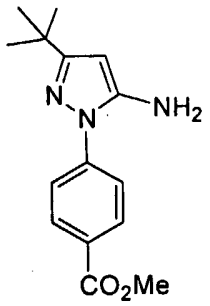
The title compound was synthesized in a manner analogous to Example 41 utilizing Example 53 (500 mg) to yield 1-{3-*tert*-butyl-1-(4-hydroxyphenyl)-1*H*-pyrazol-5-yl}-3-(4-chlorophenyl)urea as white crystals (300 mg, 62%). HPLC purity: 94%; mp: 144 - 145 ; ^{1}H NMR (DMSO-d_6): δ 9.7 (s, 1H), 9.1 (s, 1H), 8.3 (s, 1H), 7.4 (d, 2H), 7.3 (m, 4H); 6.9 (d, 2H), 6.3 (s, 1H), 1.3 (s, 9H)

EXAMPLE 55



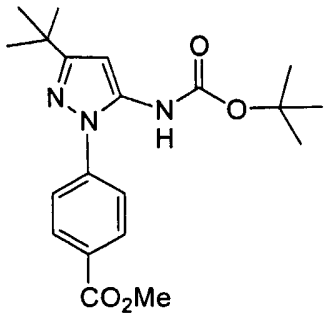
The title compound was synthesized in a manner analogous to Example 41 utilizing Example 52 (550 mg) to yield 1-{3-*tert*-butyl-1-(4-hydroxyphenyl)-1*H*-pyrazol-5-yl}-3-(4-bromophenyl)urea as a white crystalline solid (400 mg, 70%). HPLC purity: 93%; mp: 198 200 ; ^{1}H NMR (DMSO-d_6): δ 9.7 (s, 1H), 9.2 (s, 1H), 8.3 (s, 1H), 7.4 (d, 4H), 7.2 (m, 2H), 6.9 (d, 2H), 6.3 (s, 1H), 1.3 (s, 9H).

EXAMPLE X



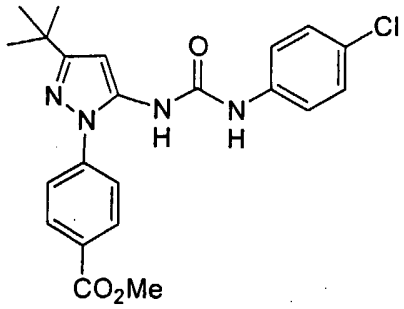
Methyl 4-(3-*tert*-butyl-5-amino-1*H*-pyrazol-1-yl)benzoate (3.67 mmol) was prepared from methyl 4-hydrazinobenzoate and pivaloylacetonitrile by the procedure of Regan, *et al.*, *J. Med. Chem.*, 45, 2994 (2002).

EXAMPLE 56



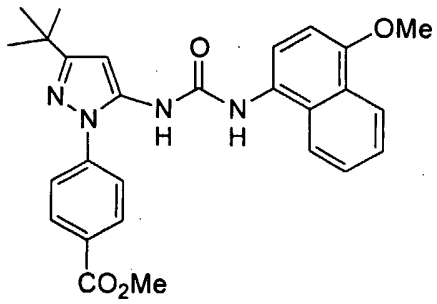
A 500mL round bottom flask was equipped with a magnetic stir bar and an ice bath. The flask was charged with Example X (1 g) and this was dissolved in CH_2Cl_2 (100 mL). Saturated sodium bicarbonate (100 mL) was added and the mixture rapidly stirred, cooled in an ice bath and treated with diphosgene (1.45 g) and the heterogeneous mixture stirred for 1 h. The layers were separated and the CH_2Cl_2 layer treated with *tert*-butanol (1.07 g) and the solution stirred overnight at RT. The solution was washed with H_2O (2 x150 mL), dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by flash chromatography using 1:2 ethyl acetate: hexane as the eluent to yield *tert*-buthyl 1-(4-(methoxycarbonyl)phenyl)-3-*t*ert-butyl-1*H*-pyrazol-5-ylcarbamate (100 mg) as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 9.2 (s, 1H), 8.1 (d, 2H), 7.7 (d, 2H), 6.3 (s, 1H), 3.3 (s, 3H), 1.3 (s, 18H).

EXAMPLE 57



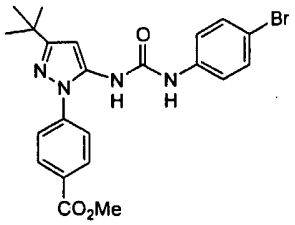
The title compound was synthesized in a manner analogous to Example 41 utilizing Example X (1.37 g) and *p*-chlorophenylisocyanate (768 mg) to yield methyl 4-{3-*tert*-butyl-5-[3-(4-chlorophenyl)ureido]-1*H*-pyrazol-1-yl}benzoate as white crystals (1.4 g 66%). HPLC purity: 98%; mp: 160 - 161 ; ^{1}H NMR (DMSO-d_6): δ 9.2 (s, 1H), 8.6 (s, 1H), 8.1 (d, 2H), 7.8 (d, 2H), 7.5 (d, 2H), 7.3 (d, 2H), 6.4 (s, 1H), 3.9 (s, 3H), 1.3 (s, 9H).

EXAMPLE 58



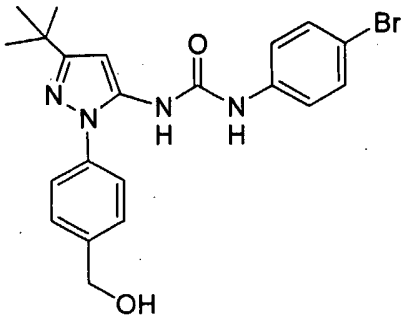
The title compound was synthesized in a manner analogous to Example 41 utilizing Example X (1.27 g) and 1-isocyanato-4-methoxy-naphthalene (996 mg) to yield methyl 4-{3-*tert*-butyl-5-[3-(1-methoxynaphthalen-4-yl)ureido]-1*H*-pyrazol-1-yl}benzoate as white crystals (845 mg, 36%). HPLC purity: 98%; mp: 278 280 ; ^{1}H NMR (DMSO-d_6): δ 8.76 (s, 1H), 8.73 (s, 1H), 8.1 (m, 3H), 7.9 (d, 1H), 7.7 (d, 2H), 7.6 (m, 3H), 7.0 (d, 1H), 7.0 (d, 1H), 6.3 (s, 1H), 4.0 (s, 3H), 3.9 (s, 3H),1.3 (s, 9H).

EXAMPLE 59



The title compound was synthesized in a manner analogous to Example 41 utilizing Example X (1.37 g) and *p*-bromophenylisocyanate (990 mg) to yield methyl 4-{3-*tert*-butyl-5-[3-(4-bromophenyl)ureido]-1*H*-pyrazol-1-yl}benzoate as white crystals (1.4 g, 59%). HPLC purity: 94%; mp: 270 272 ; ^{1}H NMR (DMSO-d_6): δ 9.2 (s, 1H), 8.6 (s, 1H), 8.1 (d, 2H), 7.7 (d, 2H), 7.4 (d, 4H), 6.4 (s, 1H), 3.9 (s, 3H), 1.3 (s, 9H).

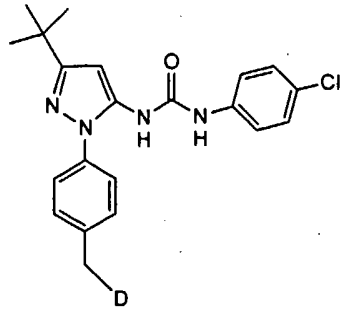
EXAMPLE 60



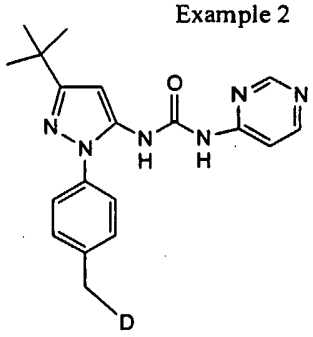
To a solution of Example 59 (700 mg) in 30 mL of toluene at -78 °C, was added dropwise a solution of diisobutylaluminum hydride in toluene (1M in toluene, 7.5 mL) over 10 min. The reaction mixture was stirred for 30 min at -78 °C, and then 30 min at 0 °C. The reaction mixture was concentrated in vacuo to dryness and treated with H_2O. The solid was filtered and treated with acetonitrile. The solution was evaporated to dryness and the residue was dissolved in ethyl

acetate, and precipitated by hexanes to afford yellow solid which was dried under vacuum to give 1-[3-*tert*-butyl-1-(4-hydroxymethyl)phenyl)-1*H*-pyrazol-5-yl]urea (400 mg, 61%). HPLC purity: 95%; ^{1}H NMR (DMSO-d_6): δ 9.2 (s, 1H), 8.4 (s, 1H), 7.5 (m, 8H), 6.4 (s, 1H), 5.3 (t, 1H), 4.6 (d, 2H), 1.3 (s, 9H).

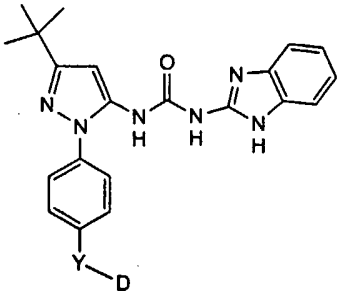
Example 1



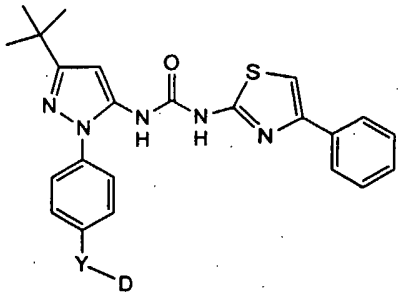
Example 2



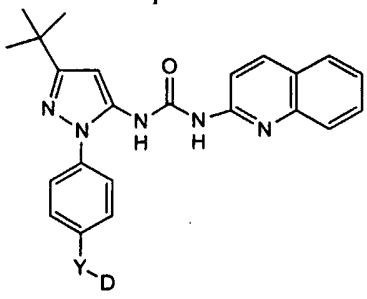
Example 3



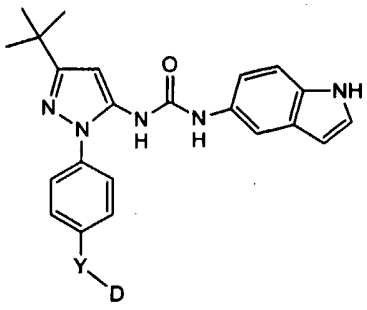
Example 4



Example 5

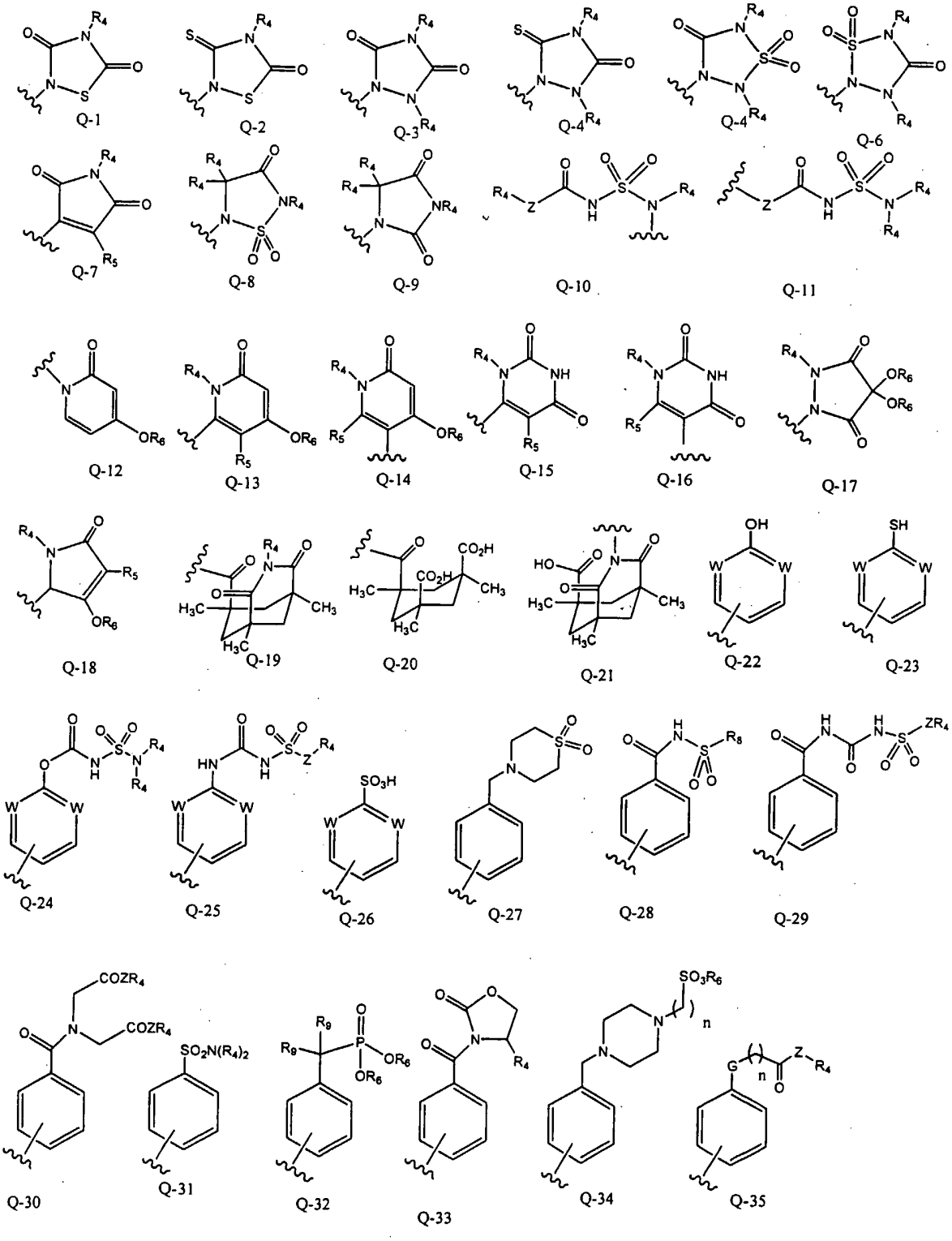


Example 6

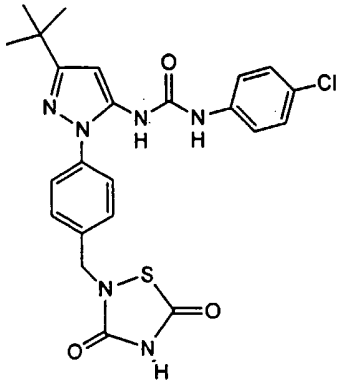


Wherein Y is O, S, NR6, -NR6SO2-, NR6CO-, alkylene, O-(CH2)n-, NR6-(CH2)n-, wherein one of the methylene units may be substituted with an oxo group, or Y is a direct bond; D is taken from the groups identified in Chart I:

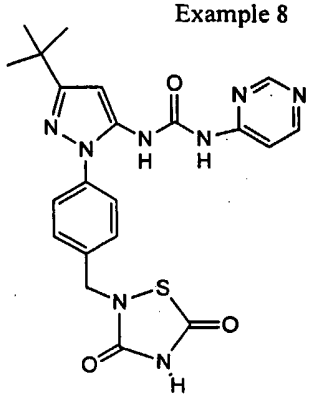
Chart 1


Q-1
Q-2
Q-3
Q-4
Q-4
Q-6
Q-7
Q-8
Q-9
Q-10
Q-11
Q-12
Q-13
Q-14
Q-15
Q-16
Q-17
Q-18
Q-19
Q-20
Q-21
Q-22
Q-23
Q-24
Q-25
Q-26
Q-27
Q-28
Q-29
Q-30
Q-31
Q-32
Q-33
Q-34
Q-35

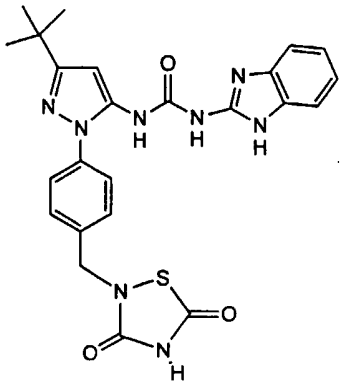
Example 7



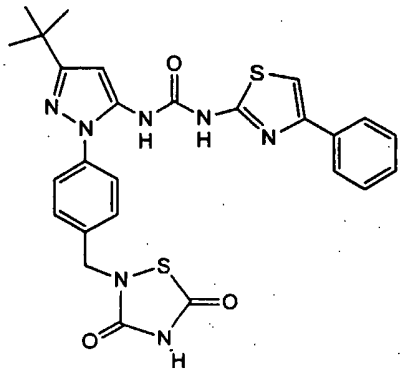
Example 8



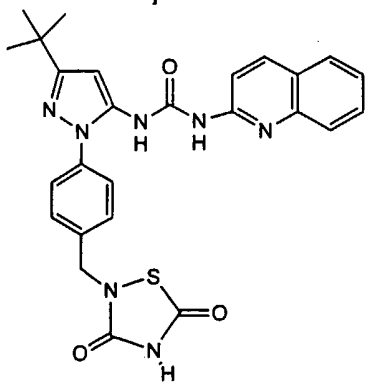
Example 9



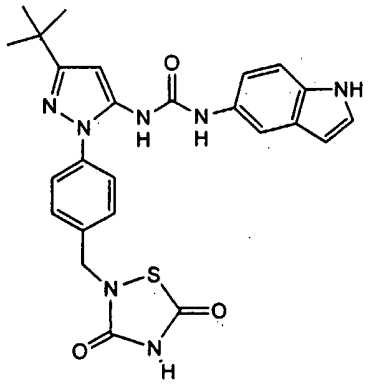
Example 10



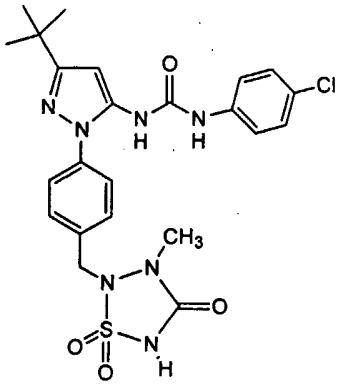
Example 11



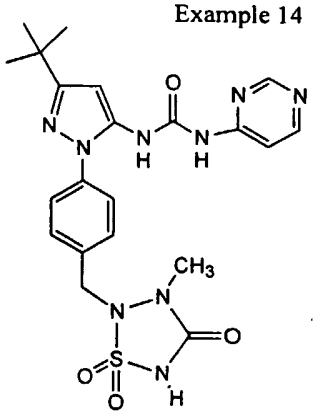
Example 12



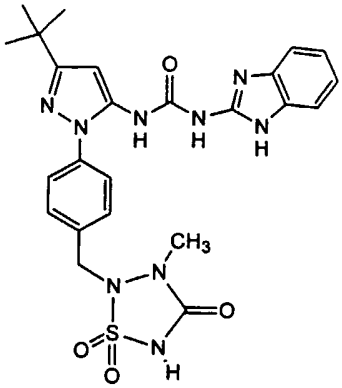
Example 13



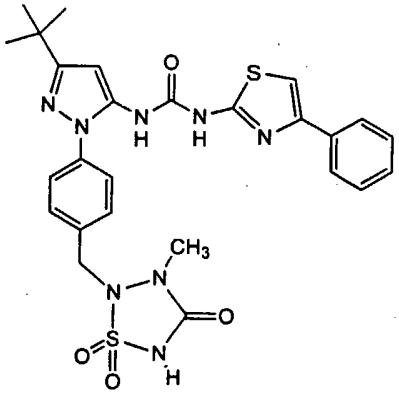
Example 14



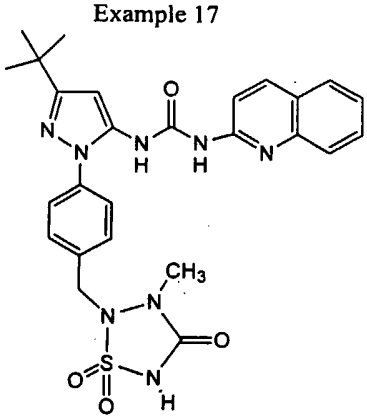
Example 15



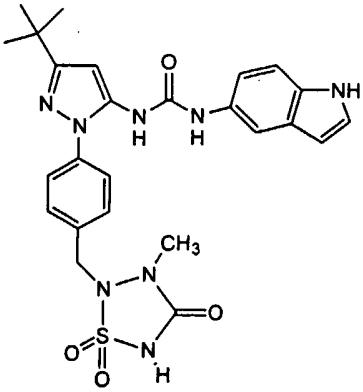
Example 16



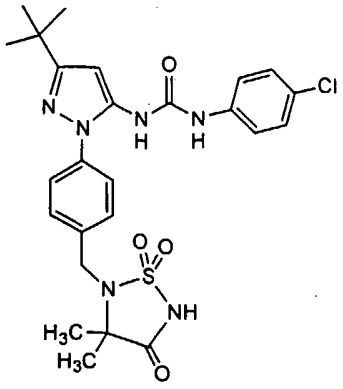
Example 17



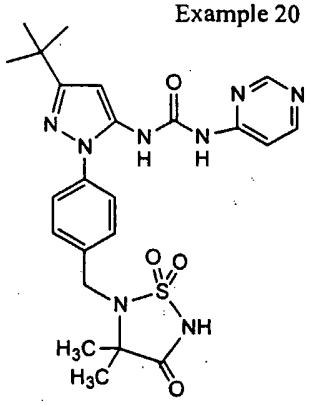
Example 18



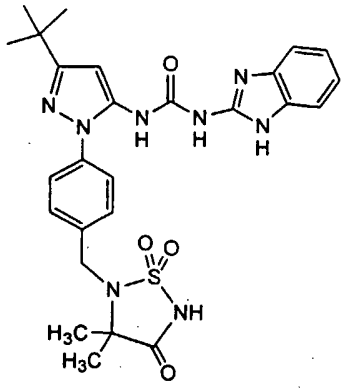
Example 19



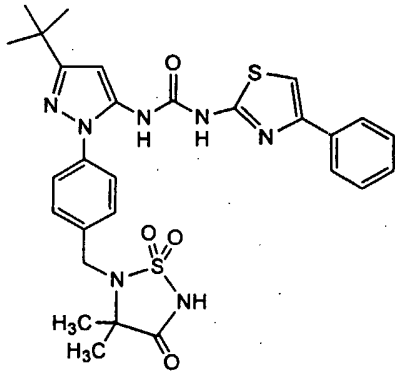
Example 20



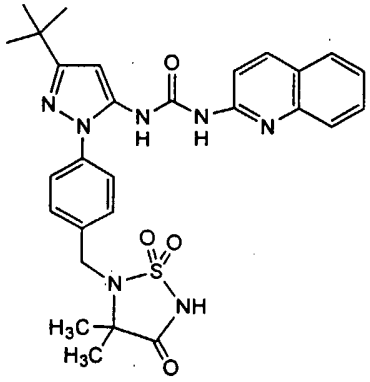
Example 21



Example 22



Example 23



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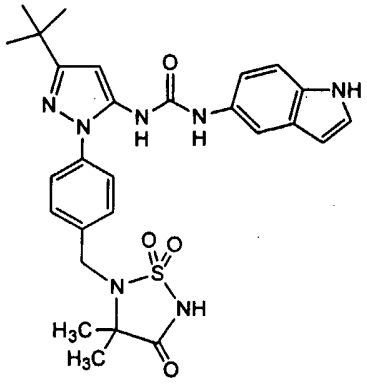
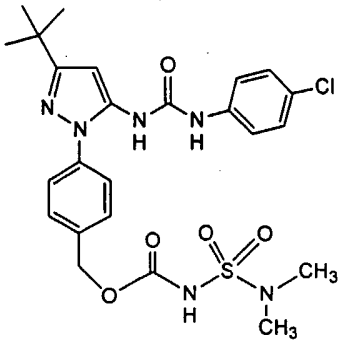
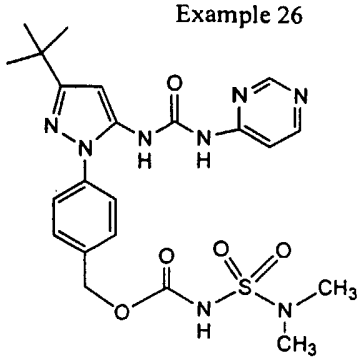


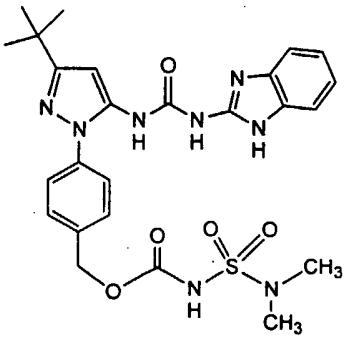
Example 25



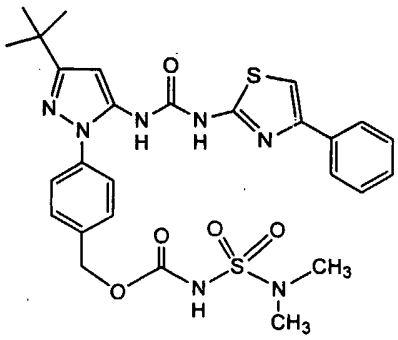
Example 26



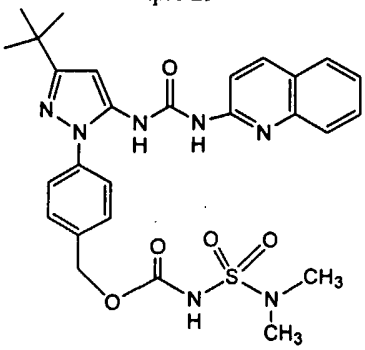
Example 27



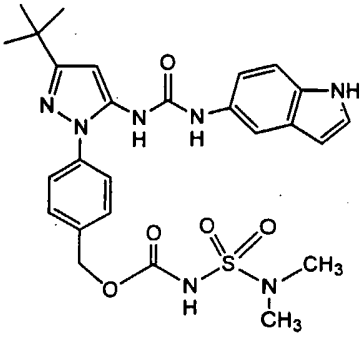
Example 28



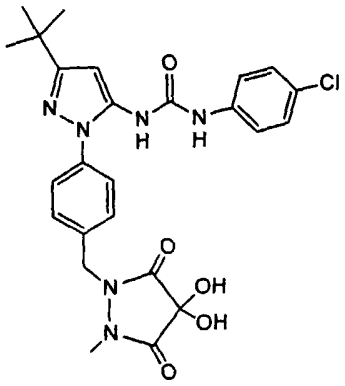
Example 29



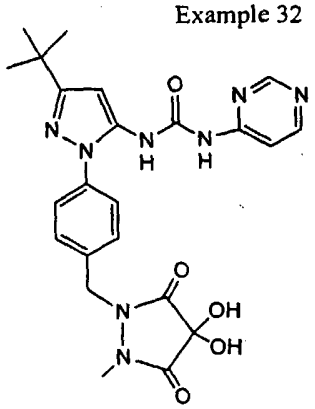
Example 30



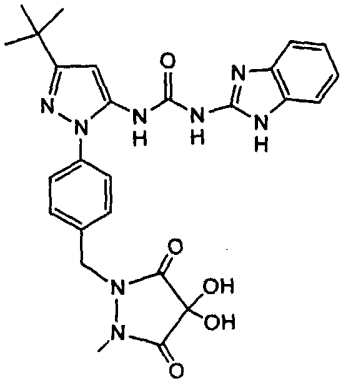
Example 31



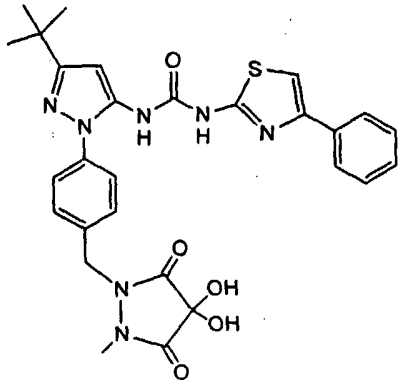
Example 32



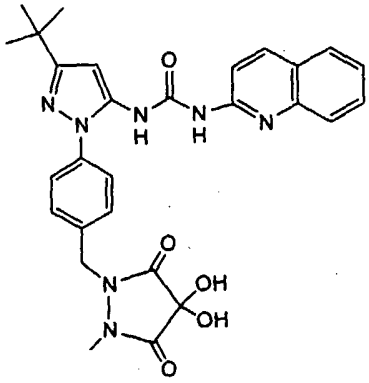
Example 33



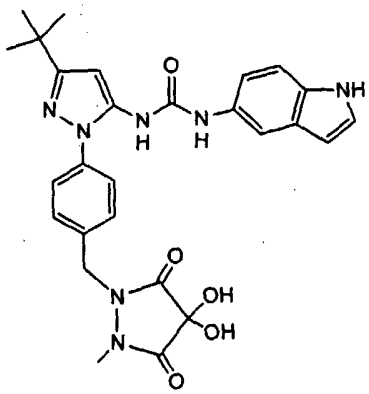
Example 34



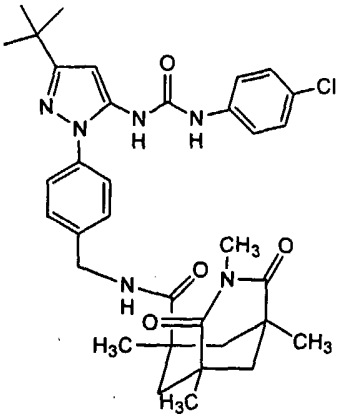
Example 35



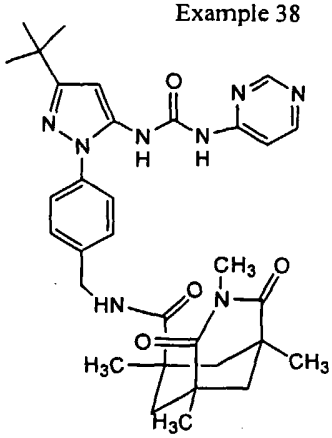
Example 36



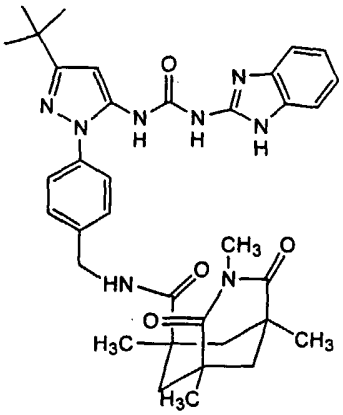
Example 37



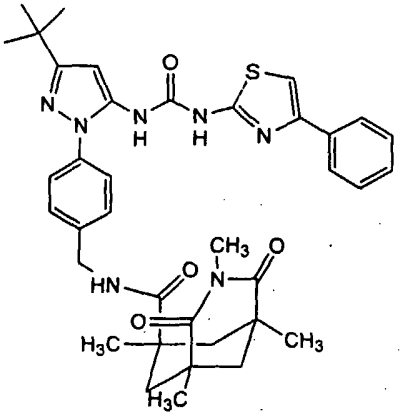
Example 38



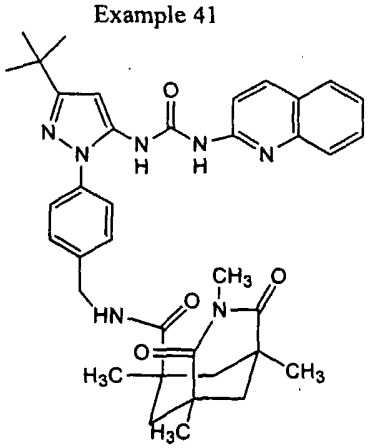
Example 39



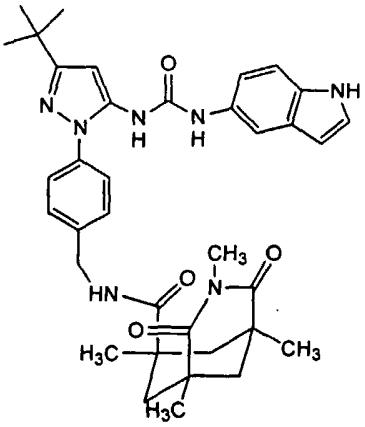
Example 40



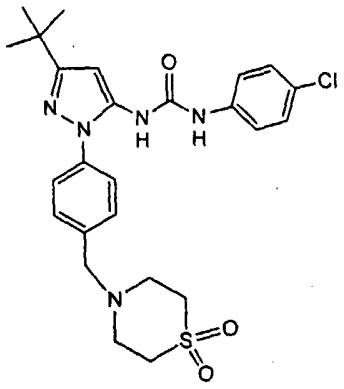
Example 41



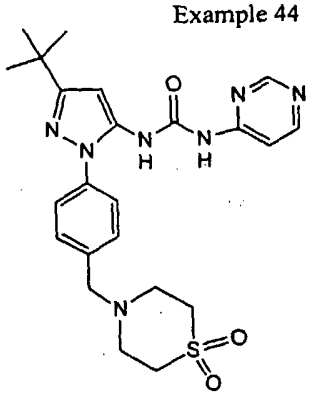
Example 42



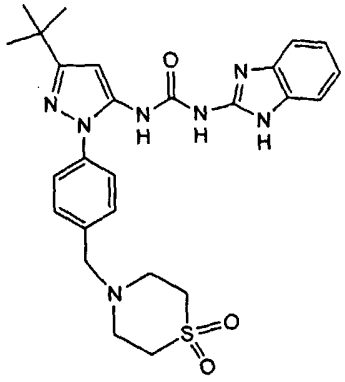
Example 43



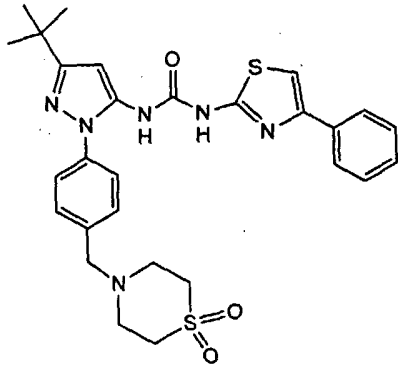
Example 44



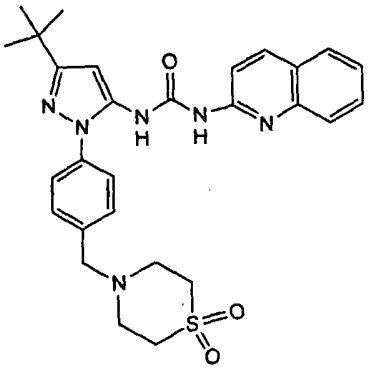
Example 45



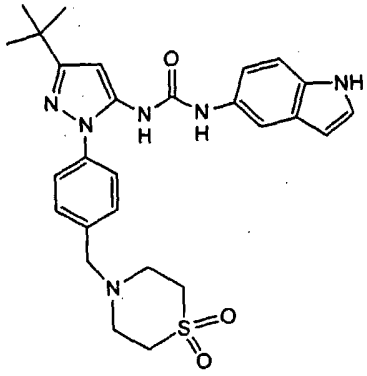
Example 46



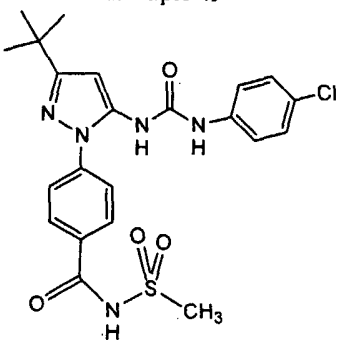
Example 47



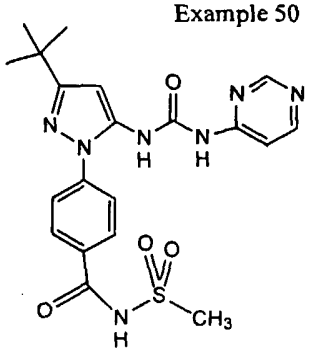
Example 48



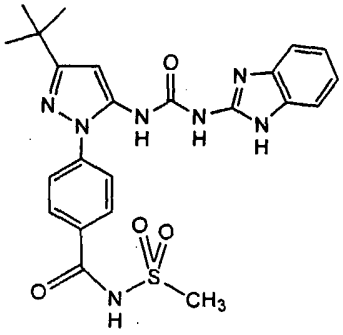
Example 49



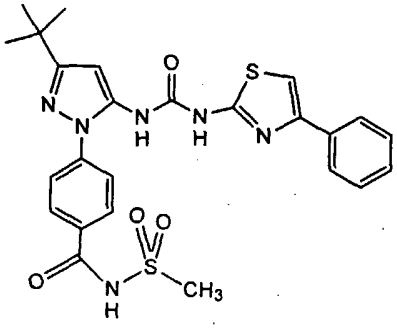
Example 50



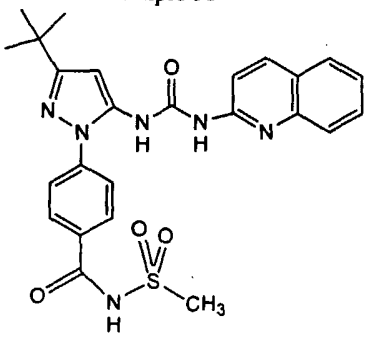
Example 51



Example 52



Example 53



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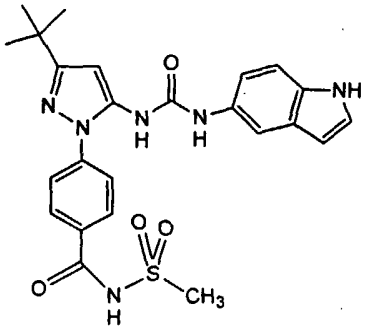
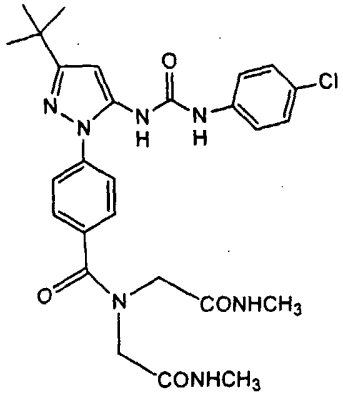


Example 55



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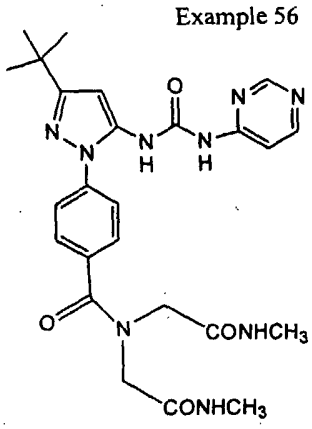

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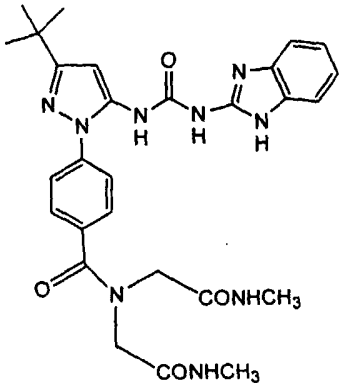

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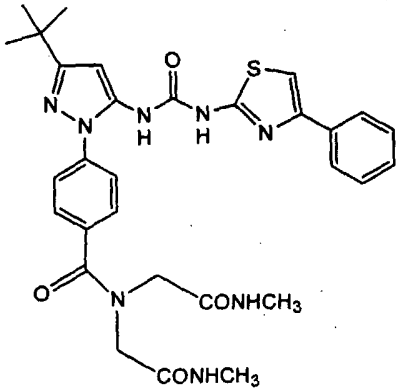
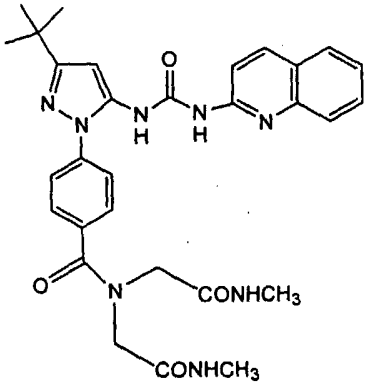
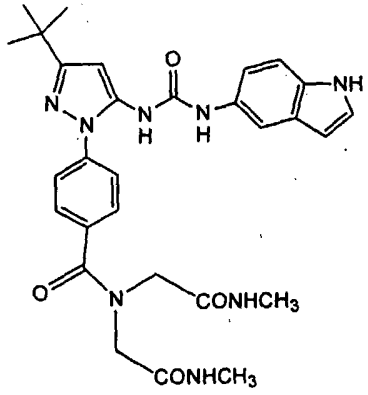


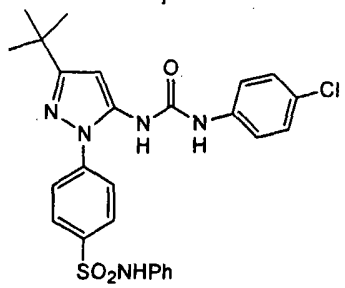
Example 59



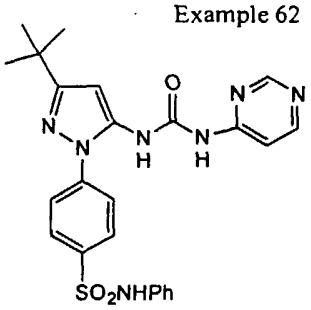
Example 60



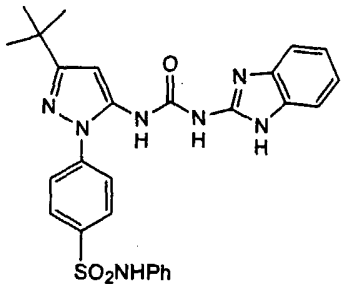
Example 61



Example 62



Example 63



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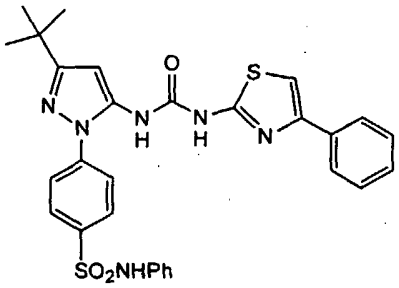
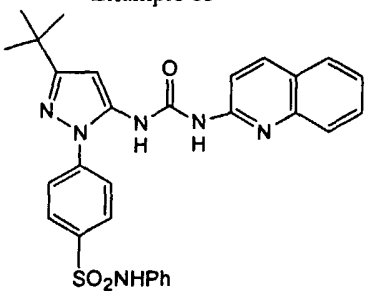
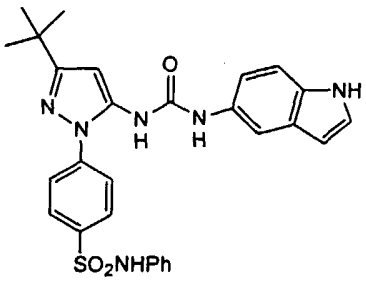


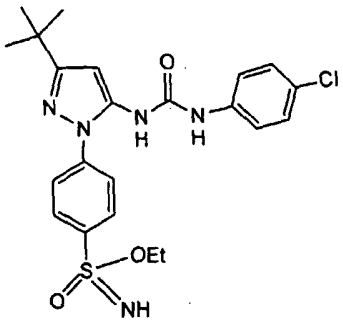
Example 65



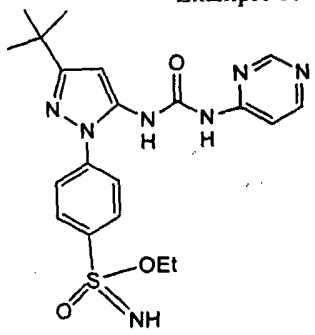
Example 66



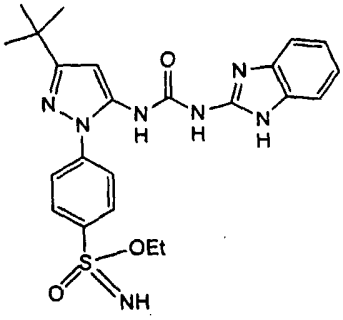
Example 67



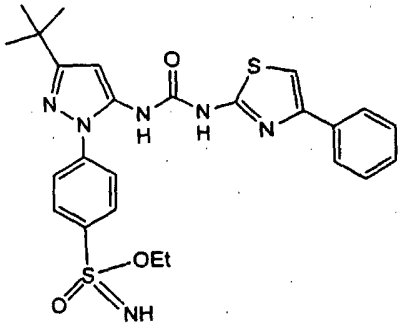
Example 68



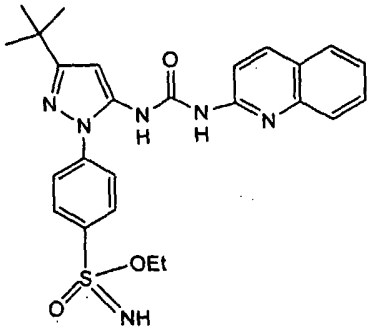
Example 69



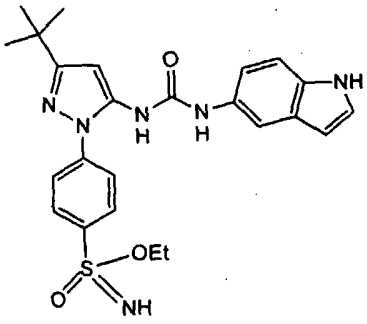
Example 70



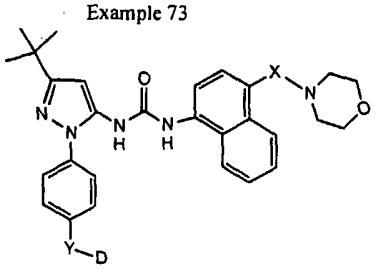
Example 71



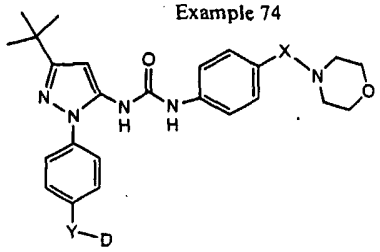
Example 72



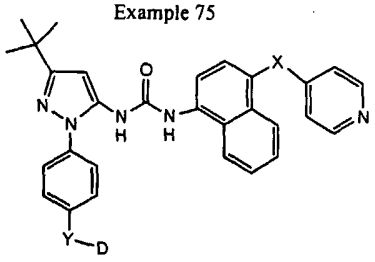
Example 73



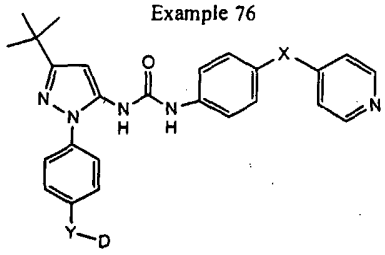
Example 74



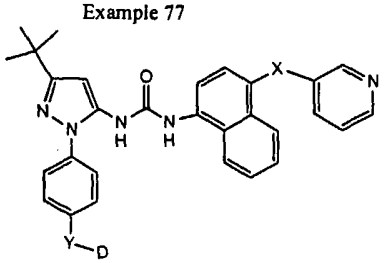
Example 75



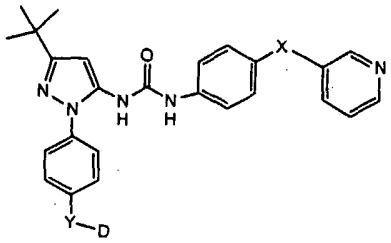
Example 76



Example 77

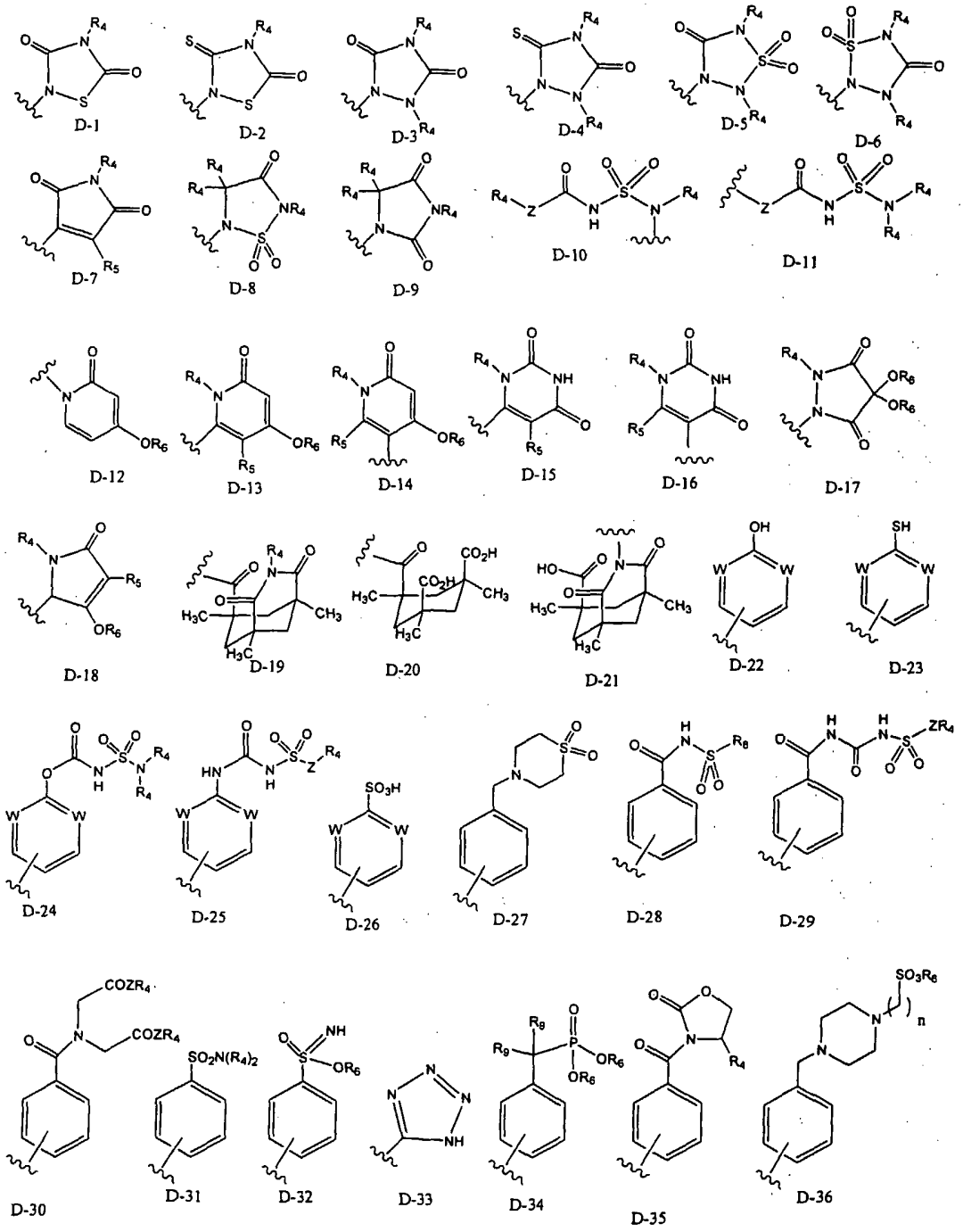


Example 78



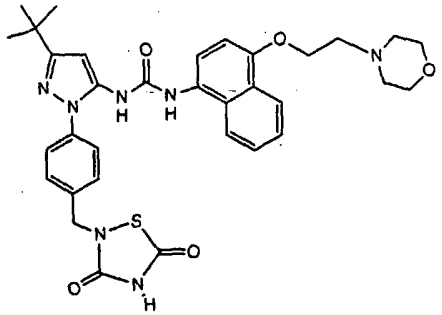
wherein X or Y is O, S, NR6, -NR6SO2-, NR6CO-, alkylene, O-(CH2)n-, NR6-(CH2)n-, wherein one of the methylene units may be substituted with an oxo group, or X or Y is a direct bond; D is taken from the groups identified in Chart I:

Chart 1

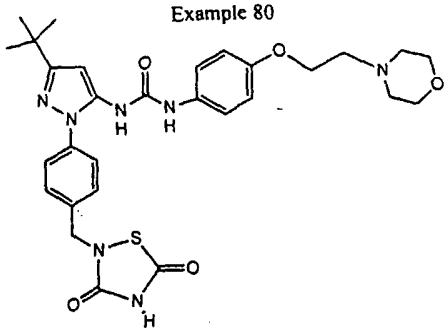


Specific examples of the present invention are illustrated by their structural formulae below:

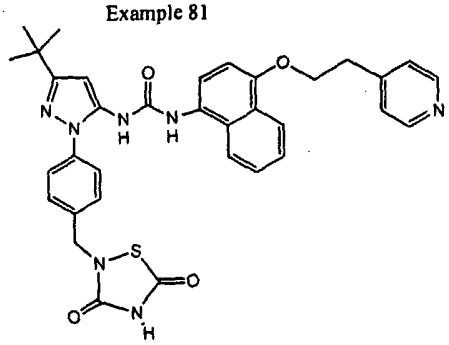
Example 79



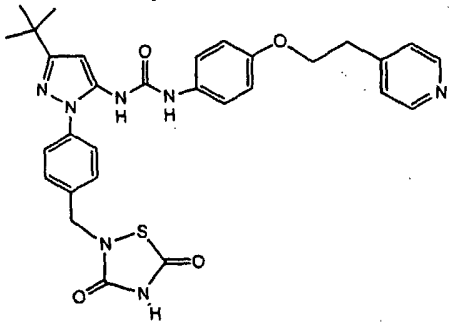
Example 80



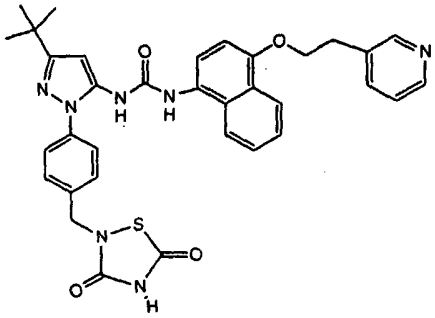
Example 81



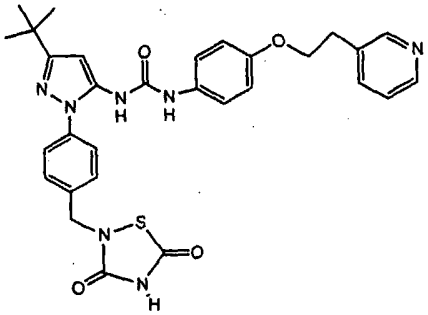
Example 82



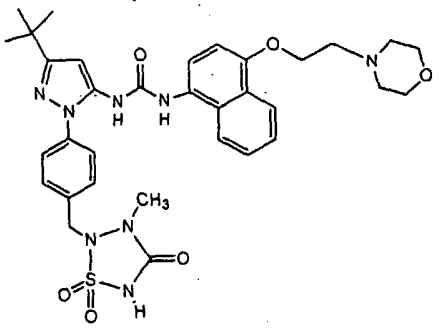
Example 83



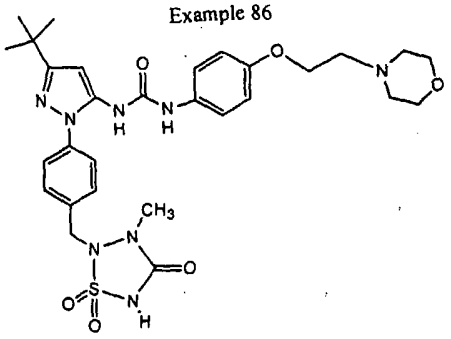
Example 84



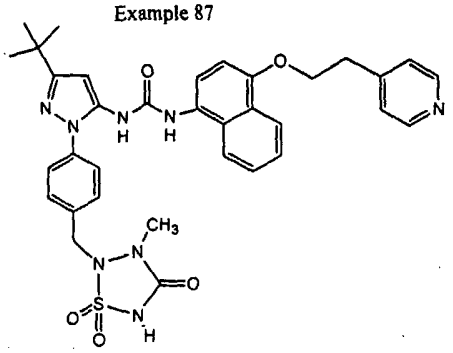
Example 85



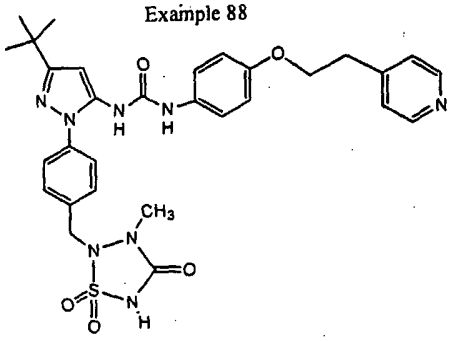
Example 86



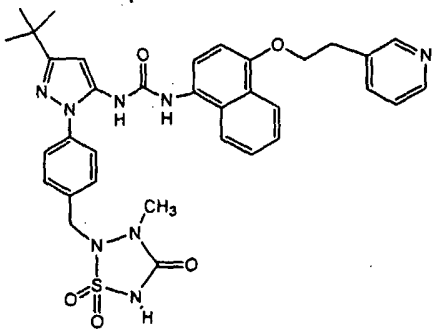
Example 87



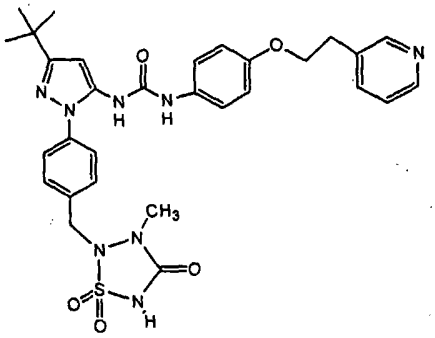
Example 88



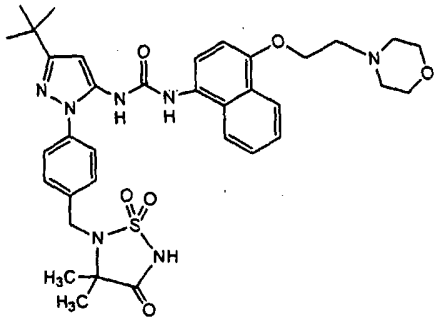
Example 89



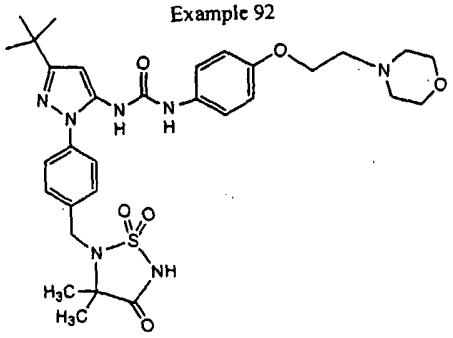
Example 90



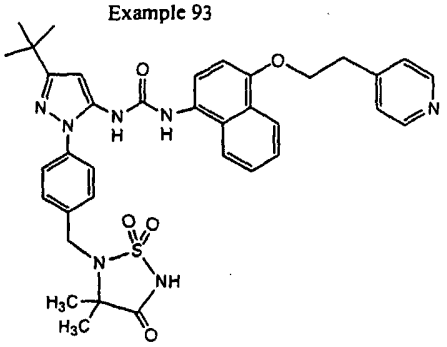
Example 91



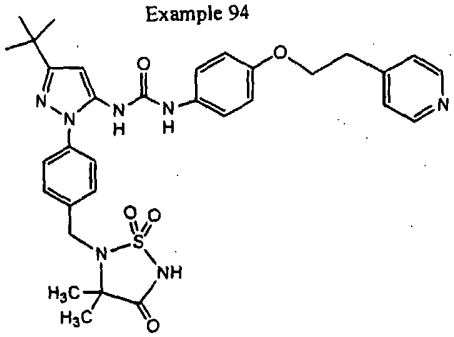
Example 92



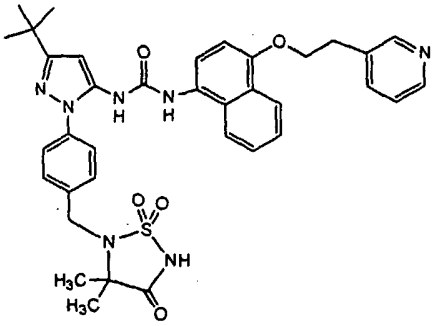
Example 93



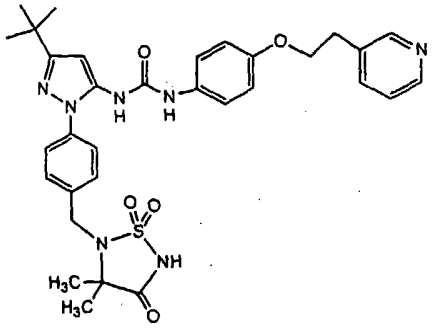
Example 94



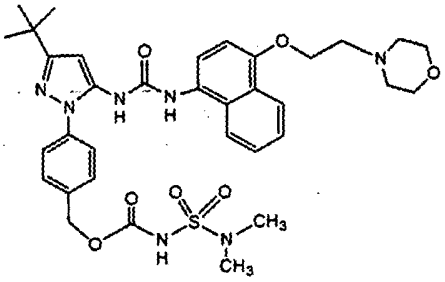
Example 95



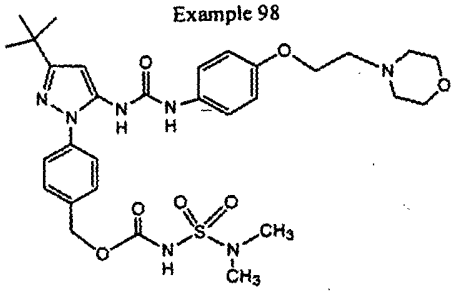
Example 96



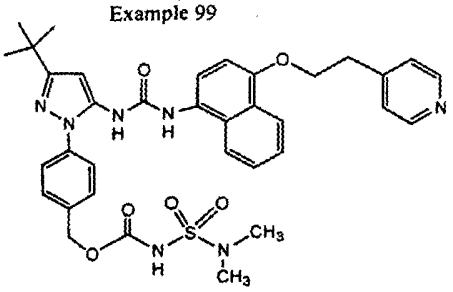
Example 97



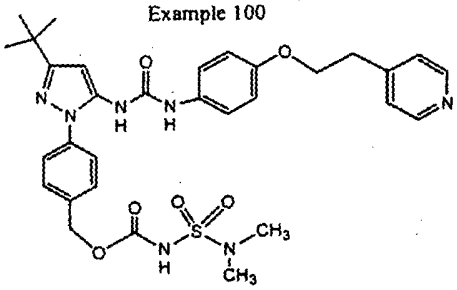
Example 98



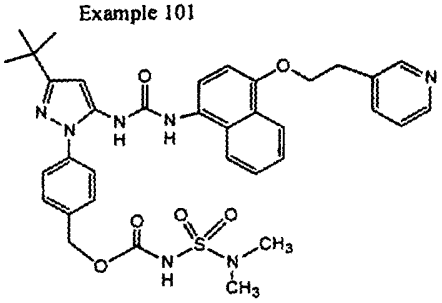
Example 99



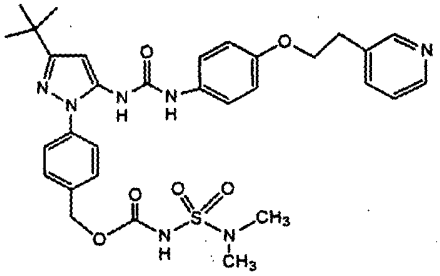
Example 100



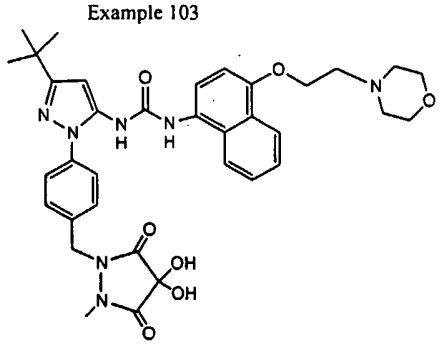
Example 101



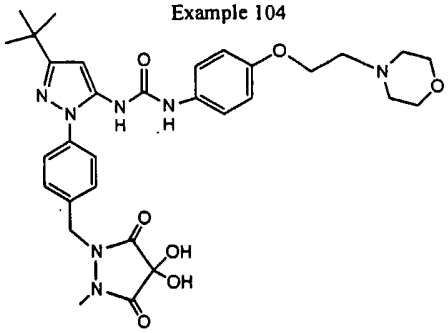
Example 102



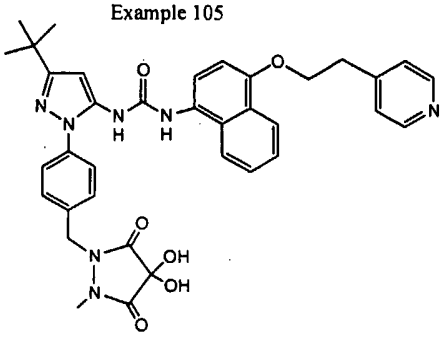
Example 103



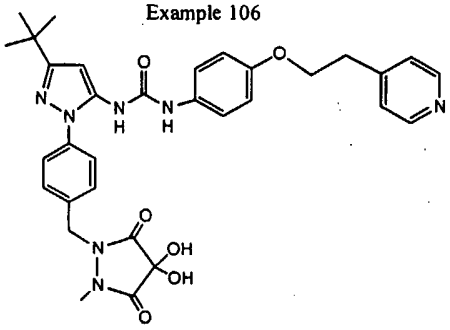
Example 104



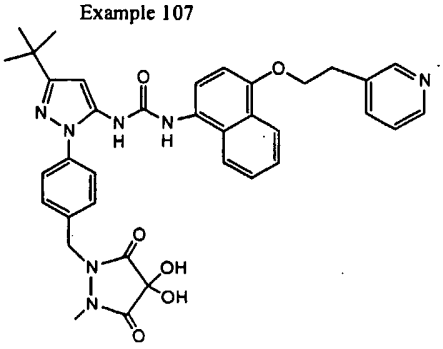
Example 105



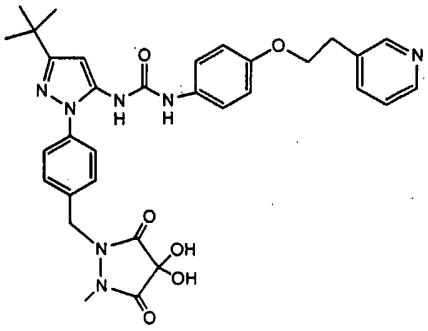
Example 106



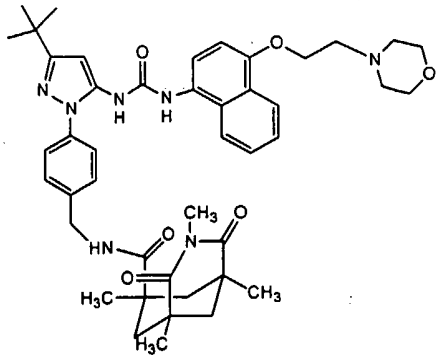
Example 107



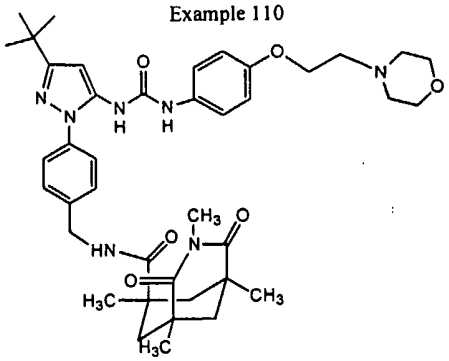
Example 108



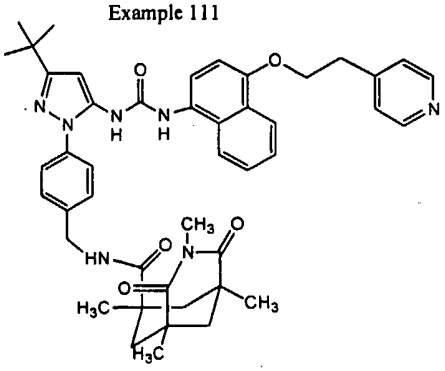
Example 109



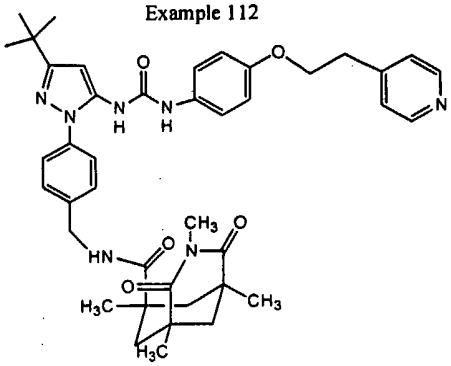
Example 110



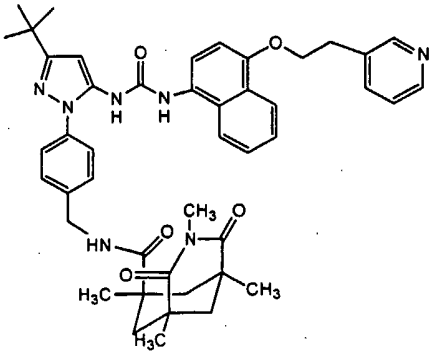
Example 111



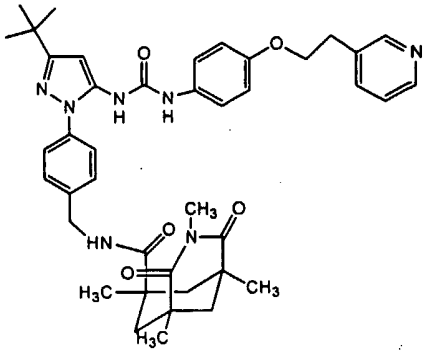
Example 112



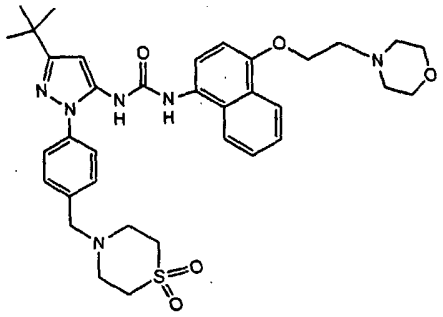
Example 113



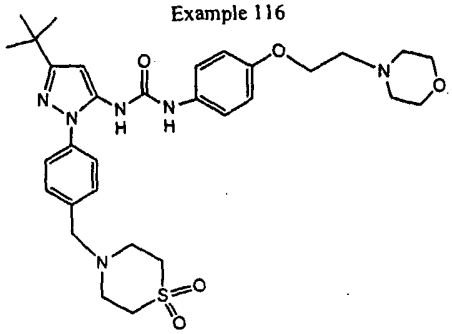
Example 114



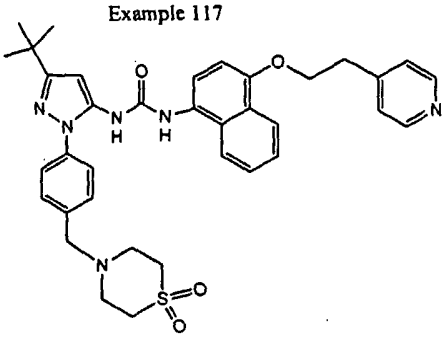
Example 115



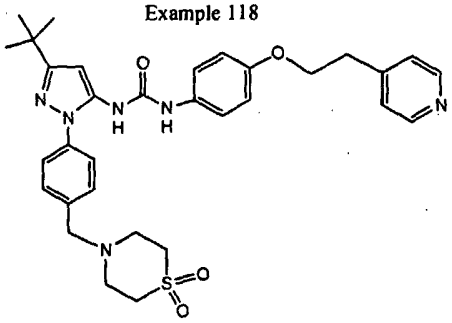
Example 116



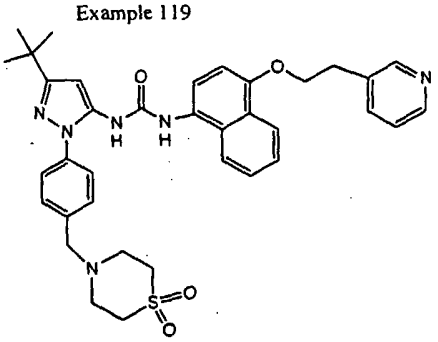
Example 117



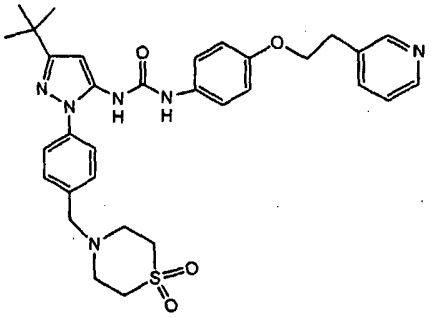
Example 118



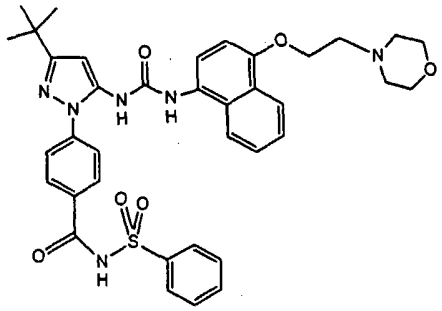
Example 119



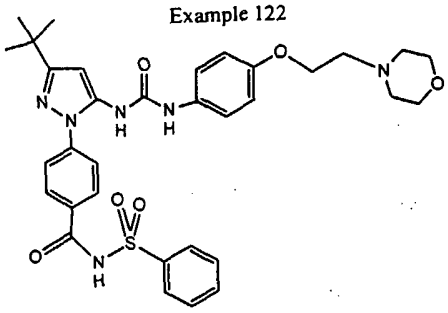
Example 120



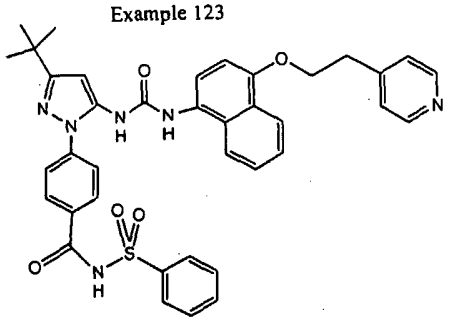
Example 121



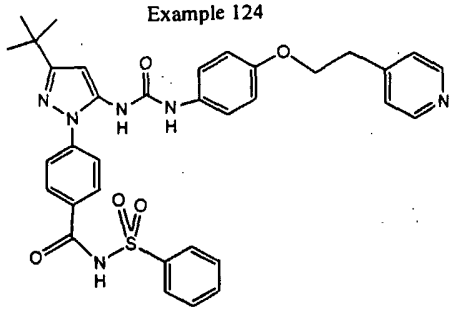
Example 122



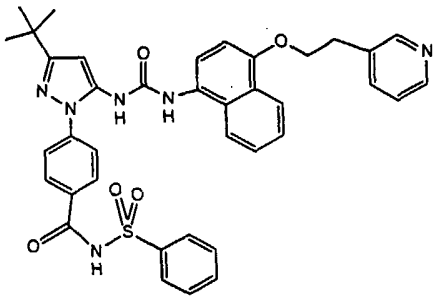
Example 123



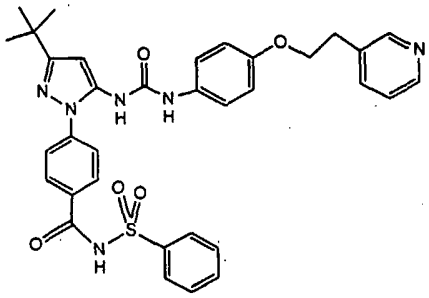
Example 124



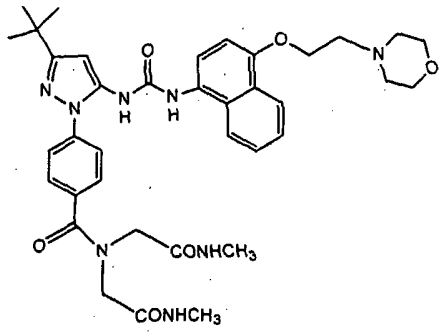
Example 125



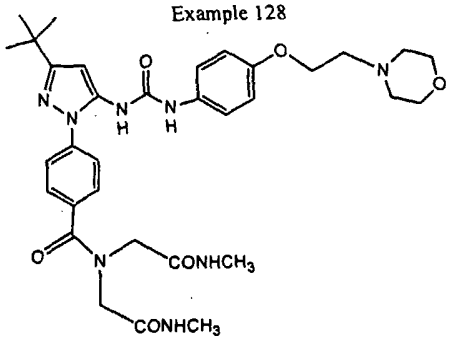
Example 126



Example 127



Example 128



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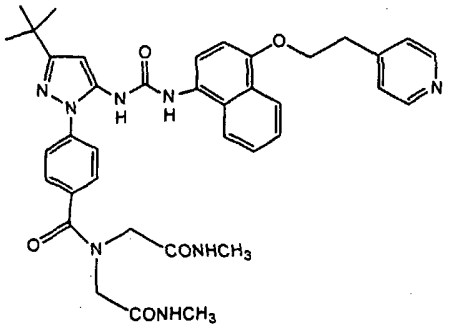
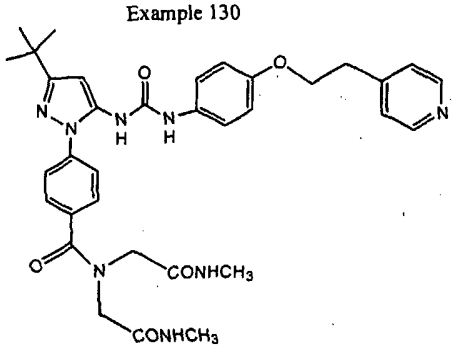
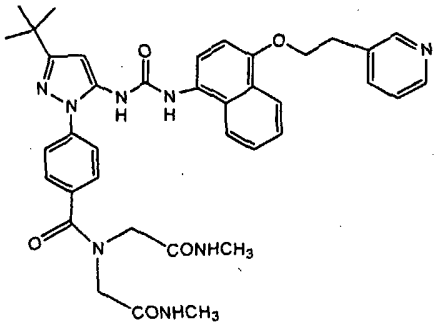


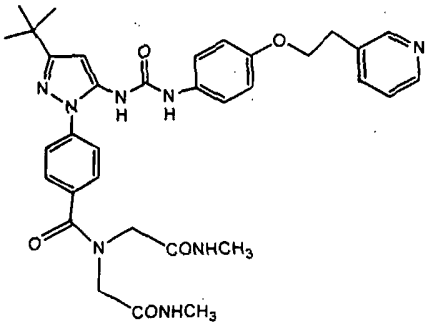
Example 130



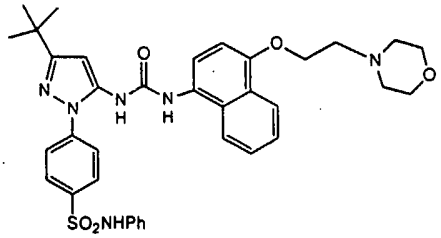
Example 131



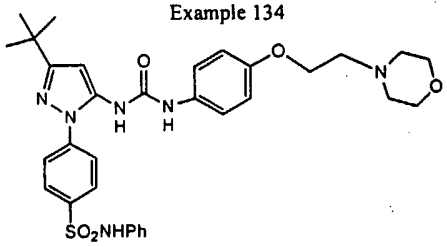
Example 132



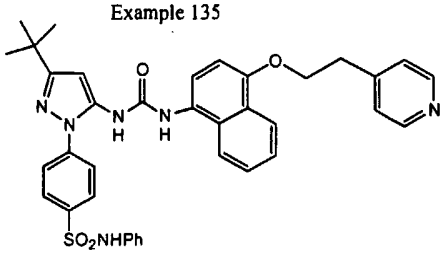
Example 133



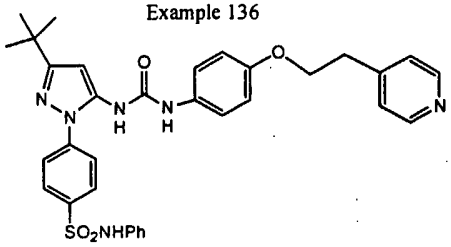
Example 134



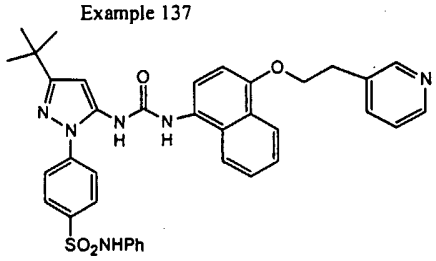
Example 135



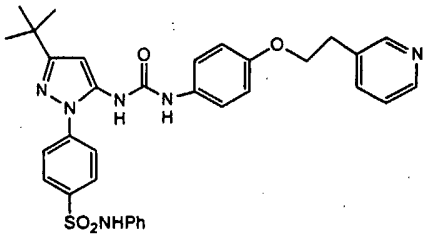
Example 136



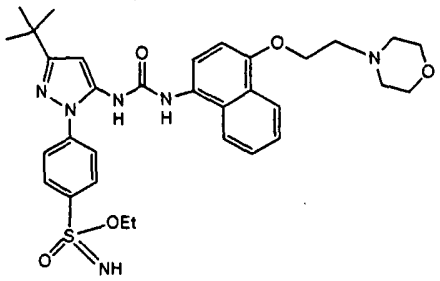
Example 137



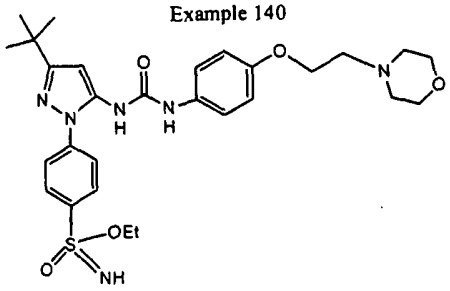
Example 138



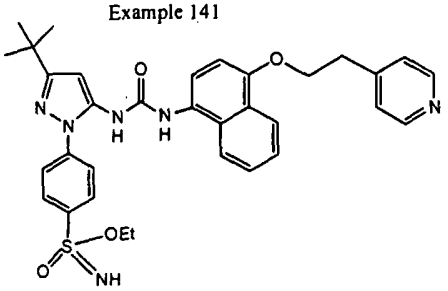
Example 139



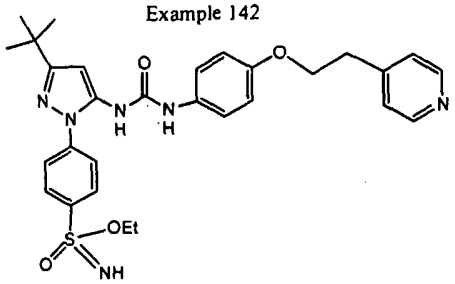
Example 140



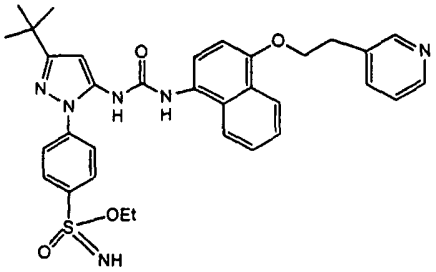
Example 141



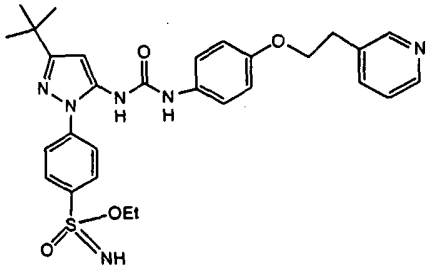
Example 142



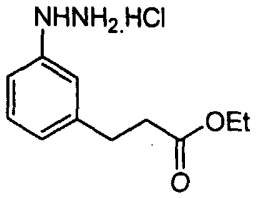
Example 143



Example 144



Example Y

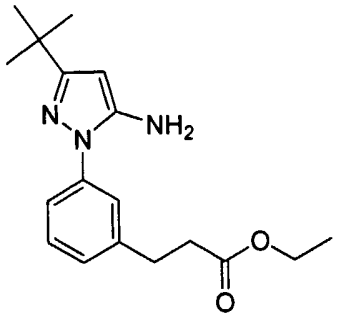


To a solution of 3-nitro-benzaldehyde (15.1 g, 0.1 mol) in CH_2Cl_2 (200 mL) was added (triphenyl-l5-phosphanylidene)-acetic acid ethyl ester (34.8 g, 0.1 mol) in CH_2Cl_2 (100 mL) dropwise at 0 °C, which was stirred for 2 h. After removal the solvent under reduced pressure, the residue was purified by column chromatography to afford 3-(3-nitro-phenyl)-acrylic acid ethyl ester (16.5 g, 74.6 %) ^{1}H-NMR (400 MHz, $CDCl_3$): 8.42 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 16.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 6.56 (d, J = 16.0 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 6.8 Hz, 3H).

A mixture of 3-(3-nitro-phenyl)-acrylic acid ethyl ester (16.5 g, 74.6 mmol) and Pd/C (1.65 g) in methanol (200 mL) was stirred under 40 psi of H_2 at RT for 2 h then filtered over celite. After removal the solvent, 14 g of 3-(3-amino-phenyl)-propionic acid ethyl ester was obtained and used directly without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.11 (t, J = 5.6 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 6.63-6.61 (m, 2H), 4.13 (q, J =7.2 Hz, 2H), 2.87 (t, J = 8.0 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 1.34 (t, J = 6.8 Hz, 3H).

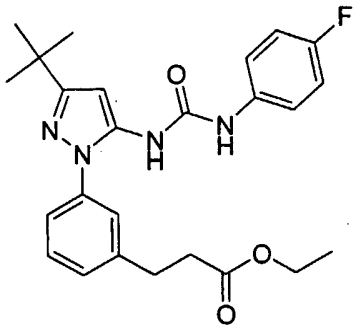
To a solution of 3-(3-amino-phenyl)-propionic acid ethyl ester (14 g, 72.5 mmol) in concentrated HCl (200 mL) was added an aqueous solution (10 mL) of $NaNO_2$ (5 g, 72.5 mmol) at 0 °C and the resulting mixture was stirred for 1 h. A solution of $SnCl_2.2H_2O$ (33 g, 145 mmol) in concentrated HCl (150 mL) was then added at 0 °C. The reaction solution was stirred for an additional 2 h at RT. The precipitate was filtered and washed with ethanol and ether to give 3-(3-hydrazino-phenyl)-propionic acid ethyl ester as a white solid, which was used without further purification.

Example Z



A mixture of Example Y (13 g, 53.3 mmol) and 4,4-dimethyl-3-oxo-pentanenitrile (6.9 g, 55 mol) in ethanol (150 mL) was heated to reflux overnight. The reaction solution was evaporated under reduced pressure. The residue was purified by column chromatography to give 3-[3-(5-amino-3-t-butyl-pyrazol-1-yl)-phenyl]- propionic acid ethyl ester (14.3 g, 45.4 mmol) as a white solid. ^{1}H NMR (DMSO-d_6): 7.39-7.32 (m, 3H), 7.11 (d, J = 6.8 Hz, 1H), 5.34 (s, 1H), 5.16 (s, 2H), 4.03 (q, J = 7.2 Hz, 2H), 2.88 (t, J =7.6 Hz, 2H), 2.63 (t, J =7.6 Hz, 2H), 1.19 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H).

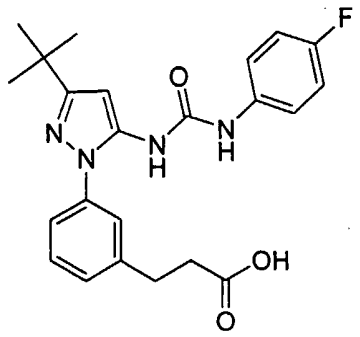
Example 145



A solution of 4-fluoro-phenylamine (111 mg, 1.0 mmol) and CDI (165 mg, 1.0 mmol) in DMF (2 mL) was stirred at RT for 30 min, and was then added to a solution of Example Z (315 mg, 1.0 mmol) in DMF (2 mL). The resulting mixture was stirred at RT overnight then added to water (50 mL). The reaction mixture was extracted with ethyl acetate (3×50 mL) and the combined organic extracts were washed with brine, dried ($NaSO_4$) and filtered. After concentrated under reduced pressure, the residue was purified by flash chromatography to afford 3-(3-{3-*t*-butyl-5-[3-(4-fluoro-phenyl)-ureido]-pyrazol-1-yl}-phenyl)-propionic acid ethyl ester (150 mg, 33%). ^{1}H-NMR ($CDCl_3$): 7.91 (s, 1H), 7.42 (d, J = 4.8 Hz, 1H), 7.37-7.34 (m, 2H), 7.28 (s, 1H), 7.17-7.16 (m, 2H),

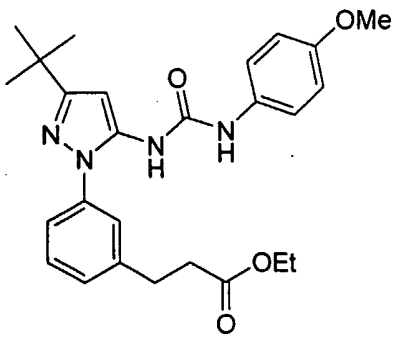
6.98 (t, J = 8.8 Hz, 2H), 6.59 (s, 1H), 4.04 (q, J = 7.2 Hz, 2H), 3.03 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 1.36 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H); MS (ESI) m/z: 453 ($M+H^+$).

Example 146



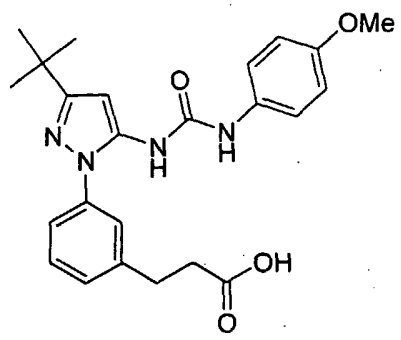
A solution of Example 145 (45 mg, 0.1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT overnight. The reaction mixture was neutralized to pH = 4, extracted with ethyl acetate (3×20 mL), the combined organic extracts were washed with brine, dried ($NaSO_4$) and filtered. The filtrate was concentrated to afford 3-(3-{3-t-butyl-5-[3- (4-fluoro-phenyl)-ureido]-pyrazol-1-yl}-phenyl)-propionic acid, (37 mg, 90%). ^1H NMR (CD_3OD): 7.63-7.62 (m, 2H), 7.56 (s, 1H), 7.53-7.48 (m, 1H), 7.41-7.38 (m, 2H), 7.04 (t, J = 8.8 Hz, 2H), 5.49 (s, 1H), 3.07 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 1.42 (s, 9H); MS (ESI) m/z: 415 ($M+H^+$).

Example 147



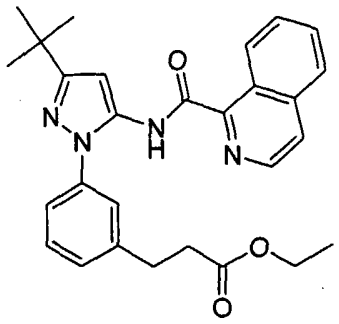
A mixture of 4-methoxy-phenylamine (123 mg, 1.0 mmol) and CDI (165 mg, 1.0 mmol) in DMF (2 mL) was stirred at RT for 30 min, and was then added a solution of Example Z (315 mg, 1.0 mmol) in DMF (2 mL). The resulting mixture was stirred at RT overnight then quenched with of water (50 mL). The reaction mixture was extracted with ethyl acetate (3×50 mL) and the combined organic extracts were washed with brine, dried ($NaSO_4$), filtered, concentrated under reduced presume to yield a residue which was purified by flash chromatography to afford 3-(3-{3-t-butyl-5-[3-(4-methoxy-phenyl)-ureido]-pyrazol-1-yl}-phenyl)-propionic acid ethyl ester (210 mg, 45%). ^{1}H-NMR (CD_3OD): 7.46 (t, J = 7.6 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.38 (s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.00 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 1.33 (s, 9H), 1.20 (t, J = 7.6 Hz, 3H); MS (ESI) m/z: 465 ($M+H^+$).

Example 148



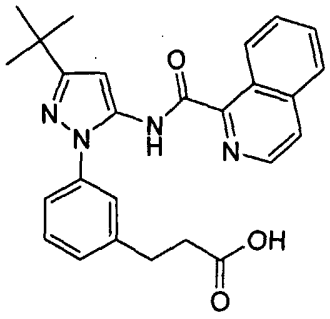
Utilizing the same synthetic procedure as for Example 61 and starting with Example 147, 3-(3-{3-t-butyl-5-[3-(4-methoxy-phenyl)-ureido]-pyrazol-1-yl}-phenyl)-propionic acid is synthesized.

Example 149



A solution of isoquinoline-1-carboxylic acid (346 mg, 2.0 mmol), Example Z (315 mg, 1.0 mmol), EDCI (394 mg, 2.0 mmol), HOBt (270 mg, 2.0 mmol), and NMM (1.0 mL) in DMF (10 mL) was stirred at RT overnight. After quenching with water (100 mL), the reaction mixture was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with brine, dried ($NaSO_4$), filtered and concentrated under reduced pressure to yield a residue which was purified by flash chromatography to afford 3-(3-{3-t-butyl-5-[(isoquinoline-1-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid ethyl ester, (380 mg, 80%). ^{1}H-NMR (DMSO-d_6): 8.83 (d, J = 8.4 Hz, 1H), 8.85 (d, J = 5.2 Hz, 1H), 8.09 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 5.2 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.57 (s, 1H), 3.98 (q, J = 7.2 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 2.57 (t, J = 7.6 Hz, 2H), 1.32 (s, 9H), 1.10 (t, J = 7.6 Hz, 1H); MS (ESI) m/z: 471 ($M+H^+$).

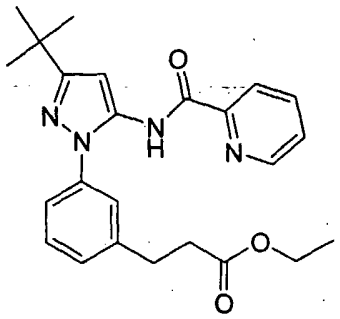
Example 150



A solution of Example 149u (47 mg, 0. 1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT overnight. The reaction mixture was neutralized to pH = 4, extracted with ethyl acetate (3×20 mL), and the combined organic extracts were washed with brine, dried ($NaSO_4$) and filtered. The filtrate was concentrated to afford 3-(3-{3-t-butyl-5-[(isoquinoline-1-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid, (39 mg,

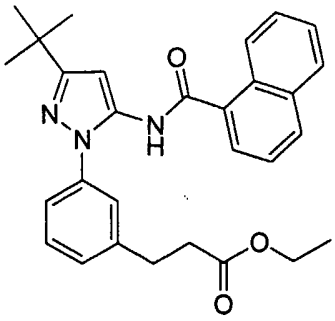
87%). ^{1}H-NMR (DMSO-*d*6): 10.77 (s, 1H), 9.68 (d, *J* = 7.6 Hz, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 7.89-7.44 (m, 2H), 7.78-7.74 (m, 2H), 7.49-7.47 (m, 3H), 7.30-7.27 (m, 3H), 6.95 (s, 1H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 1.42 (s, 9H); MS (ESI) m/z: 443 ($M+H^+$).

Example 151



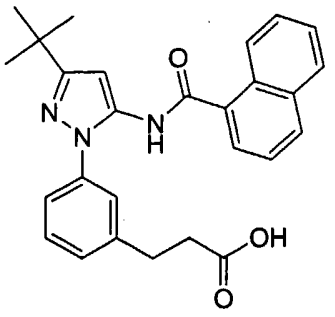
A solution of pyridine-2-carboxylic acid (246 mg, 2.0 mmol), Example Z (315mg, 1.0 mmol), EDCI (394 mg, 2.0 mmol), HOBt (270 mg, 2.0 mmol), NMM (1.0 mL) in DMF (10 mL) was stirred at RT overnight. After quenching with water (100 mL), the reaction mixture was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with brine, dried ($NaSO_4$), filtered and concentrated under reduced pressure to yield a residue which was purified by flash chromatography to afford 3-(3-{3-t-butyl-5-[(pyridine-2-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid ethyl ester (300 mg, 70%). ^{1}H-NMR ($CDCL_3$): 8.53 (d, *J* = 4.4 Hz, 1H), 8.26 (d, *J* = 7.2 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 1H), 7.48-7.43 (m, 4H), 7.27 (s, 1H), 6.87 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.39 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H); MS (ESI) m/z: 421 ($M+H^+$).

Example 152



A solution of Example Z (315 mg, 1.0 mmol) and Barton's base (0.5 mL) in anhydrous CH_2Cl_2 (5 mL) under N_2 was stirred at RT for 30 min, and then added to a solution of naphthalene-1-carbonyl fluoride (348 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5 mL). The resulting mixture was stirred at RT overnight. After quenching with water (100 mL), the reaction mixture was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with brine, dried ($NaSO_4$), filtered and concentrated under reduced pressure to yield a residue which was purified by flash chromatography to afford 3-(3-{3-*t*-butyl-5-[(naphthalene-1-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid ethyl ester, (350 mg, 74%). ^{1}H-NMR ($CDCL_3$): 8.29 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 7.2 Hz, 2H), 7.89 (d, J = 7.2 Hz, 1H), 7.62-7.57 (m, 3H), 7.49-7.28 (m, 4H), 7.03 (s, 1H), 3.94 (q, J = 7.2 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 1.45 (s, 9H), 1.13 (t, J = 7.2 Hz, 3H); MS (ESI) m/z: 470 ($M+H^+$).

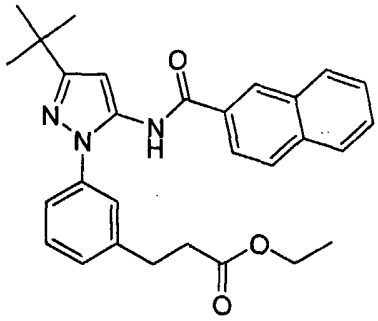
Example 153



A solution of Example 152 (47 mg, 0.1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT overnight. The reaction mixture was neutralized to pH = 4, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, and dried ($NaSO_4$) and filtered. The filtrate was concentrated to afford 3-(3-{3-t-butyl-5-[(isoquinoline-1-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid, (38 mg,

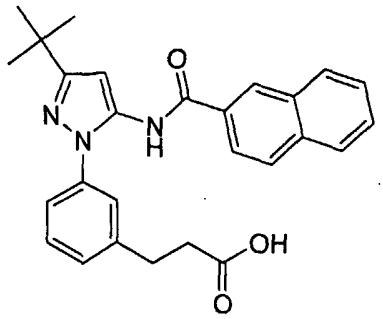
86%). ^{1}H NMR (DMSO-*d*6): 7.99 (d, *J* = 8.0 Hz, 1H), 7.90 (m, 2H), 7.62 (m, 1H), 7.54-7.42 (m, 6H), 7.35 (m, 1H), 6.54 (s, 1H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.38 (s, 9H); MS (ESI) m/z: 443 ($M+H^+$).

Example 154



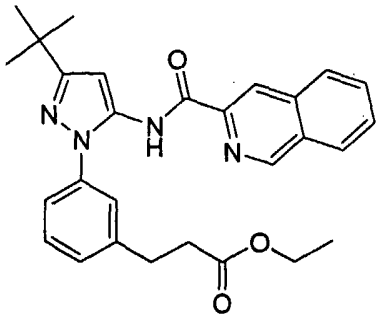
A solution of naphthalene-2-carboxylic acid (344 mg, 2.0 mmol) in $SOCl_2$ (10 mL) was heated to reflux for 2 h. After concentration under reduced pressure, the residue was dissolved into CH_2Cl_2 (5 mL) and was dropped into a solution of Example Z (315 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at 0°C, and was then stirred at RT overnight. After quenching with water (50 mL), the reaction mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with brine, dried ($NaSO_4$), filtered and concentrated under reduced pressure to yield a residue which was purified by flash chromatography to afford 3-(3-{3-*t*-butyl-5-[(naphthalene-2-carbonyl)-amino]- pyrazol-1-yl}-phenyl)-propionic acid ethyl ester (180 mg, 38%). ^{1}H-NMR ($CDCL_3$): 8.24 (s, 1H), 8.21 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.63-7.49 (m, 3H), 7.45-7.26 (m, 3H), 6.94 (s, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.43 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H); MS (ESI) m/z: 470 ($M+H^+$).

Example 155



A solution of Example 154 (47 mg, 0. 1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT overnight. The reaction mixture was neutralized to pH = 4, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, and dried ($NaSO_4$) and filtered. The filtrate was concentrated to afford 3-(3-{3-t-butyl-5-[(isoquinoline-2-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid, (37 mg, 84%). ^{1}H-NMR (CDCL3): 8.25 (s, 1H), 8.18 (s, 1H), 7.91-7.86 (m, 3H), 7.75 (d, J = 8.0 Hz, 1H), 7.59-7.55 (m, 2H), 7.48-7.39 (m, 3H), 7.28 (s, 1H), 6.81 (s, 1H), 3.02 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.42 (s, 9H); MS (ESI) m/z: 442 ($M+H^+$).

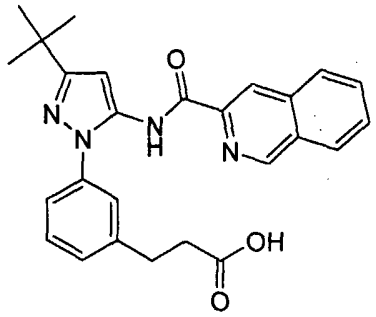
Example 156



A solution of isoquinoline-3-carboxylic acid (346 mg, 2.0 mmol), example Z (315 mg, 1.0 mmol), EDCI (394 mg, 2.0 mmol), HOBt (270 mg, 2.0 mmol), and NMM (1.0 mL) in DMF (10 mL) was stirred at RT overnight. After quenching with water (50 mL), the reaction mixture was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with brine, dried ($NaSO_4$) and filtered. After concentrated under reduced pressure, the residue was purified by flash chromatography to afford 3-(3-{3-t-butyl-5-[(isoquinoline-3-carbonyl)-amino]-pyrazol-1- yl}-phenyl)-propionic acid ethyl ester (250 mg, 54%). ^{1}H-NMR (CD_3OD): 9.24 (s, 1H), 8.63 (s, 1H), 8.17 (d, J = 8.0 Hz,

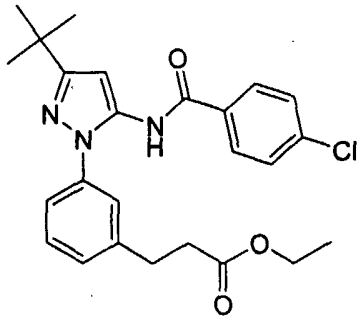
1H), 8.11 (d, J = 8.0 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.50 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 6.75 (s, 1H), 4.04 (q, J = 7.6 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.39 (s, 9H), 1.14 (t, J = 7.6 Hz, 3H); MS (ESI) m/z: 471 ($M+H^+$).

Example 157



A solution of Example 156 (47 mg, 0.1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT overnight. The reaction mixture was neutralized to pH = 4, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, and dried ($NaSO_4$) and filtered. The filtrate was concentrated to afford 3-(3-{3-*t*-butyl-5-[(isoquinoline-3-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid, (39 mg, 88%). ^1H NMR (CDCL3): 10.49 (s, 1H), 9.16 (s, 1H), 8.69 (s, 1H), 8.03 (d, J = 7.6 Hz, 2H), 7.81 (t, J = 7.2 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.48-7.39 (m, 3H), 7.28 (br s, 1H), 6.94 (s, 1H), 3.02 (t, J = 7.6 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 1.42 (s, 9H); MS (ESI) m/z: 442 ($M+H^+$).

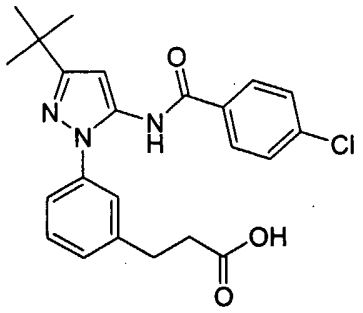
Example 158



A solution of 4-chlorobenzoic acid (312 mg, 2.0 mmol) in $SOCl_2$ (10 mL) was heated to reflux for 2 h. After removal of the solvent, the residue was dissolved into

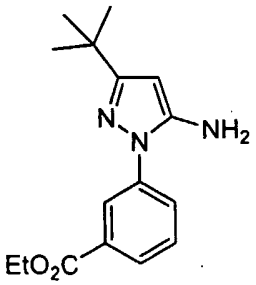
CH_2Cl_2 (5 mL) and was dropped into a solution of Example Z (315 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was then stirred at RT overnight. After quenching with water (50 mL), the reaction mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with brine, dried ($NaSO_4$) and filtered. After concentrated under reduced pressure, the residue was purified by flash chromatography to afford 3-{3-[3-*t*-butyl-5-(4-chloro-benzoylamino)-pyrazol-1-yl]- phenyl}-propionic acid ethyl ester (290 mg, 64%). ^{1}H-NMR ($CDCL_3$): 8.02 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 8.4 Hz, 3H), 6.87 (s, 1H), 4.06 (q, J = 7.6 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 1.40 (s, 9H), 1.12 (t, J = 7.6 Hz, 3H); MS (ESI) m/z: 454 ($M+H^+$).

Example 159



A solution of Example 158 (45 mg, 0. 1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT overnight. The reaction mixture was neutralized to pH = 4, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, and dried ($NaSO_4$) and filtered. The filtrate was concentrated to afford 3-{3-[3-*t*-butyl-5- (4-chloro-benzoylamino)-pyrazol-1-yl]-phenyl}-propionic acid, (38.5 mg, 87%). ^{1}H NMR (DMSO-*d6*): 10.38 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.32 (d, J = 4.8 Hz, 2H), 7.15 (t, J = 4.8 Hz, 1H), 6.38 (s, 1H), 2.80 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 1.29 (s, 9H); MS (ESI) m/z: 426 ($M+H^+$).

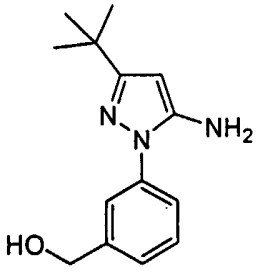
Example AA



To a solution of m-aminobenzoic acid (200.0 g, 1.46 mmol) in concentrated HCl (200 mL) was added an aqueous solution (250 mL) of $NaNO_2$ (102 g, 1.46 mmol) at 0 °C and the reaction mixture was stirred for 1 h. A solution of $SnCl_2.2H_2O$ (662 g, 2.92 mmol) in concentrated HCl (2000 mL) was then added at 0 °C. The reaction solution was stirred for an additional 2 h at RT. The precipitate was filtered and washed with ethanol and ether to give 3-hydrazino-benzoic acid hydrochloride as a white solid, which was used for the next reaction without further purification. ^{1}H NMR (DMSO-d_6): 10.85 (s, 3 H), 8.46 (s, 1 H), 7.53 (s, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.37 (m, J = 7.6 Hz, 1 H), 7.21 (d, J = 7.6 Hz, 1 H).

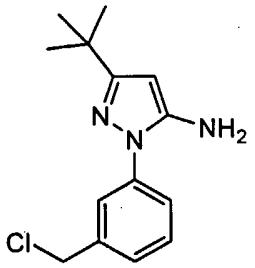
A mixture of 3-hydrazino-benzoic acid hydrochloride (200 g, 1.06 mol) and 4,4-dimethyl-3-oxo-pentanenitrile (146 g, 1.167 mol) in ethanol (2 L) was heated to reflux overnight. The reaction solution was evaporated under reduced pressure. The residue was purified by column chromatography to give 3-(5-amino-3-t-butyl-pyrazol-1-yl)-benzoic acid ethyl ester (116 g, 40%) as a white solid together with 3-(5-amino-3-t-butyl-pyrazol-1-yl)- benzoic acid (93 g, 36%). 3- (5-amino-3-t-butyl-pyrazol-1-yl)-benzoic acid and ethyl ester: ^{1}H NMR (DMSO-d_6): 8.09 (s, 1 H), 8.05 (brd, J = 8.0 Hz, 1 H), 7.87 (br d, J = 8.0 Hz, 1 H), 7.71 (t, J = 8.0 Hz, 1 H), 5.64 (s, 1 H), 4.35 (q, J = 7.2 Hz, 2 H), 1.34 (t, J = 7.2 Hz, 3 H), 1.28 (s, 9H).

Example BB



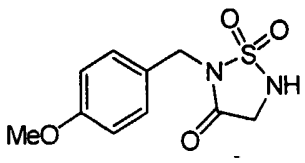
To a stirred solution of Example AA (19.5 g, 68.0 mmol) in THF (200 mL) was added $LiAlH_4$ powder (5.30 g, 0.136 mol) at -10 °C under N_2. The mixture was stirred for 2 h at RT and excess $LiAlH_4$ was destroyed by slow addition of ice. The reaction mixture was acidified to pH = 7 with diluted HCl, the solution concentrated under reduced pressure, and the residue was extracted with ethyl acetate. The combined organic extracts were concentrated to give [3-(5-amino-3-t-butyl-pyrazol-1-yl)-phenyl]-methanol (16.35 g, 98%) as a white powder. ^1H NMR (DMSO-d6): 9.19 (s, 1 H), 9.04 (s, 1 H), 8.80 (s, 1 H), 8.26-7.35 (m, 1 H), 6.41 (s, 1H), 4.60 (s, 2 H), 1.28 (s, 9 H); MS (ESI) m/z: 415 ($M+H^+$).

Example CC



A solution of Example BB (13.8 g, 56.00 mmol) and $SOCl_2$ (8.27 mL, 0.11 mol) in THF (200 mL) was refluxed for 3 h and concentrated under reduced pressure to yield 5-*t*-butyl-2-(3-chloromethyl-phenyl)-2H-pyrazol-3-ylamine (14.5 g, 98%) as white powder which was used without further purification. ^1H NMR (DMSO-d6), δ7.62 (s, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.43 (t, J = 8.0 Hz, 1 H), 7.31 (d, J = 7.2 Hz,1 H), 5.38 (s, 1 H), 5.23 (br s, 2 H), 4.80 (s, 2H), 1.19 (s, 9 H). MS (ESI) m/z: 264 ($M+H^+$).

Example DD



To a stirred solution of chlorosulfonyl isocyanate (1.43 g, 10.0 mmol) in CH_2Cl_2 (20 mL) at 0°C was added 2-methyl-propan-2-ol (0.74 g, 10.0 mmol) at such a rate that

the reaction solution temperature did not rise above 5°C. After being stirred for 1.5 h, a solution of glycine ethyl ester (1.45 g, 12.0 mmol) and Et_3N (3.2 mL, 25.0 mmol) in CH_2Cl_2 (20 mL) was added at such a rate that the reaction temperature didn't rise above 5°C. When the addition was completed, the solution was warmed to RT and stirred overnight. The reaction mixture was poured into 10% HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl, dried (Mg_2SO_4) and filtered. After removal of the solvent, the crude product was washed with CH_2Cl_2 to afford ethyl 2-((N-(butyloxycarbonyl)sulfamoyl)amino)acetate (2.4 g, 85 %). ^{1}H-NMR(DMSO): δ 10.85 (s, 1H), 8.04 (t, J = 6.0 Hz, 1H), 4.07 (q, J = 5.6 Hz, 2H), 3.77 (d, J = 6.0 Hz, 2H), 1.40 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H).

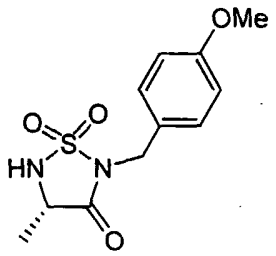
To a solution of (4-methoxyphenyl)-methanol (1.4 g, 8.5 mmol) and triphenyl-phosphane (2.6 g, 8.5 mol) in dry THF was added a solution of ethyl 2-((N-(butyloxycarbonyl)sulfamoyl)amino)acetate from the previous step (2.4 g, 8.5 mol) and DIAD (2.0 g, 8.5 mmol) in dry THF dropwise at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 2 h, warmed to RT and stirred overnight. After the solvent was removed in *vacuo,* the residue was purified by column chromatography to afford ethyl 2-((N-(butyloxycarbonyl)-N-(p-methoxybenzyl)sulfamoyl)amino)acetate (2.3 g, 69%) as a white solid. ^{1}H-NMR($CDCl_3$): δ 7.32 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.71 (m, 1H), 4.76 (s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 3.55 (d, J = 5.2 Hz, 2H), 1.54 (s, 9H), 1.25 (t, J = 7.2 Hz,3H).

To a solution of HCl in methanol (2 M) was added ethyl 2-((N-(butyloxycarbonyl)-N-(p-methoxybenzyl)sulfamoyl)amino)acetate from the previous step (2.0 g, 5.0 mmol) in portions at RT and the mixture was stirred for 3 h. After the solvent was removed in *vacuo*, the residue was washed with diethyl ether to afford ethyl 2-((N-(p-methoxybenzyl)sulfamoyl)amino)acetate (1.0 g, 70%). ^{1}H-NMR (DMSO-d_6): δ 7.43 (t, J = 6.0 Hz,1H), 7.287 (t, J = 6.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 3.94 (d, J = 4.8 Hz, 2H), 3.71 (s, 3H), 3.64 (d, J = 6.0 Hz, 2H), 3.62 (s, 3H),

To a solution of ethyl 2-((N-(p-methoxybenzyl)sulfamoyl)amino)acetate from the previous step (1.0 g, 3.47 mmol) in DMF (50 mL) was added KO-t-Bu (1.56 g, 13.88

mmol) in portions under N_2 atmosphere at RT. The mixture was stirred overnight then quenched with HCl/ methanol (2 M). After the solvent was removed in *vacuo,* the residue was washed with water to afford 2-(4-methoxy-benzyl)-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one (480 mg, 54 %). ^{1}H-NMR($CDCl_3$): δ 7.36 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.87 (m, 1H), 4.68 (s, 2H), 4.03 (d, *J* = 7.2 Hz, 2H), 3.80 (s, 3H).

Example EE



To a stirred solution of chlorosulfonyl isocyanate (1.43 g, 10.0 mmol) in CH_2Cl_2 (20 mL) at 0°C was added benzyl alcohol (1.08 g, 10.0 mmol) at such a rate that the reaction solution temperature did not rise above 5°C. After stirring for 1.5 h, a solution of L-alanine methyl ester (1.45 g, 12.0 mmol) and Et_3N (3.2 mL, 25.0 mmol) in CH_2Cl_2 (20 mL) was added at such a rate that the reaction temperature didn't rise above 5°C. When the addition was completed, the reaction solution was allowed to warm up to RT and stirred overnight. The reaction mixture was poured into 10% HCl, extracted with CH_2Cl_2, the organic extracts washed with saturated NaCl, dried (Mg_2SO_4), and filtered. After removal of the solvent, the crude product was recrystallized in PE/EA (10:1) to afford the desired product (2.5 g, 79 %), which was used directly in the next step. ^{1}H-NMR(DMSO): δ 11.31 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.37-7.32 (m, 5H), 5.11 (s, 2H), 4.03 (m, 1H), 3.57 (s, 3H), 1.23 (d, *J* = 7.2 Hz, 3H).

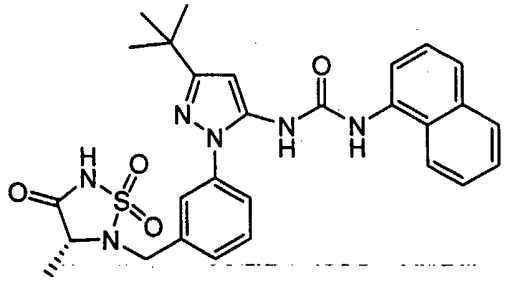
A mixture of material from the previous reaction (2.5 g, 12 mmol) and Pd/C (10 %, 250 mg) in methanol was stirred for 4 h at 50 °C under H_2 atmosphere (55 psi). After the catalyst was removed by suction, the filtrate was evaporated to afford the desired compound (1.37 g, 92%) as a white solid, which was used directly in the next step. ^{1}H-

NMR ($CDCl_3$): δ 5.51 (d, J = 5.6 Hz, 1H), 4.94 (br, 2H), 4.18 (m, 1H), 3.78 (s, 3H), 1.46 (d, J = 7.2 Hz, 3H).

To a solution of 2.0 N of NaOMe in methanol (20 mL) was added a solution of compound form the previous reaction (1.2 g, 6.1 mmol) in methanol and the resulting mixture was heated to reflux overnight. After cooling down, a solution of HCl in methanol was added to acidify to pH 7. The resulted salt was filtered off and the filtrate was evaporated to dryness to afford a light yellow solid which was used directly in the next step (600 mg, 66%). ^{1}H-NMR (DMSO-d_6): δ 6.04 (d, J = 4.8 Hz, 1H), 3.60 (m, 1H), 1.11 (d, J = 7.2 Hz, 3H).

A mixture of compound from the previous step (500 mg, 3.33 mmol) and 1-chloromethyl-4-methoxybenzene (156 mg, 1.0 mmol) in acetonitrile was heated to reflux overnight together with K_2CO_3 (207 mg, 1.5 mmol) and KI (250 mg, 1.5 mmol) under N_2 atmosphere. After cooling, the salt was filtered off and the filtrate was purified by column to afford 2-(4-methoxybenzyl)-(S)-4-methyl-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one as a white solid (200 mg), which was used without further purification.

Example 160

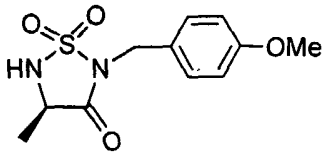


To a solution of Example EE (100 mg, 0.37 mmol) in anhydrous DMF (3 mL) was added NaH (18 mg, 0.44 mmol) at 0 °C. After stirring for 0.5h at 0°C, a solution of Example E (160 mg, 0.37 mmol) in anhydrous DMF (3 mL) was added to the reaction mixture, which was stirred overnight at RT and subsequently concentrated under reduced pressure to yield a crude solid which was used without further purification.

A solution of the crude material from the previous reaction (60 mg, 0.090 mmol) in trifluoroacetic acid (3 mL) was stirred at 50 °C for 4h. After the solvent was removed,

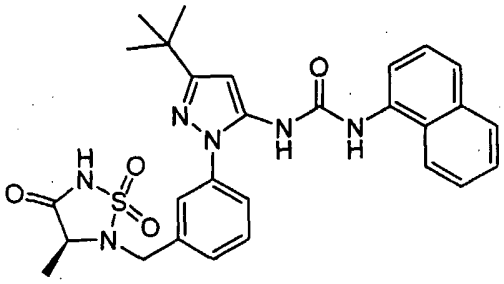
the residue was purified by preparative HPLC to afford 1-{5-t-butyl-2-[3-((S)-3-methyl-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl)-phenyl]-2H-pyrazol-3-yl}-3-naphthalen-1-yl-urea as white power (45 mg). ^{1}H NMR (DMSO-d_6): 9.04 (s, 1H), 8.87 (s, 1H), 8.02 (d, J = 8.0 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H), 7.62 (d, J = 8.0 Hz, 2 H), 7.41-7.52 (m, 6 H), 6.40 (s, 1 H), 4.31-4.49 (dd, J = 8.0 Hz, 2 H), 4.03 (q, J = 6.8 Hz, 1 H), 1.27 (s, 9 H), 1.17 (d, J = 8.0 Hz, 3 H). MS (ESI) m/z: 547 (M+H$^+$).

Example FF



2-(4-methoxy-benzyl)-(R)-4-methyl-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one was prepared from D-alanine ethyl ester using the same procedure as Example EE.

Example 161

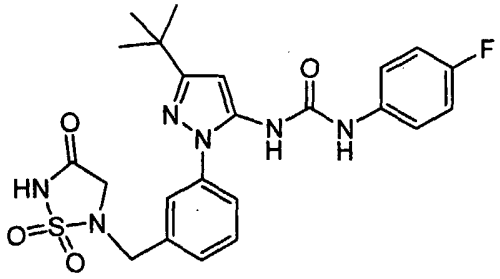


To a solution of Example FF (60 mg, 0.22 mmol) in anhydrous DMF (2 mL) was added NaH (11mg, 0.27 mmol) at 0 °C. After stirring for 0.5h at 0 °C, a solution of Example D (100 mg, 0.22 mmol) in anhydrous DMF (2 mL) was added to the reaction mixture, which was stirred overnight at RT. The crude reaction mixture was concentrated unjder reduced pressure and the residue by purified through preparative HPLC to yield 1-(5-t-butyl-2-{3-[5-(4-methoxy-benzyl)-(R)-3-methyl-1,1,4-trioxo-1λ^6-[1,2,5]-thiadiazolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-3-naphthalene-1-yl-urea (20 mg). ^{1}H NMR (DMSO-d_6): 8.98 (s, 1H), 8.81 (s, 1H), 8.00 (d, J = 8.0 Hz, 1 H), 7.90 (d, J = 7.2 Hz,2 H), 7.62(s, 2 H), 7.51-7.55 (m, 6H), 7.44 (d, J = 7.6 Hz, 2 H), 7.22 (d, J = 8.8 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 6.40 (s, 1H), 4.57-4.62 (dd, J = 8.0 Hz, 4 H), 4.53 (q,

J = 7.6 Hz, 1 H), 3.71 (s, 3H), 1.30 (d, J = 8.0 Hz, 3 H), 1.27 (s, 9 H). MS (ESI) m/z: 653 ($M+H^+$).

A solution of 1-(5-t-Butyl-2-{3-[5-(4-methoxy-benzyl)-(R)-3-methyl-1,1,4-trioxo-1λ^6-[1,2,5]- thiadiazolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-3-naphthalen-1-yl-urea (20 mg, 0.030 mmol) in trifluoroacetic acid (2 mL) was stirred at 50 °C for 4h. After the solvent was removed, the residue was purified by preparative-HPLC to afford 1-{5-t-butyl-2-[3-((R)-3-methyl-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl)-phenyl]-2H-pyrazol-3-yl}-3- naphthalen-1-yl-urea `as a white power (6 mg). ^{1}H NMR (DMSO-d_6): 8.99 (s, 1H), 8.80 (s, 1 H), 8.00 (d, J = 7.2 Hz, 1 H), 7.90 (d, J = 7.2 Hz, 2 H), 7.60-7.64 (m, 2 H), 7.44-7.54 (m, 7 H), 6.41 (s, 1 H), 4.31-4.49 (dd, J = 8.0 Hz, 2 H), 4.03 (q, J = 7.6 Hz, 1 H), 1.27 (s, 9 H), 1.19 (d, J = 8.0 Hz, 3 H). MS (ESI) m/z: 533 ($M+H^+$).

Example 162



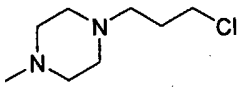
To a solution of Example CC (0.263 g, 1.0 mmol) in THF (2.0 mL) was added a solution of 1-fluoro-4-isocyanato-benzene (0.114 mL, 1.10 mmol) in THF (5.0 mL) at 0 °C. The mixture was stirred at RT for 1h then heated until all solids were dissolved. The mixture was stirred at RT for 3 h and poured into water (20 mL). The resulting precipitate was filtered, washed with diluted HCl and H_2O, dried under reduced pressure to yield 1-[5-t-butyl-2-(3-chloromethyl-phenyl)-2H-pyrazol-3-yl]-3-(4-fluoro-phenyl)-urea (400 mg) as a white power. ^{1}H NMR (DMSO-d_6): 8.99 (s, 1H), 8.38 (s, 1H), 7.59 (s, 1H), 7.44-7.51 (m, 3H), 7.38-7.40 (m, 2H), 7.08 (t, J = 8.8 Hz, 2H), 6.34 (s, 1H), 4.83 (s, 2H), 1.26 (s, 9H). MS (ESI) m/z: 401 ($M+H^+$).

To a solution of 2-(4-methoxy-benzyl)-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one (64 mg, 0.25 mmol) in anhydrous DMF (2 mL) was added NaH (11mg, 0.27 mmol) at 0 °C. After stirred for 0.5h at 0 °C, a solution of 1-[5-t-butyl-2-(3-chloromethyl-phenyl)-

2H-pyrazol-3-yl]-3- (4-fluoro-phenyl)-urea from the previous reaxtion (100 mg, 0.25 mmol) in anhydrous DMF (2 mL) was added to the reaction mixture, then was stirred overnight at RT. The crude was purified through prepared-HPLC to yield 1-(5-t-butyl-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-3-(4-fluoro- phenyl)-urea (45 mg). ^{1}H NMR (DMSO-d_6): 8.95 (s, 1H), 8.37 (s, 1H), 7.50-7.54 (m, 3H), 7.36-7.41 (m, 3H), 7.25 (d, J = 8.8 Hz, 2H), 7.07 (t, J = 8.8 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.35 (s, 1H), 4.64 (s, 2H), 4.47 (s, 2H), 4.19 (s, 2H), 3.75 (s, 3H), 1.26 (s, 9H). MS (ESI) m/z: 515 ($M+H^+$).

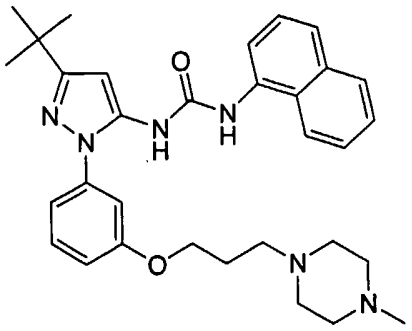
A solution of 1-(5-t-butyl-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1λ^6-[1,2,5]thiadia- zolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-3-(4-fluoro-phenyl)-urea (40 mg, 0.060 mmol) in trifluoroacetic acid (3 mL) was stirred at 50 °C for 4h. After the solvent was removed, the residue was purified by preparative HPLC to afford 1-{5-t-butyl-2-[3-(3-(R)-methyl-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl)-phenyl]-2H-pyrazol-3-yl}-3-naphthalen-1-yl-urea as a white power (12 mg). ^{1}H NMR (DMSO-d_6): 8.98 (s, 1 H), 8.39 (s, 1 H), 7.37-7.51 (m, 6 H), 7.07 (t, J = 8.8 Hz, 2 H), 6.35 (s, 1 H), 4.21 (s, 2 H), 3.88 (s, 2 H), 1.26 (s, 9 H). MS (ESI) m/z: 501 ($M+H^+$).

Example GG



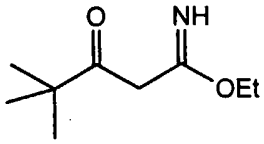
To a stirred suspension of K_2CO_3 (5.5 g, 40 mmol) and 1-bromo-3-chloro-propane (3.78 g, 24 mmol) in acetonitrile (10mL) was added a solution of N-methyl piperazine (2.0 g, 20 mmol) in acetonitrile (10mL) dropwise at RT. After the addition was completed, the reaction mixture was stirred for 3 h then filtered. The filtrate was concentrated and dissolved in CH_2Cl_2, washed with brine, dried ($NaSO_4$) and filtered. After removal of the solvent, the residue was dissolved in ether. To the above solution was added the solution of HCl and filtered to afford the desired product (2.3g, 65.7%). ^{1}H NMR (D_2O): 3.61 (t, J = 6.0 Hz, 2H), 3.59 (br, 8H), 3.31 (t, J = 8.0 Hz, 2H), 2.92 (s, 3H), 2.15 (m, 2H).

Example 163



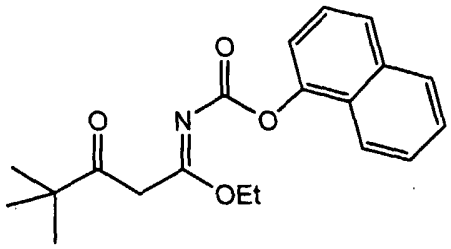
To a solution of Example 41 (100 mg, 0.25 mmol) in acetonitrile (10mL) was added Example GG (75 mg, 0.30 mmol) and K_2CO_3 (172 mg, 1.25 mmol). The resulting mixture was stirred at 45 °C for 3 h before filtered. After the filtrate was concentrated, the residue was purified by preparative TLC to afford 1-(5-t-Butyl-2-{3-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-2H-pyrazol-3-yl)-3-naphthalen-1-yl-urea (31mg, 23 %). ^{1}H-NMR (CD_3OD): 7.93 (m, 1H), 7.88 (m, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.43-7.50 (m, 4H), 7.14 (m, 2H), 7.05 (m, 1H), 6.43 (s, 1H), 4.10 (t, J = 6.0 Hz, 2H), 3.09-3.15 (br, 4H), 2.74-2.86(br, 6H), 2.72 (s, 3H), 1.99 (t, J = 6.8 Hz, 2H), 1.35 (s, 9H). MS (ESI) m/z: 541 ($M+H^+$).

Example HH



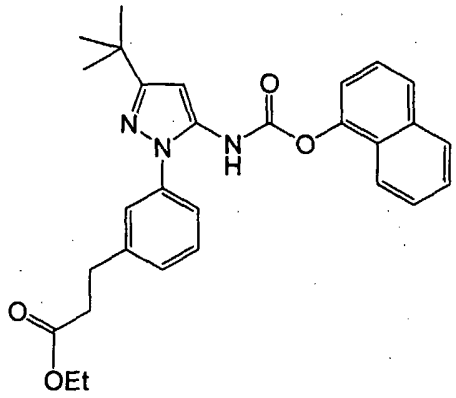
Intermediate HH was synthesized according to literature procedures starting from 4,4-dimethyl-3-oxo-pentanenitrile (10 mmole) in absolute ethanol and HCl in quantitative afford.

Example II



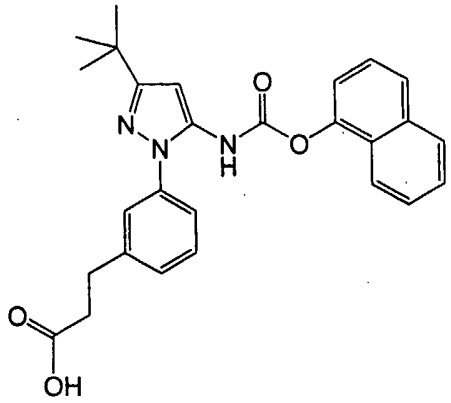
Intermediate HH (5 g, 0.0241 mol) is added to pyridine (5 mL) in CH_2Cl_2 (25 mL) and cooled in an ice bath. The suspension is stirred for 5 min and 1-napthylchloroformate is added dropwise over 5 min. The reaction mixture is stirred an additional 5 min at 0 °C, and the reaction is warmed and stirred at RT for 1 h. The reaction is pour into ethyl acetate (100 mL) and water (100 ml). After shaking, the aqueous layer is removed, the organic layer washed with water, dried ($MgSO_4$) and concentrated to afford (Z)-naphthalen-1-yl 1-ethoxy-4,4-dimethyl-3-oxopentylidenecarbamate.

Example 164



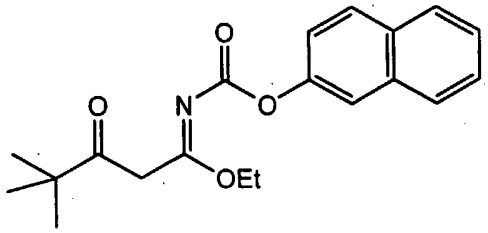
Example II (10 mmol) is dissolved in absolute EtOH (50 mL) at RT and Example Y (10.5 mmol) is added dropwise over 5 min. The reaction mixture is stirred for 30 min at RT, poured in water (100 mL) and ethyl acetate (100 mL). After shaking, the organic layer is washed with 5% HCl, water, dried ($MgSO_4$) and concentrated to afford 1-naphthyl 1-(3-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 165



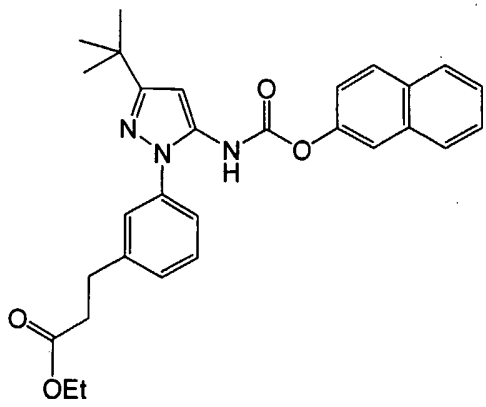
A solution of Example 164 (0.1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) is stirred at RT overnight. The reaction mixture is neutralized to pH = 4, extracted with ethyl acetate (3×20 mL), the combined organic extracts are washed with brine, dried ($NaSO_4$) and filtered. The filtrate is concentrated to afford 1-napthyl 1-(3-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example JJ



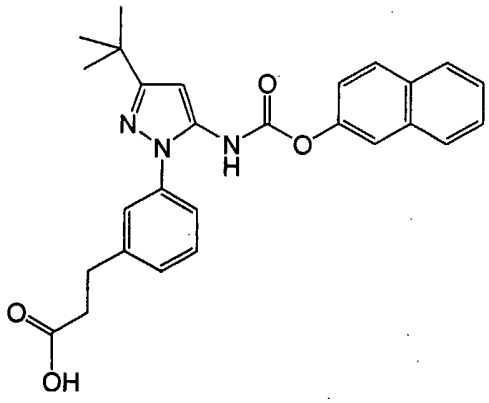
Example JJ is synthesized utilizing Example HH and 2-napthylchloroformate according to the procedure described for Example II to afford (Z)-naphthalen-2-yl-1-ethoxy-4,4-dimethyl-3-oxopentylidenecarbamate.

Example 166



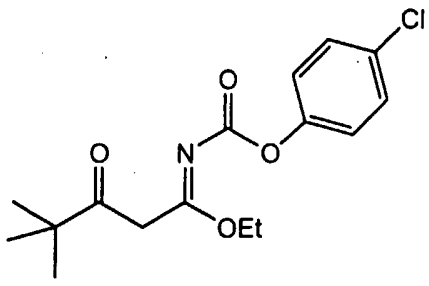
Example 166 is synthesized utilizing Example Y and Example JJ according to the procedure described for Example 79 to afford 2-naphthyl 1-(3-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 167



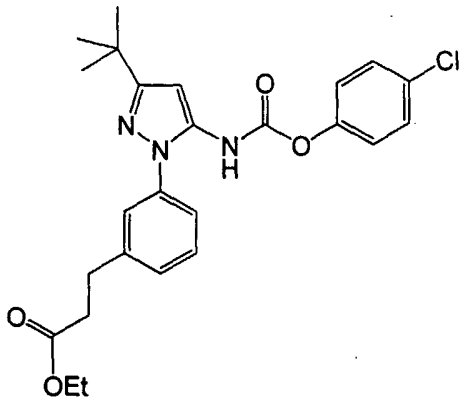
Example 167 is synthesized utilizing Example 166 according to the procedure described for Example 165 to afford 2-napthyl 1-(3-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example KK



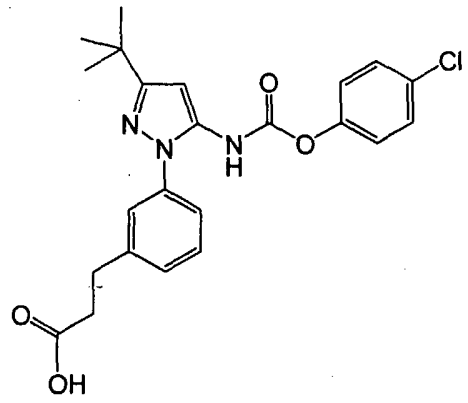
Example KK is synthesized utilizing Example HH and p-chlorophenylchloroformate according to the procedure described for Example II to afford (Z)-4-chlorophenyl 1-ethoxy-4,4-dimethyl-3-oxopentylidenecarbamate.

Example 168



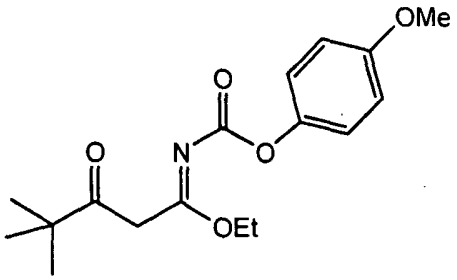
Example 168 is synthesized utilizing Example Y and Example KK according to the procedure described for Example 164 to afford 4-chlorophenyl 1-(3-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 169



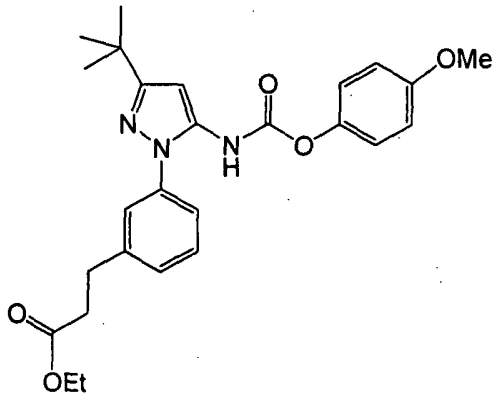
Example 169 is synthesized utilizing Example 168 according to the procedure described for Example 165 to afford 4-chlorophenyl 1-(3-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example LL



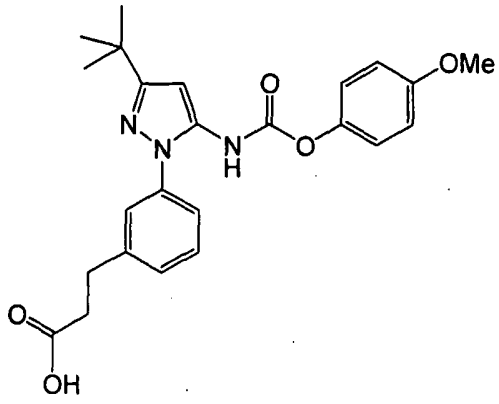
Example LL is synthesized utilizing Example HH and p-methoxyphenylchloroformate according to the procedure described for Example II to afford (Z)-4-methoxyphenyl 1-ethoxy-4,4-dimethyl-3-oxopentylidenecarbamate.

Example 170



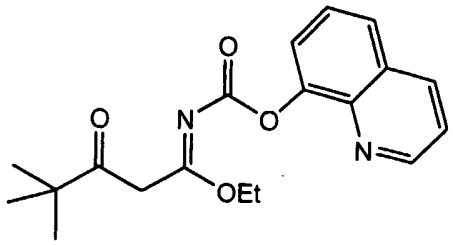
Example 170 is synthesized utilizing Example Y and Example LL according to the procedure described for Example 164 to afford 4-methoxyphenyl 1-(3-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 171



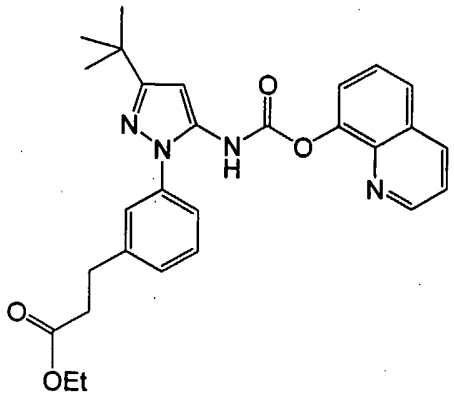
Example 171 is synthesized utilizing Example 170 according to the procedure described for Example 165 to afford 4-methoxyphenyl 1-(3-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example MM



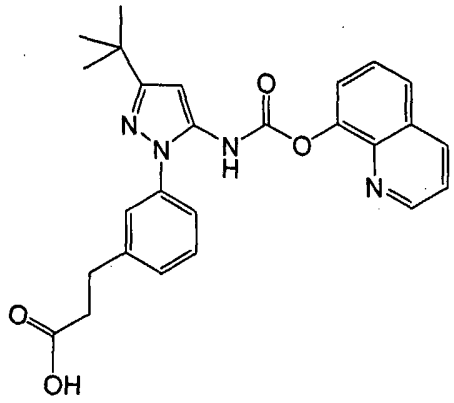
Example MM is synthesized utilizing Example HH and quinolin-8-yl-chloroformate according to the procedure described for Example II to afford (Z)-quinolin-8-yl 1-ethoxy-4,4-dimethyl-3-oxopentylidenecarbamate

Example 172



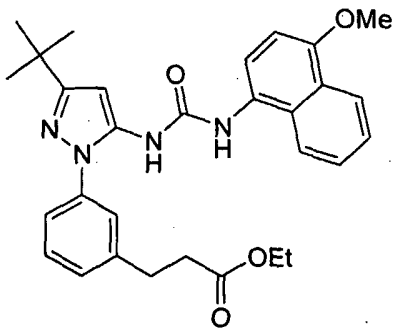
Example 172 is synthesized utilizing Example Y and Example MM according to the procedure described for Example 164 to afford quinolin-8-yl 1-(3-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 173



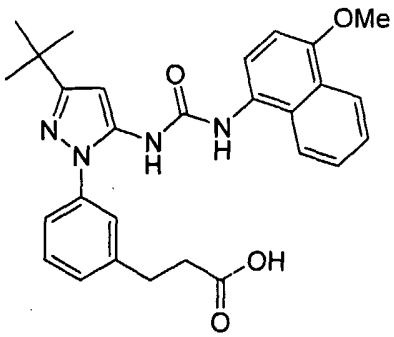
Example 173 is synthesized utilizing Example 172 according to the procedure described for Example 165 to afford quinolin-8-yl 1-(3-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 174



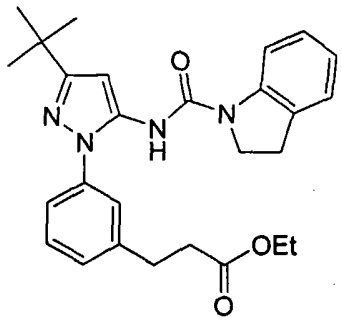
Example 174 is synthesized utilizing a mixture of 4-methoxy-1-naphthylamine and Example Z according to the procedure described for Example 147 to afford 3-(3-{3-t-butyl-5-[3-(4-methoxy-1-naphthyl)-ureido]-pyrazol-1-yl}-phenyl)-propionic acid ethyl ester.

Example 175



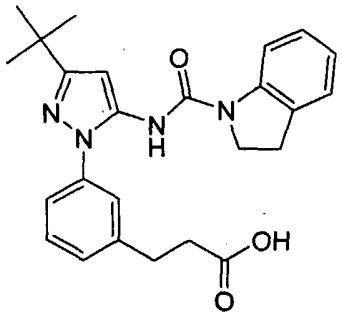
Utilizing the same synthetic procedure as for Example 146 and starting with Example 174, 3-(3-{3-t-butyl-5-[3-(4-methoxy-1-naphthtyl)-ureido]-pyrazol-1-yl}-phenyl)-propionic acid is synthesized.

Example 176



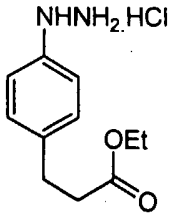
Example 176 is synthesized utilizing a mixture of indoline and Example Z according to the procedure described for Example 147 to afford ethyl 3-(3-(3-t-butyl-5-(indoline-1-carboxamido)-1H-pyrazol-1-yl)phenyl)propanoate.

Example 177



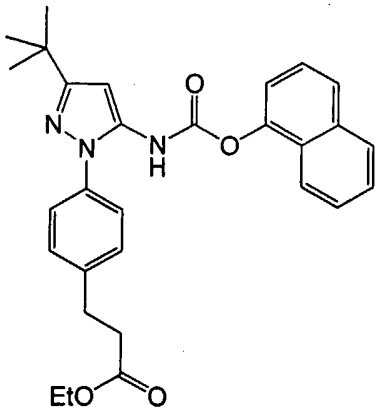
Utilizing the same synthetic procedure as for Example 146 and starting with Example 173, 3-(3-(3-t-butyl-5-(indoline-1-carboxamido)-1H-pyrazol-1-yl)phenyl) propionic acid is synthesized.

Example NN



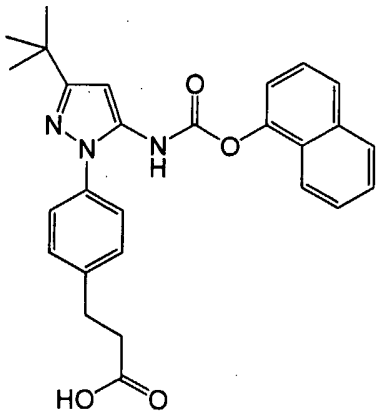
Utilizing the same synthetic procedure as for Example Y and starting with p-bromo nitrobenzene, 3-(4-hydrazino-phenyl)-propionic acid ethyl ester is synthesized.

Example 178



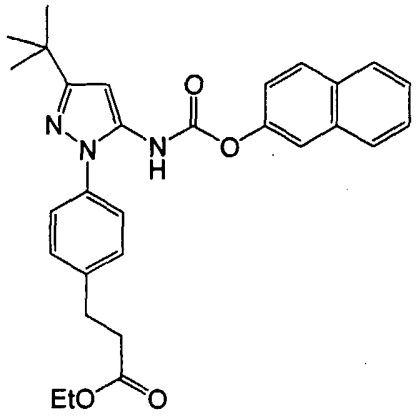
Utilizing the same synthetic procedure as for Example 164, Example II (10 mmol) and Example NN (10.5 mmol) are combined to afford 1-naphthyl 1-(4-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 179



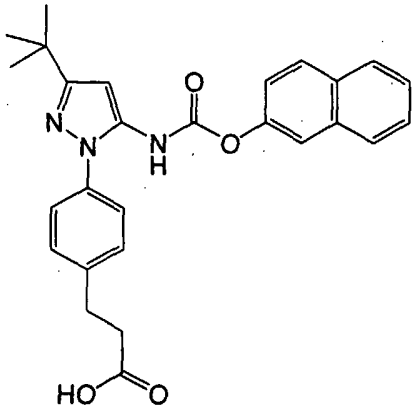
Example 179 is synthesized utilizing Example 178 according to the procedure described for Example 165 to afford 1-napthyl 1-(4-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 180



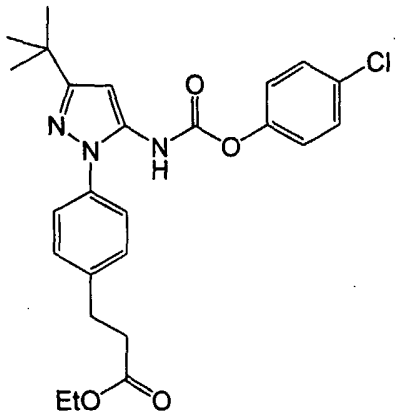
Utilizing the same synthetic procedure as for Example 164, Example JJ (10 mmol) and Example NN (10.5 mmol) are combined to afford 2-naphthyl 1-(4-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 181



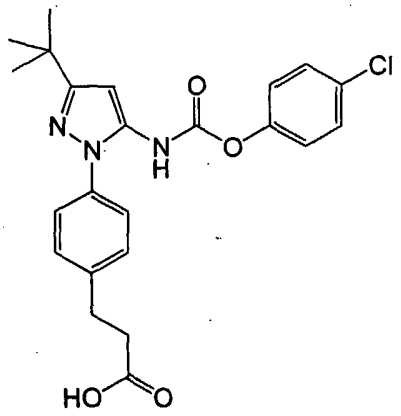
Example 181 is synthesized utilizing Example 180 according to the procedure described for Example 165 to afford 2-napthyl 1-(4-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 182



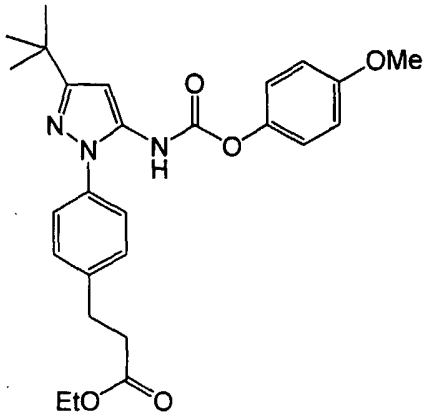
Utilizing the same synthetic procedure as for Example 164, Example KK (10 mmol) and Example NN (10.5 mmol) are combined to afford p-chlorophenyl 1-(4-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 183



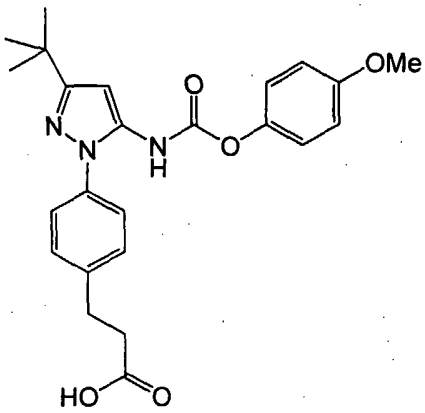
Example 183 is synthesized utilizing Example 182 according to the procedure described for Example 165 to afford 4-chlorophenyl 1-(4-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 184



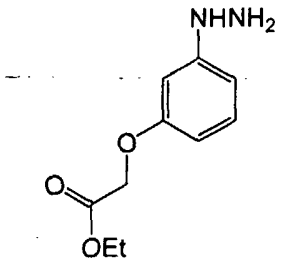
Utilizing the same synthetic procedure as for Example 164, Example LL (10 mmol) and Example NN (10.5 mmol) are combined to afford p-methoxyphenyl 1-(4-(2-(ethoxycarbonyl)ethyl)phenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example 185



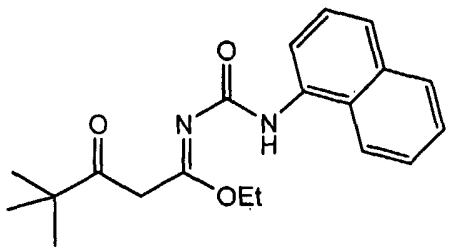
Example 185 is synthesized utilizing Example 184 according to the procedure described for Example 165 to afford p-methoxyphenyl 1-(4-(2-carboxyethylphenyl)-3-t-butyl-1H-pyrazol-5-ylcarbamate.

Example OO



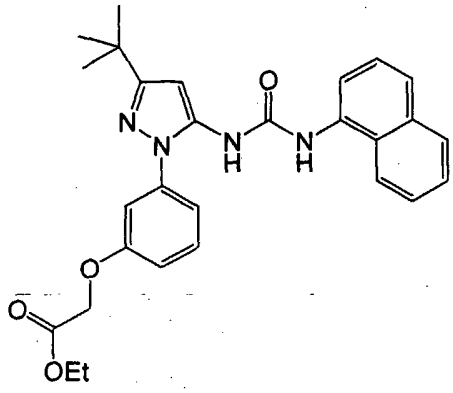
Ethyl bromoacetate is reacted with meta-nitrophenol under standard conditions to afford ethyl 2-(3-nitrophenoxy)acetate, which is elaborated to ethyl 2-(3-hydrazinophenoxy)acetate using the reduction/oxidation sequence described for Example Y.

Example PP



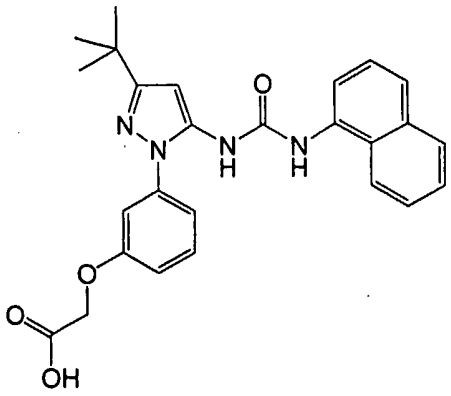
Example HH and 1-naphthylisocyanate are combined utilizing the same synthetic procedure as for Example II to afford (Z)-1-(1-ethoxy-4,4-dimethyl-3-oxopentylidene)-3-(naphthalen-1-yl)urea.

Example 186



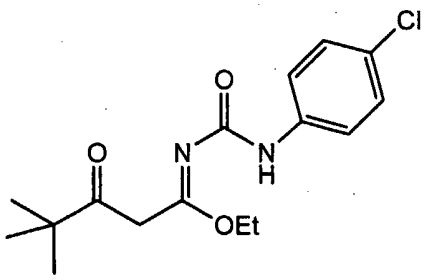
Utilizing the same synthetic procedure as for Example 164, Example PP (10 mmol) and Example OO (10.5 mmol) are combined to afford 3-(3-{3-t-butyl-5-[3-(1-naphthyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid ethyl ester.

Example 187



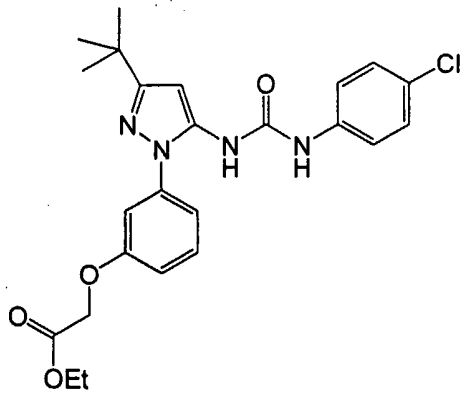
Utilizing the same synthetic procedure as for Example 146 and starting with Example 186, 3-(3-{3-t-butyl-5-[3-(1-naphthyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid is synthesized.

Example QQ



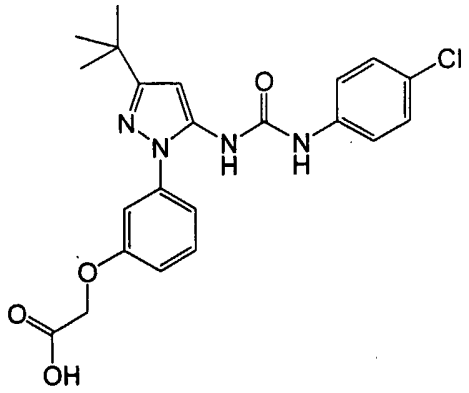
Example HH and 4-chlorophenylisocyanate are combined utilizing the same synthetic procedure as for Example II to afford (Z)-1-(4-chlorophenyl)-3-(1-ethoxy-4,4-dimethyl-3-oxopentylidene)urea

Example 188



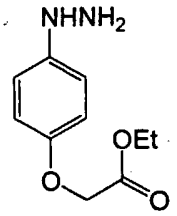
Utilizing the same synthetic procedure as for Example 164, Example QQ (10 mmol) and Example OO (10.5 mmol) are combined to afford 3-(3-{3-t-butyl-5-[3-(1-4-chlorophenyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid ethyl ester.

Example 189



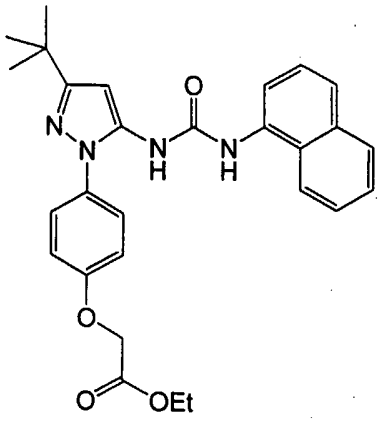
Utilizing the same synthetic procedure as for Example 146 and starting with Example 188, 3-(3-{3-t-butyl-5-[3-(14-chlorophenyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid is synthesized.

Example RR



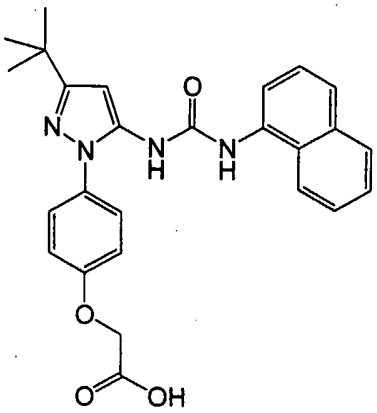
Ethyl bromoacetate is reacted with para-nitrophenol under standard conditions to afford ethyl 2-(4-nitrophenoxy)acetate, which is elaborated to ethyl 2-(4-hydrazinophenoxy)acetate using the reduction/oxidation sequence described for Example Y.

Example 190



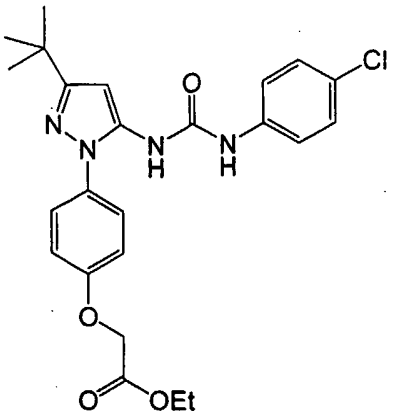
Utilizing the same synthetic procedure as for Example 164, Example PP (10 mmol) and Example RR (10.5 mmol) are combined to afford 4-(3-{3-t-butyl-5-[3-(1-naphthyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid ethyl ester.

Example 191



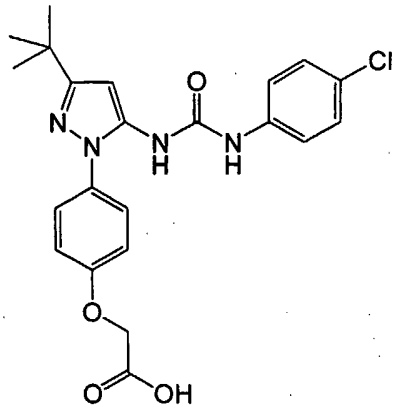
Utilizing the same synthetic procedure as for Example 146 and starting with Example 190, 4-(3-{3-t-butyl-5-[3-(1-naphthyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid is synthesized.

Example 192



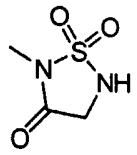
Utilizing the same synthetic procedure as for Example 164, Example QQ (10 mmol) and Example RR (10.5 mmol) are combined to afford 4-(3-{3-t-butyl-5-[3-(1-4-chlorophenyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid ethyl ester.

Example 193



Utilizing the same synthetic procedure as for Example 146 and starting with Example 192, 4-(3-{3-t-butyl-5-[3-(14-chlorophenyl)-ureido]-pyrazol-1-yl}-phenoxy)-acetic acid is synthesized.

Example DD



To a stirred solution of chlorosulfonyl isocyanate (1.43 g, 10.0 mmol) in CH_2Cl_2 (20 mL) at 0°C was added 2-methyl-propan-2-ol (0.74 g, 10.0 mmol) at such a rate that the reaction solution temperature did not rise above 5°C. After being stirred for 1.5 h, a solution of glycine ethyl ester (1.45 g, 12.0 mmol) and Et_3N (3.2 mL, 25.0 mmol) in CH_2Cl_2 (20 mL) was added at such a rate that the reaction temperature didn't rise above 5°C. When the addition was completed, the solution was warmed to RT and stirred overnight. The reaction mixture was poured into 10% HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl, dried (Mg_2SO_4) and filtered. After removal of the solvent, the crude product was washed with CH_2Cl_2 to afford ethyl 2-((N-(butyloxycarbonyl)sulfamoyl)amino)acetate (2.4 g, 85 %). ^{1}H-NMR(DMSO): δ 10.85 (s, 1H), 8.04 (t, J = 6.0 Hz, 1H), 4.07 (q, J = 5.6 Hz, 2H), 3.77 (d, J = 6.0 Hz, 2H), 1.40 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H).

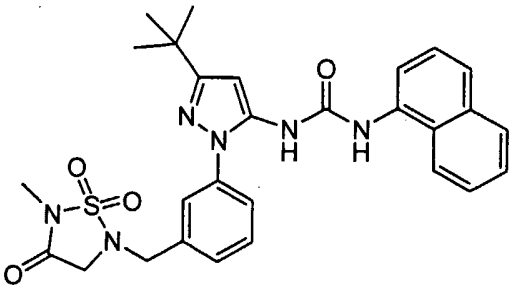
To a solution of methanol (8.5 mmol) and triphenylphosphine (2.6 g, 8.5 mol) in dry THF is added a solution of ethyl 2-((N-(butyloxycarbonyl)sulfamoyl)amino)acetate from the previous step (2.4 g, 8.5 mol) and DIAD (2.0 g, 8.5 mmol) in dry THF dropwise at 0 °C under N_2 atmosphere. The mixture is stirred at 0 °C for 2 h, warmed to RT and is stirred overnight. After the solvent is removed in *vacuo,* the residue is purified by column chromatography to afford ethyl 2-((N-(butyloxycarbonyl)-N-methylsulfamoyl)amino)acetate.

To a solution of HCl in methanol (2 M) is added ethyl 2-((N-(butyloxycarbonyl)-N-methylsulfamoyl)amino)acetate from the previous step (5.0 mmol) in portions at RT and the mixture is stirred for 3 h. After the solvent is removed in *vacuo*, the residue is washed with diethyl ether to afford ethyl 2-((N-methylsulfamoyl)amino)acetate

To a solution of ethyl 2-((N-methylsulfamoyl)amino)acetate from the previous step (3.5 mmol) in DMF (50 mL) is added KO-t-Bu (1.56 g, 13.88 mmol) in portions under N_2 at RT. The mixture is stirred overnight then quenched with HCl/ methanol (2 M). After the solvent is removed in *vacuo,* the residue is washed with water to afford 2-methyl-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one (480 mg, 54 %). ^{1}H-NMR($CDCl_3$): δ

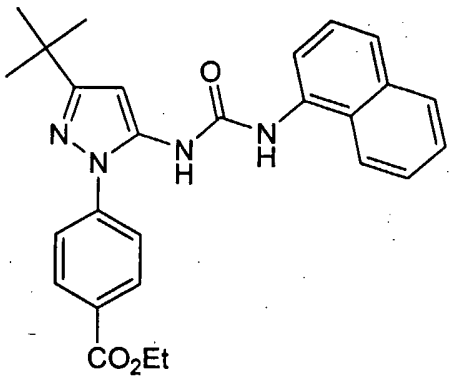
7.36 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.87 (m, 1H), 4.68 (s, 2H), 4.03 (d, J = 7.2 Hz, 2H), 3.80 (s, 3H).

Example 194



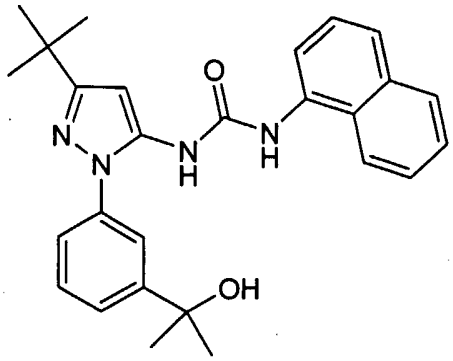
Example E and Example OO are combined utilizing the procedure for Example 160 to afford 1-(5-t-butyl-2-{3-[5-methyl-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-3-naphthyl-urea.

Example 195



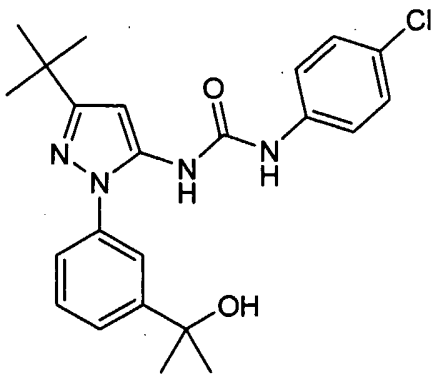
To a solution of Example X (2.9 g, 10 mmol) in THF (50 mL) was added a solution of 1-naphthyl isocyanate (1.7 g, 10 mmol) in THF (20 mL) at 0 °C. The mixture was stirred at RT for 1 h and heated until all solids dissolved. The mixture was then stirred at RT for 3 h and poured into water (200 mL). The precipitate was filtered, washed with diluted HCl and H_2O, dried under vacuum to give 4.3 g of 4-[3-t-butyl-5-(3-naphthalen-1-yl-ureido)-pyrazol- 1-yl]-benzoic acid ethyl ester, which was used without further purification.

Example 196



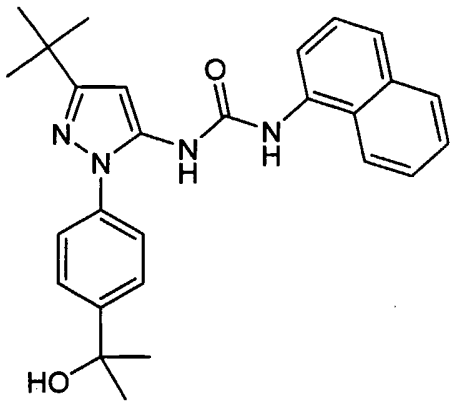
To a solution of Example B (228 mg, 0.5 mmol) in dry THF (20 mL) was added dropwise a solution of methyl magnesium bromide in toluene/THF (3.6 mL, 5.0 mmol) at –78 °C under N_2. After stirring for 1 h, the mixture was allowed to rise to RT and stirred for another 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and aqueous HCl solution (10%), extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), the solvent removed in *vacuo* and the residue purified by column chromatography to afford 1-{5-t-butyl-2-[3-(1-hydroxy-1-methyl-ethyl)-phenyl]-2H-pyrazol-3-yl}-3-naphthalen-1-yl-urea (150 mg, 67 %). ^1H NMR (DMSO-d6): 9.00 (s, 1H), 8.75 (s, 1 H), 7.98 (d, J = 7.6 Hz, 1 H), 7.92-7.89 (m, 2 H), 7.65-7.62 (m, 2 H), 7.52-7.44 (m, 5 H), 7.37 (d, J = 6.8 Hz, 1 H), 6.39 (s, 1 H), 5.13 (s, 1 H), 1.45 (s, 6 H), 1.27 (s, 9 H); MS (ESI) m/z: 443 ($M+H^+$).

Example 197



To a solution of Example C (220 mg, 0.5 mmol) in dry THF (20 mL) was added dropwise a solution of methyl magnesium bromide in toluene/THF (3.6 mL, 5.0 mmol) at –78 °C under N_2. After stirring for 1 h, the mixture was allowed to rise to RT and stirred for another 2 h. The reaction mixture was quenched with saturated NH_4Cl and aqueous HCl solution (10 %), and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), the solvent was removed in *vacuo* and the residue was purified by column chromatography to afford 1-{5-t-butyl-2-[3-(1-hydroxy-1-methyl-ethyl)-phenyl]- 2H-pyrazol-3-yl}-3-(4-chloro-phenyl)-urea (174 mg, 81 %). ^1H NMR (DMSO-d6): 9.11 (s, 1 H), 8.34 (s, 1 H), 7.59 (s, 1H), 7.46 (t, J = 8.8 Hz, 1 H), 7.43-7.40 (m, 3 H), 7.31-7.28 (m, 3 H), 6.34 (s, 1 H), 5.13 (s, 1 H), 1.42 (s, 6H), 1.27 (s, 9 H); MS (ESI) m/z: 428 ($M+H^+$).

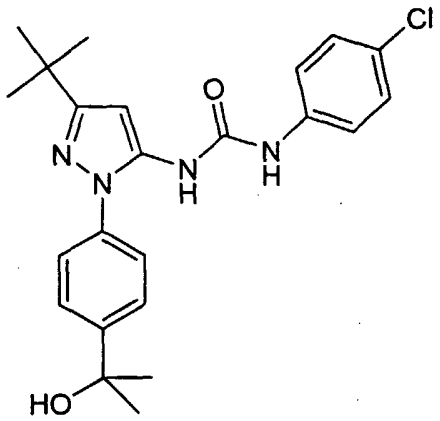
Example 198



To a solution of Example 195 (228 mg, 0.5 mmol) in dry THF (20 mL) was added dropwise a solution of methylmagnesium bromide in toluene/THF (3.6 mL, 5.0 mmol) at –78 °C under N_2. After stirring for 1 h, the mixture was allowed to rise to RT and stirred for another 2 h. The reaction mixture was quenched with saturated NH_4Cl and aqueous HCl solution (10%), extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), the solvent was removed in *vacuo* and the residue purified by column chromatography to afford 1-{5-t-butyl-2-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-2H-pyrazol-3-yl}-3-naphthalen-1-yl-urea (180 mg, 81 %). ^1H NMR (DMSO-d6): 9.06 (s, 1H), 8.83 (s, 1 H), 7.99 (d, J = 8.0 Hz, 1 H), 7.92 (t, J = 8.0 Hz,

2H), 7.64-7.61 (m, 3H), 7.55-7.43 (m, 5H), 6.40 (s, 1H), 5.13 (s, 1H), 1.47 (s, 6H), 1.27 (s, 9 H); MS (ESI) m/z: 443 ($M+H^+$).

Example 199

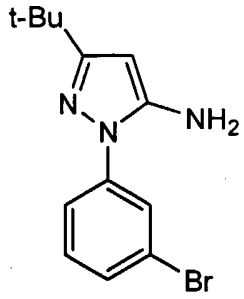


To a solution of Example 57 (220 mg, 0.5 mmol) in dry THF (20 mL) was added dropwise a solution of methyl magnesium bromide in toluene/THF (3.6 mL, 5.0 mmol) at –78 °C under N_2. After stirring for 1 h, the mixture was allowed to rise to RT and stirred for another 2 h. The reaction mixture was quenched with saturated NH_4Cl and aqueous HCl solution (10 %), and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), the solvent removed in *vacuo* and the residue was purified by column chromatography to afford 1-{5-t-butyl-2-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]- 2H-pyrazol-3-yl}-3-(4-chloro-phenyl)-urea (187 mg, 87 %). ^{1}H-NMR ($CDCl_3$): 9.14 (s, 1 H), 8.42 (s, 1H), 7.58 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 5.6 Hz, 2 H), 7.40 (d, J = 4.8 Hz, 2 H), 7.29 (d, J = 8.8 Hz, H), 6.34 (s, 1 H), 5.11 (s, 1 H), 1.44 (s, 6 H), 1.25 (s, 9 H); MS (ESI) m/z: 427 ($M+H^+$).

Example PP

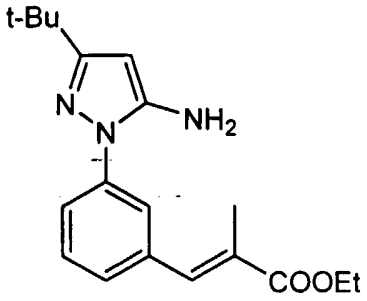
To a solution of 3-bromo-phenylamine (17 g, 0.1 mol) in concentrated HCl (200 mL) was added an aqueous solution (20 mL) of $NaNO_2$ (7 g, 0.1 mol) at 0 °C and the resulting mixture was stirred for 1 h. A solution of $SnCl_2.2H_2O$ (45 g, 0.2 mmol) in concentrated HCl (500 mL) was then added at 0 °C. The reaction solution was stirred for an additional 2 h at RT. The precipitate was filtered and washed with ethanol and ether to give (3-bromo-phenyl)-hydrazine as a white solid, which was used for the next reaction without further purification

Example QQ



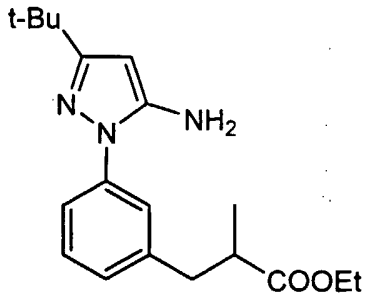
A mixture of Example PP (22.2 g, 0.1 mol) and 4,4-dimethyl-3-oxo-pentanenitrile (18.7 g, 0.15 mol) in ethanol (250 mL) was heated to reflux overnight. The reaction solution was concentrated under reduced pressure, and the residue purified by column chromatography to afford 2-(3-bromo-phenyl)-5-t-butyl-2H-pyrazol-3-ylamine as a white solid. ^{1}H NMR (DMSO-d_6): 7.85 (s, 1H), 7.68 (d, J =7.6 Hz, 1H), 7.62 (d, J =7.2 Hz, 1H), 7.50 (t, J =8.0 Hz, 1H), 5.62 (s, 1H), 1.27 (s, 9H).

Example RR



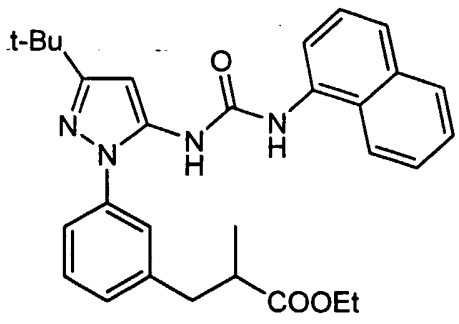
To a mixture of Example QQ (2.94 g, 10 mmol), $Pd(OAc)_2$ (1 mmol), PPh_3 (20 mmol), and K_2CO_3 (20 mmol) in MeCN (50 mL) was added 2-methyl-acrylic acid ethyl ester (20 mmol). The resulting mixture was heated to reflux overnight, filtered, concentrated, and the residue was purified by column chromatography to afford 1.2 g of 3-[3-(5-Amino-3-t-butyl-pyrazol-1-yl)-phenyl]- 2-methyl-acrylic acid ethyl ester. ^1H NMR ($CDCl_3$): 7.41 (s, 1H), 7.40-7.36 (m, 2H), 7.15 (d, J = 6.8 Hz, 1H), 6.24 (s, 1H), 5.51 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 2.12 (s, 3H), 1.33 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H).

Example SS



A mixture of Example RR (1.2 g,) and Pd / C (120 mg, 10 %) in methanol (50 mL) was stirred under 40 psi of H_2 at RT overnight, filtered. And concentrated to afford 3-[3-(5-amino-3-t-butyl-pyrazol-1-yl)-phenyl]-2-methyl-propionic acid ethyl ester as a racemate (1.1 g), which was used for the next reaction without further purification.

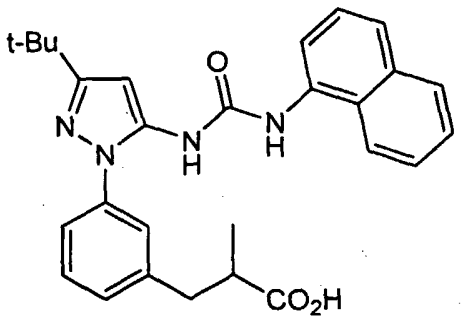
Example 200



To a solution of Example SS (100 mg, 0.3 mmol) and Et_3N (60 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) was added 1-isocyanato-naphthalene (77 mg, 0.45 mmol). The resulting

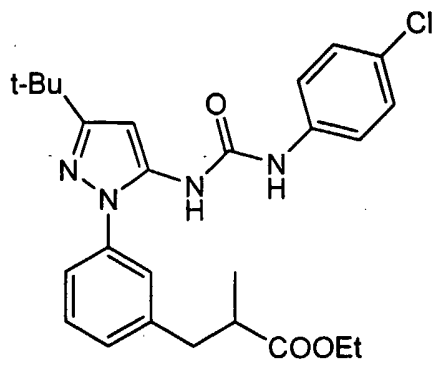
mixture was stirred at RT overnight, added to water (50 mL), extracted with CH_2Cl_2 (3x30 mL) and the combined organic extracted were washed with brine, dried (Na_2SO_4), and filtered. After concentration under reduced pressure, the residue was purified by preparative-TLC to afford 3-(3-{3-*t*-butyl-5-[3-(4-fluoro-phenyl)-ureido]-pyrazol-1-yl}-phenyl)-propionic acid ethyl ester as a racemate (50 mg, 33 %). ^{1}H-NMR ($CDCl_3$): 7.99 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.84 (t, J = 7.2 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.49-7.41 (m, 3H), 7.35-7.33 (m, 3H), 7.21 (s, 1H), 7.14-7.13 (m, 1H), 6.65 (s, 1H), 3.98 (q, J = 6.0 Hz, 2H), 2.92-2.88 (m, 3H), 1.36 (s, 9H), 1.24 (d, J = 6.0 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H); MS (ESI) m/z: 499 ($M+H^+$).

Example 201



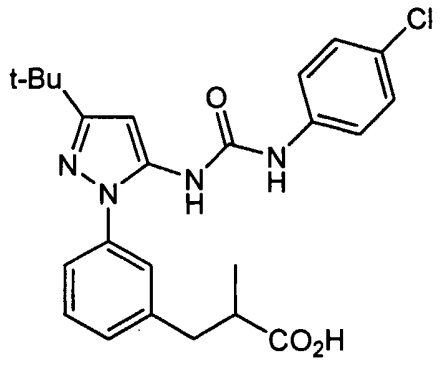
A solution of Example 200 (17 mg, mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT over night. The reaction mixture was adjusted to pH = 4, and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered. After the filtrate was concentrated, the residue was purified by preparative-TLC to afford 3-{3-[3-t-butyl-5-(3-naphthalen-1-yl-ureido)-pyrazol-1-yl]-phenyl}-2-methyl-propionic acid as a racemate (15 mg, 92 %). ^{1}H NMR (DMSO): 11.81 (br s, 1H), 9.58 (s, 1H), 8.56 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.45-7.35 (m, 5H), 7.28 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.52 (s, 1H), 3.77 (m, 1H), 2.65 (m, 1H), 2.36 (m, 1H), 1.27 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H); MS (ESI) m/z: 471 ($M+H^+$).

Example 202



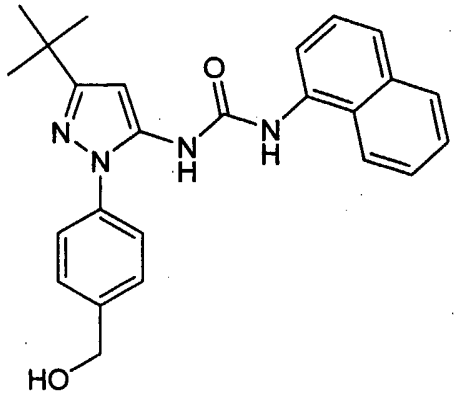
To a solution of Example SS (100 mg, 0.3 mmol) and Et_3N (60 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) was added 1-chloro-4-isocyanato-benzene (77 mg, 0.45 mmol). The resulting mixture was stirred at RT overnight, and then added to water (50 mL). The solution was extracted with CH_2Cl_2 (3x30 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4),and filtered. After concentration under reduced pressure, the residue was purified by preparative-TLC to afford 3-(3-{3-t-butyl-5-[3-(4-chloro-phenyl)-ureido]-pyrazol-1-yl}-phenyl)-2-methyl- propionic acid ethyl ester as a racemate (51 mg, 35 %). ^{1}H-NMR ($CDCl_3$): 8.20 (s, 1H), 7.39 (d, J = 4.4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.21 (t, J = 8.4 Hz, 2H), 7.14-7.11 (m, 2H), 6.59 (s, 1 H), 4.04-3.99 (m, 2H), 3.00 (m, 1H), 2.93 (m, 1H), 2.83 (m, 1H), 1.34 (s, 9H), 1.17 (d, J = 6.4 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); MS (ESI) m/z: 483 ($M+H^+$).

Example 203



A solution of Example 202 (15 mg, mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT overnight. The reaction mixture was adjusted to pH = 4, extracted with ethyl acetate (3×20 mL), the combined organic extracts were washed with brine, dried (Na_2SO_4),and filtered. After the filtrate was concentrated, the residue was purified by preparative-TLC to afford 3-(3-{3-t-butyl-5-[3-(4-chloro-phenyl)- ureido]-pyrazol-1-yl}-phenyl)-2-methyl-propionic acid as a racemate (13 mg, 90%). ^{1}H NMR (DMSO): 12.48 (br s, 1H), 9.35 (br s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.34-7.32 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 7.6 Hz, 1H), 6.45 (s, 1H), 2.74 (m, 1H), 2.65 (m, 1H), 2.31 (m, 2H), 1.26 (s, 9H), 0.99 (d, J = 6.8 Hz, 3H); MS (ESI) m/z: 455 ($M+H^+$).

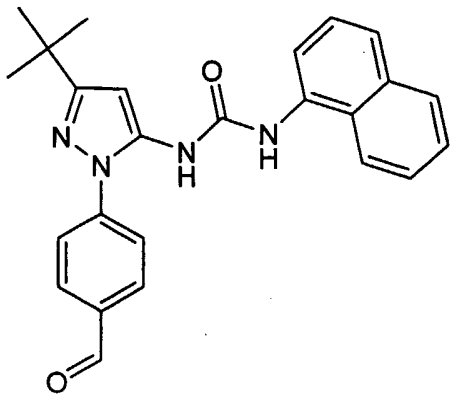
Example 204



To a stirred solution of Example 195 (500 mg, 0.83 mmol) in THF (10 mL) was added $LiAlH_4$ powder (65 mg, 1.66 mmol) in portion at 0 °C under N_2. The mixture was stirred for 2 h at RT, excess $LiAlH_4$ was destroyed by a slow addition of ice, and the reaction mixture was acidified to pH = 7 with dilute HCl. After the solvent was removed, the residue was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered. After concentration *in vacuo*, the crude product was purified by preparative-TLC to afford 1-[2-(4-hydroxymethyl-phenyl)- 5-isopropyl-2H-pyrazol-3-yl]-3-naphthalen-1-yl-urea (415 mg, 92 %). ^{1}H NMR (DMSO-d6): 9.04 (s, 1H), 8.78 (s, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.90 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 8.4

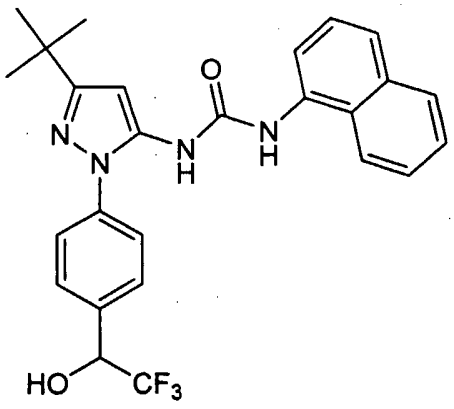
Hz, 1 H), 7.55-7.42 (m, 7 H), 6.39 (s, 1 H), 5.30 (t, J = 5.6 Hz, 1 H), 4.56 (d, J = 5.6 Hz, 2 H), 1.27 (s, 9 H); MS (ESI) m/z: 415 ($M+H^+$).

Example 205



To a solution of Example 204 (200 mg) in CH_2Cl_2 (50 mL) was added MnO_2 (450 mg) at RT. The suspension was stirred for 2 h then filtered through celite. The filtrate was concentrated under reduced pressure to afford 150 mg of 1-[5-t-butyl-2-(4-formyl-phenyl)-2H-pyrazol-3-yl]-3-naphthalen-1-yl- urea, which was used without further purification.

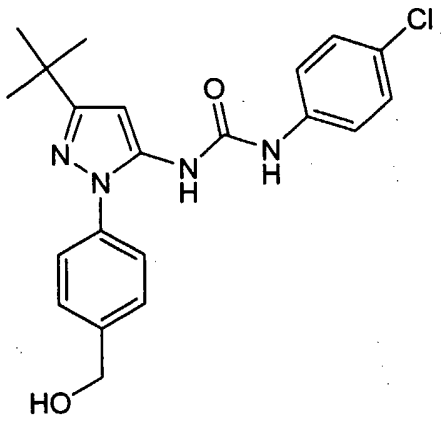
Example 206



To a solution of (trifluoromethyl)trimethylsilane (77 mg) and TBAF (10 mg) in THF (10 mL) was added Example 205 (150 mg) in THF (10 mL) under N_2 atmosphere in ice-bath. The resulting mixture was stirred at 0 °C for 1 h and then warmed to RT for an

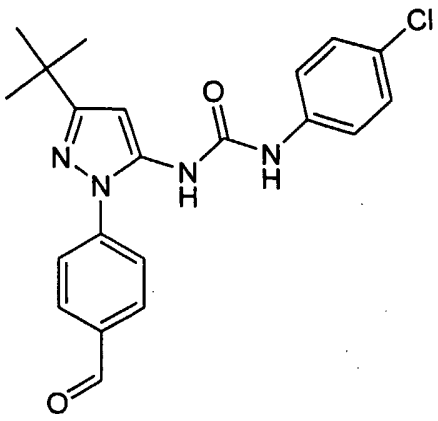
additional hour. To the reaction was then added 0.5 mL of 3 N HCL, which was then stirred at RT overnight. After removal the solvent, the residue was dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. After the filtrate was concentrated under reduced pressure, the residue was purified by preparative-TLC to afford the final product 1-{5-t-Butyl-2-[4-(2,2,2-trifluoro-1-hydroxy- ethyl)-phenyl]-2H-pyrazol-3-yl}-3-naphthalen-1-yl-urea (110 mg, 63 %). ^{1}H NMR (DMSO-d_6): 9.07 (s, 1H), 8.89 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.67-7.62 (m, 5H), 7.55-7.51 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 6.0 Hz, 1H), 6.42 (s, 1H), 5.27 (m, 1H), 1.28 (s, 9H). MS (ESI) m/z: 483 ($M+H^+$).

Example 207



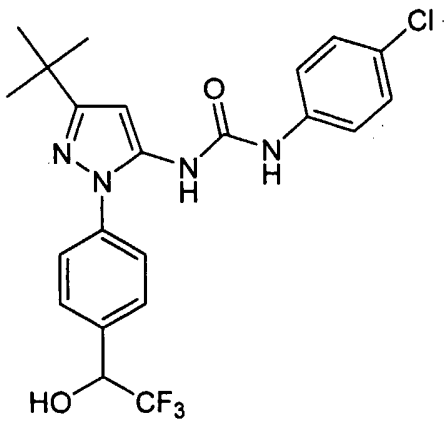
To a stirred solution of Example 57 (500 mg, 1.1 mmol) in THF (10 mL) was added $LiAlH_4$ powder (65 mg, 1.66 mmol) in portion at 0 °C under N_2. The mixture was stirred for 2 h at RT, excess $LiAlH_4$ was destroyed by a slow addition of ice, and the reaction mixture was acidified to pH = 7 with diluted HCl. After the solvent removal, the residue was extracted with ethyl acetate, and the combined organic extracts were washed with brine, d dried (Na_2SO_4), and filtered, After solvent removal, the crude product was purified by preparative TLC to 1-[5-t-butyl-2-(4-hydroxymethyl-phenyl)-2H-pyrazol-3-yl]-3-(4-chloro-phenyl)-urea (380 mg, 92%) as a white powder. ^{1}H-NMR ($CDCl_3$): 8.17 (br s, 1 H), 7.22 (s, 4 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.09 (d, J = 8.0 Hz, 2 H), 7.04 (s, H), 6.38 (s, 1 H), 4.51 (s, 1 H), 1.22 (s, 9 H); MS (ESI) m/z: 399 ($M+H^+$).

Example 208



To a solution of Example 207 (200 mg) in CH_2Cl_2 (50 mL) was added MnO_2 (450 mg) at RT. The suspension was stirred for 2 h, then filtered through celite. The filtrate was concentrated to afford 160 mg of 1-[5-t-butyl-2-(4-formyl-phenyl)-2H-pyrazol-3-yl]-3-(4-chloro-phenyl)-urea, which was used without further purification.

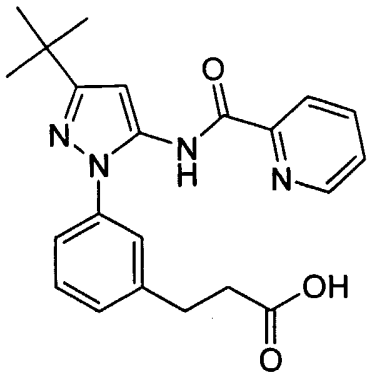
Example 209



To a solution of (trifluoromethyl)trimethylsilane (86 mg) and TBAF (10 mg) in THF (10 mL) was added Example 208 (160 mg) in THF (20 mL) under N_2 atmosphere in ice-bath. The resulting mixture was stirred at 0 °C for 1 h and then warmed to RT for an additional hour. To the reaction was added 0.5 mL of 3 N HCl, which was then stirred at RT overnight. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (100 mL). The organic extracts were washed with saturated $NaHCO_3$ and brine, dried

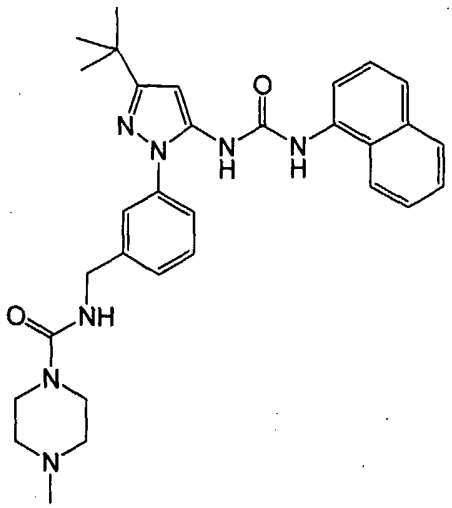
(Na_2SO_4), and filtered. After the filtrate was concentrated under reduced pressure, the residue was purified by preparative-TLC to afford the final product 1-{5-t-butyl-2-[4-(2,2,2-trifluoro-1- hydroxy-ethyl)-phenyl]-2H-pyrazol-3-yl}-3-(4-chloro-phenyl)-urea (120 mg, 64 %). ^{1}H-NMR (DMSO-d6): 9.15(s, 1H), 8.50 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2 H), 7.28 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 5.6 Hz, 1 H), 6.36 (s, 1 H), 5.25 (m, 1H), 1.26 (s, 9 H); MS (ESI) m/z: 467 ($M+H^+$).

Example 210



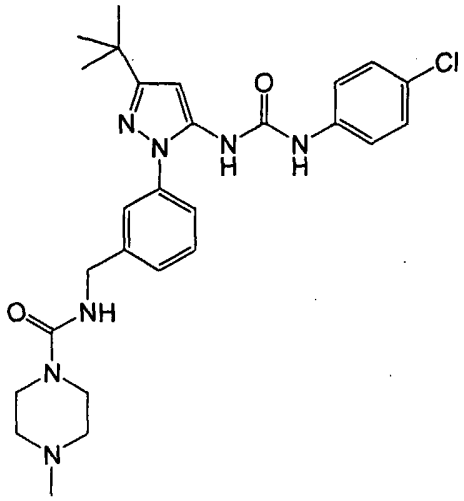
A solution of Example 151 (42 mg, 0.1 mmol) and 2N LiOH (3 mL) in MeOH (3 mL) was stirred at RT over night. The reaction mixture was neutralized to pH = 4, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated to afford 3-(3-{3-t-butyl-5-[(pyridine-2-carbonyl)-amino]-pyrazol-1-yl}-phenyl)-propionic acid (30 mg, 76%). 8.45 (d, 4.0 Hz, 1H), 8.24 (d, 8.0 Hz, 1H), 7.92 (s, 1H), 7.88 (t, 7.6 Hz, 1H), 7.67 (d, 8.0 Hz, 1H), 7.36 (t, 5.6 Hz, 1H), 7.23 (t, 7.6 Hz , 1H), 6.96 (d, 6.8 Hz, 1H), 6.67 (s , 1H), 2.77 (t, 7.6 Hz, 2H), 2.22 (t, 7.6 Hz, 2H), 1.26 (s, 9H); MS (ESI) m/z: 393 ($M+H^+$).

Example 211



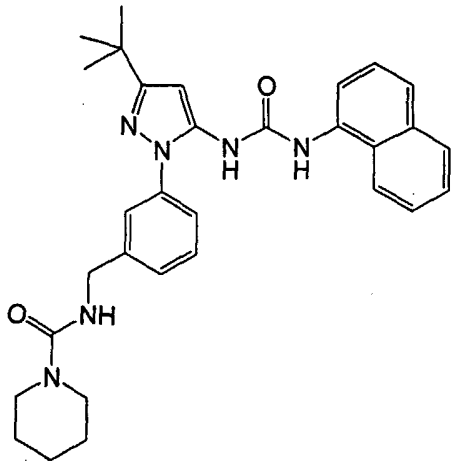
Example I is reacted with CDI and N-methyl piperazine using the procedure for Example 145 to afford the title compound.

Example 212



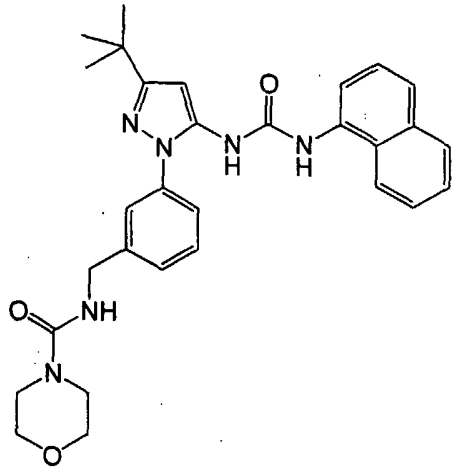
Example J is reacted with CDI and N-methyl piperazine using the procedure for Example 145 to afford the title compound.

Example 213



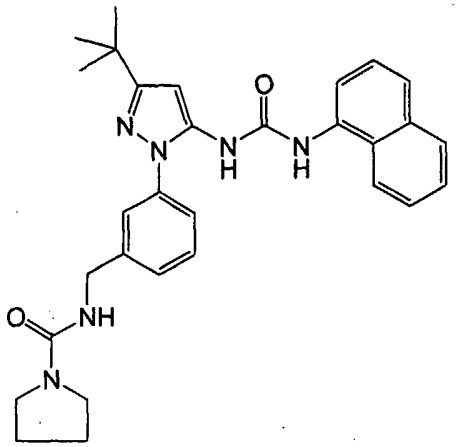
Example I is reacted with CDI and piperdine using the procedure for Example 145 to afford the title compound.

Example 214



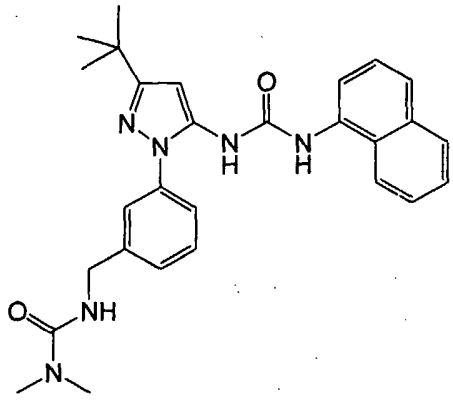
Example I is reacted with CDI and morpholine using the procedure for Example 145 to afford the title compound.

Example 215



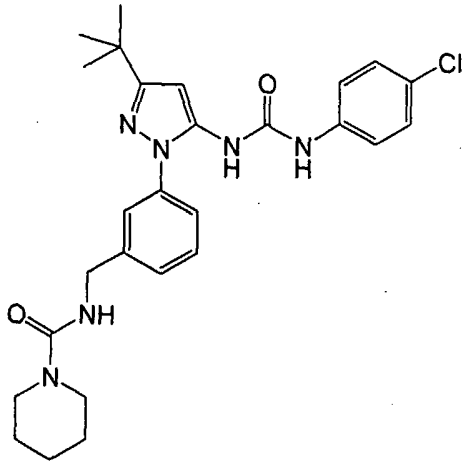
Example I is reacted with CDI and pyrrolidine using the procedure for Example 145 to afford the title compound.

Example 216



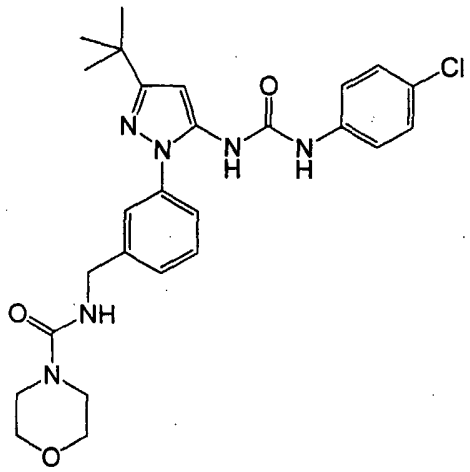
Example I is reacted with CDI and dimethylamine using the procedure for Example 145 to afford the title compound.

Example 217



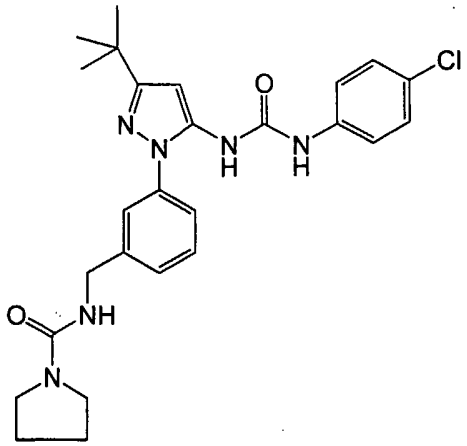
Example J is reacted with CDI and piperdine using the procedure for Example 145 to afford the title compound.

Example 218



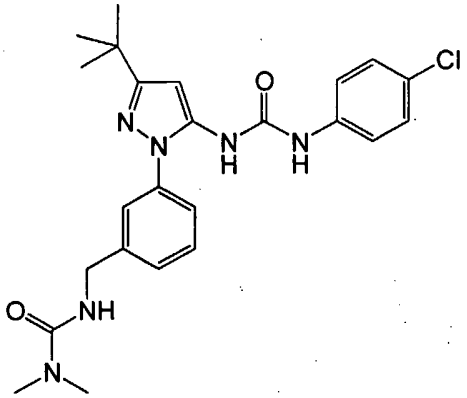
Example J is reacted with CDI and morpholine using the procedure for Example 145 to afford the title compound.

Example 219



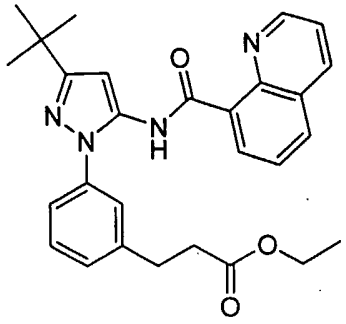
Example J is reacted with CDI and pyrrolidine using the procedure for Example 145 to afford the title compound.

Example 220



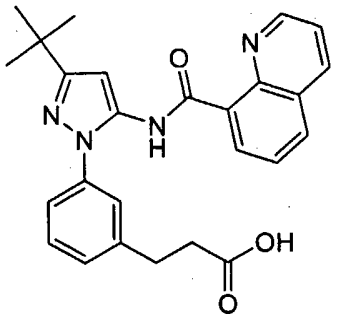
Example J is reacted with CDI and dimethylamine using the procedure for Example 145 to afford the title compound.

Example 221



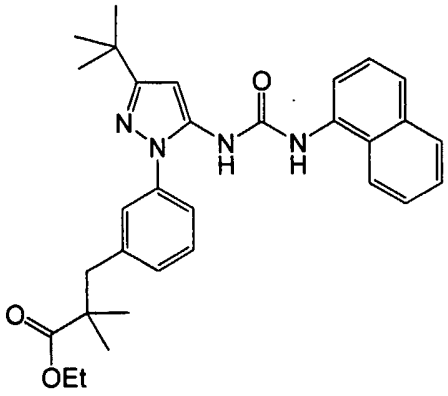
Isoquinoline-8-carboxylic acid and Example Z are reacted using the procedure for Example 149 to afford ethyl 3-(3-(3-t-butyl-5-(quinoline-8-carboxamido)-1H-pyrazol-1-yl)phenyl)propanoate.

Example 222



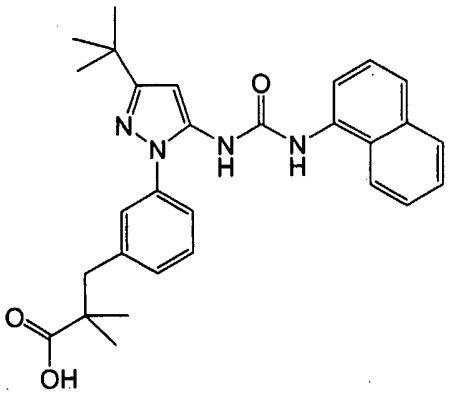
Example 222 is reacted using the procedure for Example 150 to afford 3-(3-(3-t-butyl-5-(quinoline-8-carboxamido)-1H-pyrazol-1-yl)phenyl)propanoic acid.

Example 223



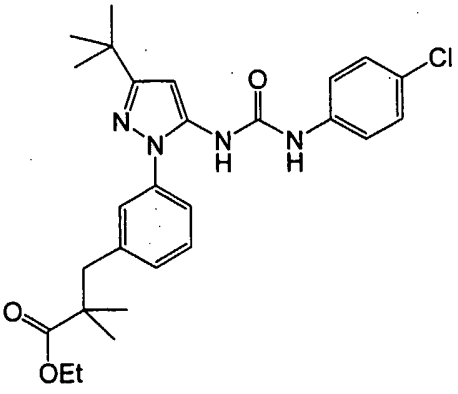
Example E is reacted with (1-ethoxy-2-methylprop-1-enyloxy)trimethylsilane under literature conditions to afford ethyl 2-(3-(3-t-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoate.

Example 224



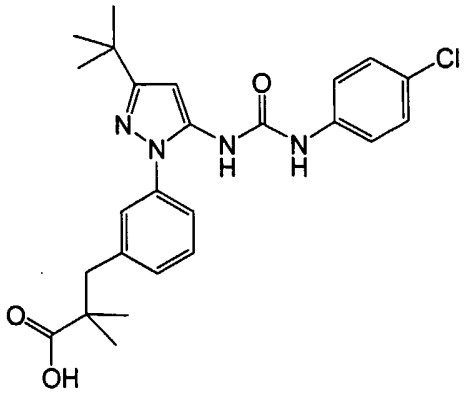
Example 224 is reacted using the procedure for Example 150 to afford 2-(3-(3-t-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoic acid

Example 225



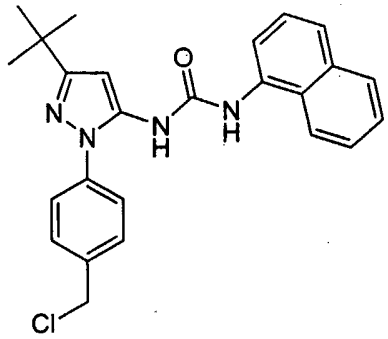
Example G is reacted with (1-ethoxy-2-methylprop-1-enyloxy)trimethylsilane under literature conditions to afford ethyl 2-(3-(3-t-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoate.

Example 226



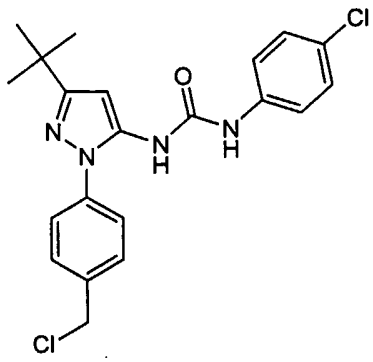
Example 226 is reacted using the procedure for Example 150 to afford 2-(3-(3-t-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoic acid.

Example TT



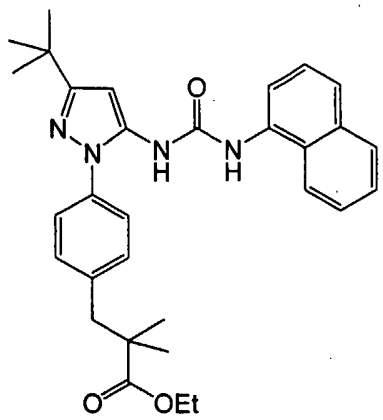
Example 204 is reacted using the procedure for Example E to afford 1-(3-t-butyl-1-(4-(chloromethyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea

Example UU



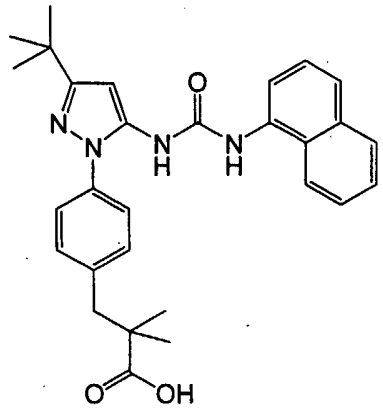
Example 122 is reacted using the procedure for Example G to afford 1-(3-t-butyl-1-(4-(chloromethyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example 227



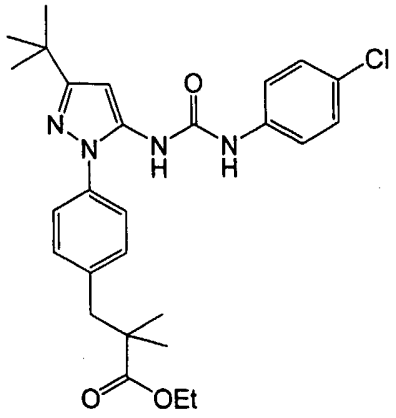
Example TT is reacted with (1-ethoxy-2-methylprop-1-enyloxy)trimethylsilane under literature conditions to afford ethyl 2-(4-(3-t-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoate.

Example 228



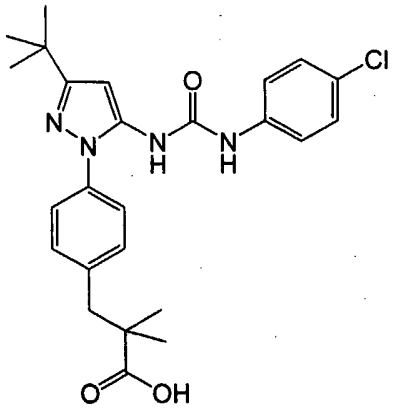
Example 227 is reacted using the procedure for Example 150 to afford 2-(4-(3-t-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoic acid.

Example 229



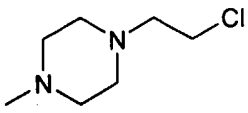
Example UU is reacted with (1-ethoxy-2-methylprop-1-enyloxy)trimethylsilane under literature conditions to afford ethyl 2-(4-(3-t-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoate

Example 230



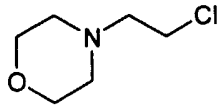
Example 144 is reacted using the procedure for Example 150 to afford 2-(4-(3-t-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)benzyl)-2-methylpropanoic acid.

Example VV



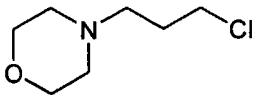
N-methyl piperazine and 1-bromo-2-chloroethane are reacted using the procedure for Example OO to afford 1-(2-chloroethyl)-4-methylpiperazine hydrochloride.

Example WW



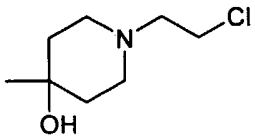
Morpholine and 1-bromo-2-chloroethane are reacted using the procedure for Example OO to afford 4-(2-chloroethyl)morpholine

Example XX



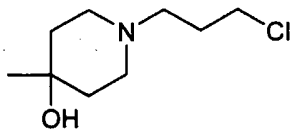
Morpholine and 1-bromo-3-chloropropane are reacted using the procedure for Example OO to afford 4-(3-chloropropyl)morpholine.

Example YY



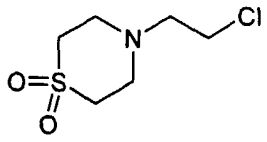
4-methylpiperidin-4-ol (made via literature methods) and 1-bromo-2-chloroethane are reacted using the procedure for Example OO to afford 1-(2-chloroethyl)-4-methylpiperidin-4-ol.

Example ZZ



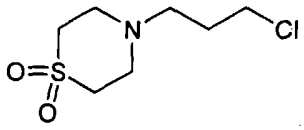
4-methylpiperidin-4-ol (made via literature methods) and 1-bromo-3-chloropropane are reacted using the procedure for Example OO to afford 1-(3-chloropropyl)-4-methylpiperidin-4-ol.

Example AAA



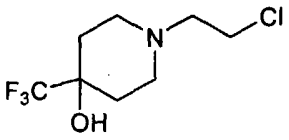
A solution of 4,4-dioxothiomorpholine and 1-bromo-2-chloroethane are reacted using the procedure for Example OO to afford 4-(2-chloroethyl)-4,4-dioxo-4-thiomorpholine.

Example BBB



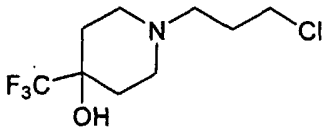
A solution of 4,4-dioxothiomorpholine and 1-bromo-3-chloropropane are reacted using the procedure for Example OO to afford 4-(3-chloropropyll)-4,4-dioxo-4-thiomorpholine.

Example CCC



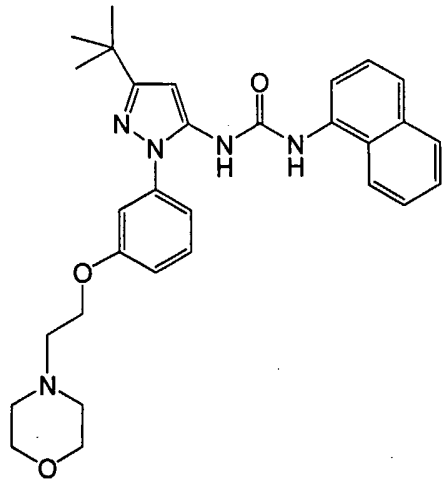
A solution of 4-(trifluoromethyl)piperidin-4-ol and 1-bromo-2-chloroethane are reacted using the procedure for Example OO to afford 1-(2-chloroethyl)-4-(trifluoromethyl)piperidin-4-ol.

Example DDD



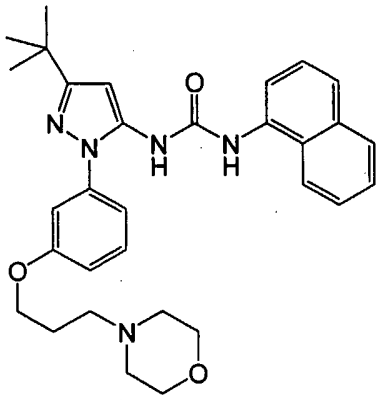
A solution of 4-(trifluoromethyl)piperidin-4-ol and 1-bromo-3-chloropropane are reacted using the procedure for Example OO to afford 1-(3-chloropropyll)-4-(trifluoromethyl)piperidin-4-ol.

Example 231



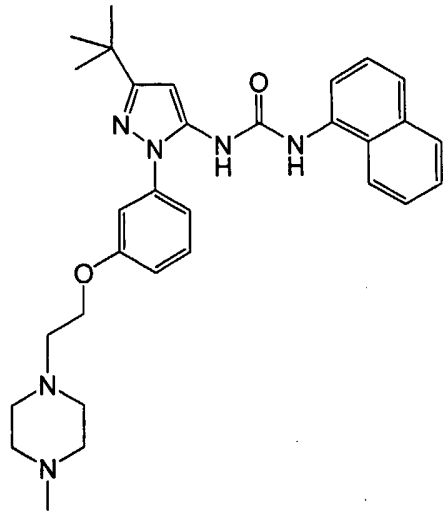
Example 41 and Example WW are reacted according to the procedure for Example 194 to afford 1-(1-(3-(2-morpholinoethoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 232



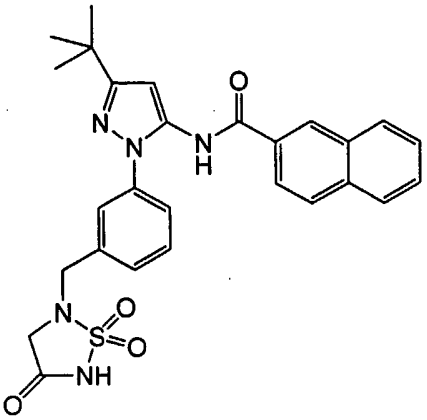
Example 41 and Example XX are reacted according to the procedure for Example 194 to afford 1-(1-(3-(3-morpholinopropoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 233



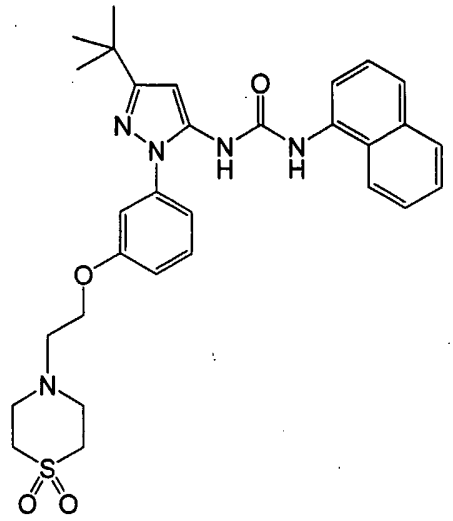
Example 41 and Example VV are reacted according to the procedure for Example 194 to afford 1-(1-(3-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 234



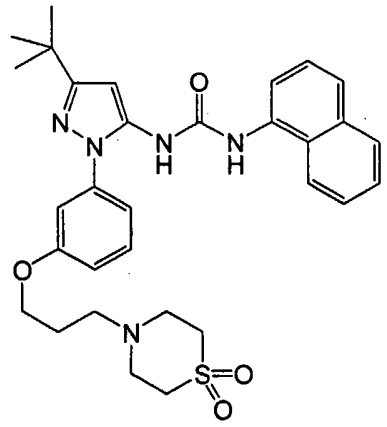
Example CC, 2-naphthoic acid chloride and Example DD were combined utilizing the same general approach for Example 162 to yield N-(3-tert-butyl-1-(3-([5-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl]phenyl)-1H-pyrazol-5-yl)-2-naphthamide. ^{1}H-NMR (DMSO-d_6): 10.50 (s, 1H), 8.45 (s, 1H), 8.15-8.05 (m, 3H), 7.90 (s, 1H), 7.60 (t, J = 7.2 Hz, 3H), 7.45 (s, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 6.44 (s, 1H), 4.05 (s, 2H), 1.31 (s, 9H). MS (ESI) m/z: 518 ($M+H^+$).

Example 235



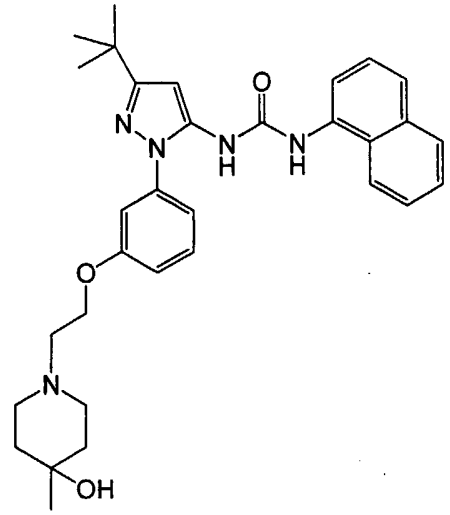
Example 41 and Example AAA are reacted according to the procedure for Example 194 to afford 1-(1-(3-(2-(4,4-dioxo-4-thio-morpholino)ethoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 236



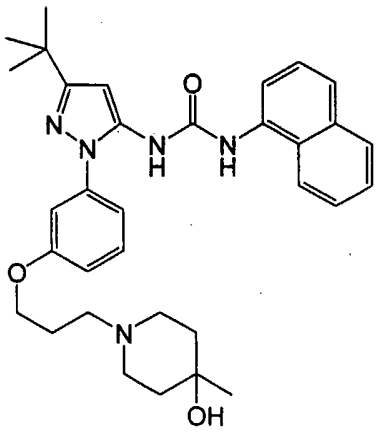
Example 41 and Example BBB are reacted according to the procedure for Example 194 to afford 1-(1-(3-(2-(4,4-dioxo-4-thio-morpholino)propoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 237



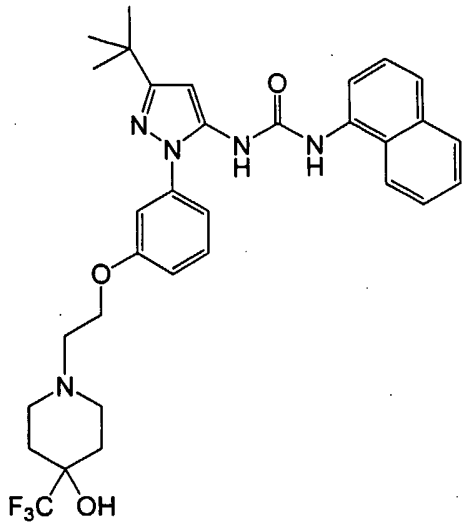
Example 41 and Example YY are reacted according to the procedure for Example 194 to afford 1-(1-(3-(2-(4-methylpiperidin-4-ol)ethoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 238



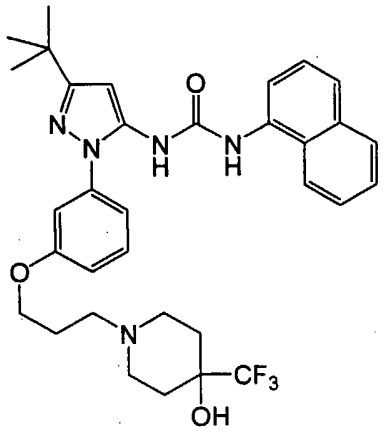
Example 41 and Example ZZ are reacted according to the procedure for Example 194 to afford 1-(1-(3-(3-(4-methylpiperidin-4-ol-)propoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 239



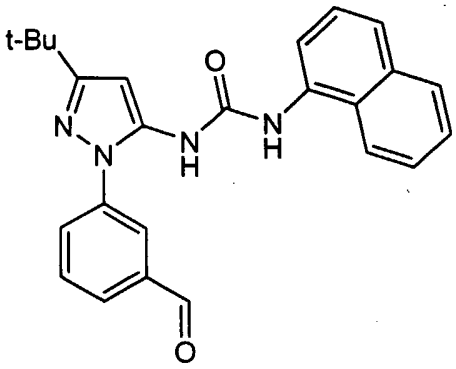
Example 41 and Example CCC are reacted according to the procedure for Example 194 to afford 1-(1-(3-(2-(4-(trifluoromethyl)piperidin-4-ol)ethoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 240



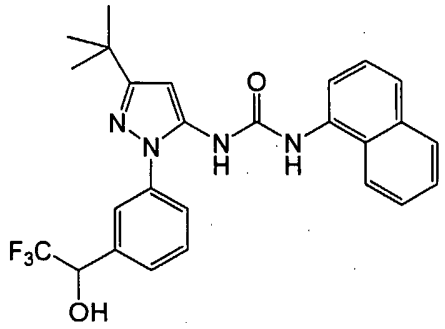
Example 41 and Example DDD are reacted according to the procedure for Example 194 to afford 1-(1-(3-(3-(4-(trifluoromethyl)piperidin-4-ol)propoxy)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 241



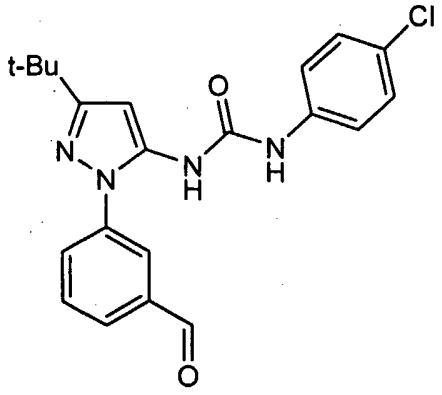
Example D is reacted using the procedure for Example 205 to afford 1-(3-t-butyl-1-(3-formylphenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 242



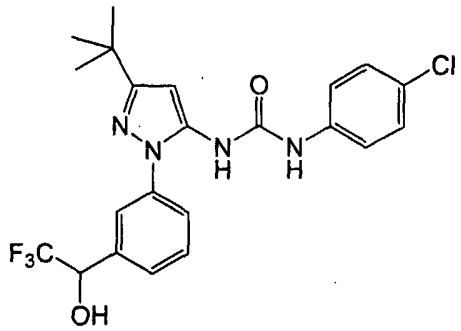
Example 242 is reacted using the procedure for Example 206 to afford 1-(3-t-butyl-1-(3-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 243



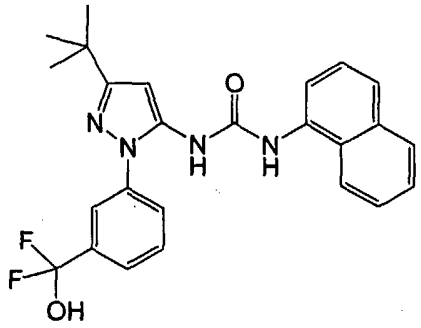
Example F is reacted using the procedure for Example 208 to afford 1-(3-t-butyl-1-(3-formylphenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example 244



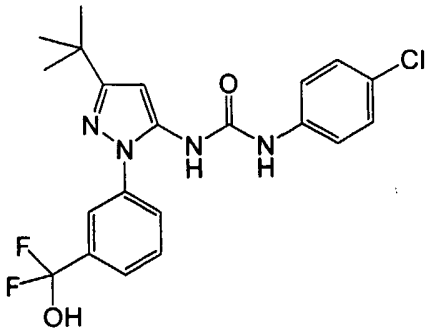
Example 244 is reacted using the procedure for Example 209 to afford 1-(3-t-butyl-1-(3-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea

Example 245



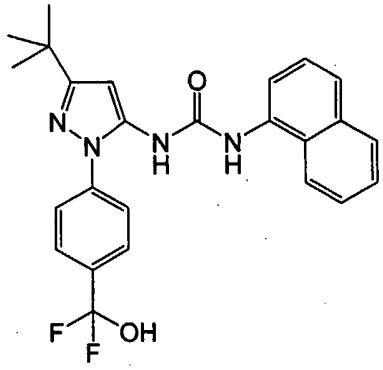
Example B is saponified using the procedure for Example 150. The resulting acid is reacted with trifluorotriazine in pyridine to afford the acid fluoride which is directly reacted with CsF and TBAF according to literature procedures (see J. Org. Chem. USSR (Engl. Transl.), 11, 1975, 315-317) to afford 1-(3-t-butyl-1-(3-(difluoro(hydroxy)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 246



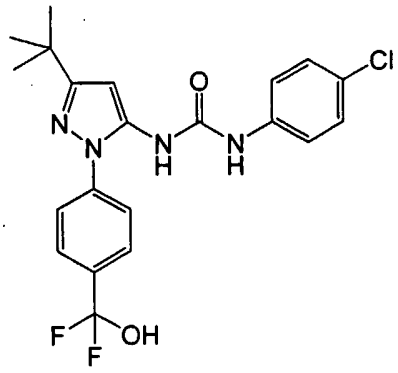
Example C is reacted according to the procedure for Example 245 to afford 1-(3-t-butyl-1-(3-(difluoro(hydroxy)methyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example 247



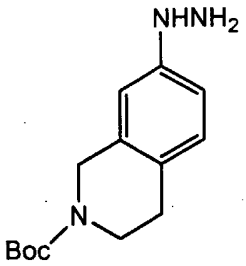
Example 205 is reacted according to the procedure for Example 245 to afford 1-(3-t-butyl-1-(4-(difluoro(hydroxy)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 248



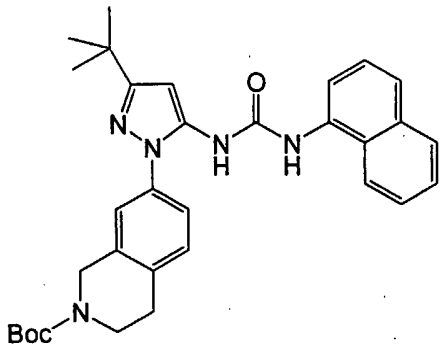
Example 57 is reacted according to the procedure for Example 245 to afford 1-(3-t-butyl-1-(4-(difluoro(hydroxy)methyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example EEE



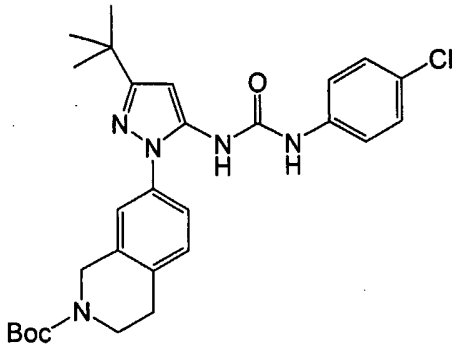
Example EEE (tert-butyl 7-hydrazinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate) was synthesized according to literature procedures.

Example 249



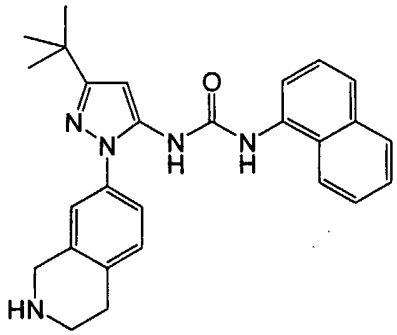
Utilizing the same synthetic procedure as for Example 164, Example EEE (10 mmol) and Example PP (10.5 mmol) are combined to afford t-butyl 7-(3-t-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate.

Example 250



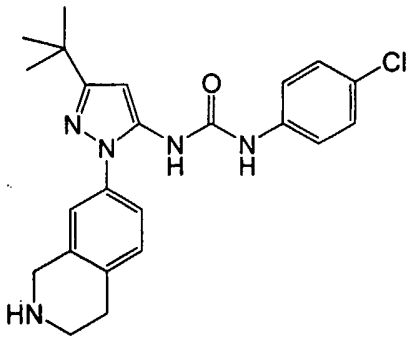
Utilizing the same synthetic procedure as for Example 164, Example EEE (10 mmol) and Example QQ (10.5 mmol) are combined to afford t-butyl 7-(3-t-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

Example 251



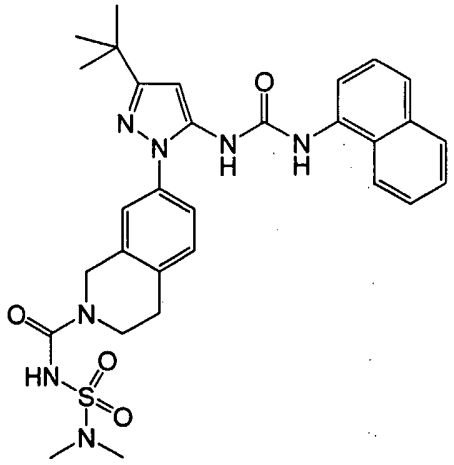
Example 249 is reacted with trifluoroacetic acid under standard conditions to afford 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 252



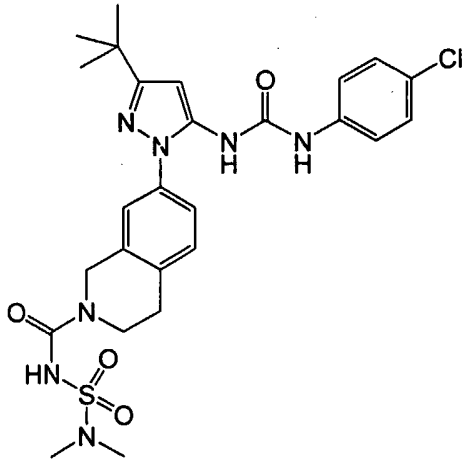
Example 250 is reacted with trifluoroacetic acid under standard conditions to afford 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example 253



Example 251 is reacted with chlorosulfonyl isocyanate then dimethylamine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[1-N-[[(1-dimethylaminolsulphonyl)amino]carbonyl]-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

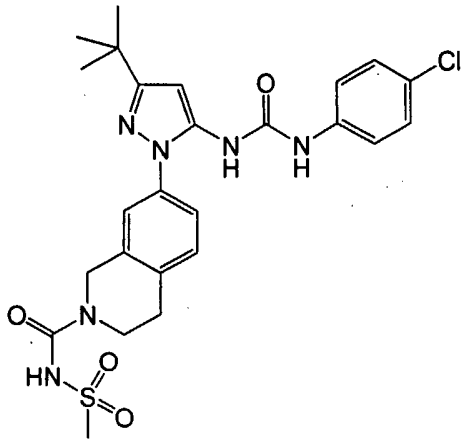
Example 254



Example 252 is reacted with chlorosulfonyl isocyanate then dimethylamine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[1-N-[[(1-

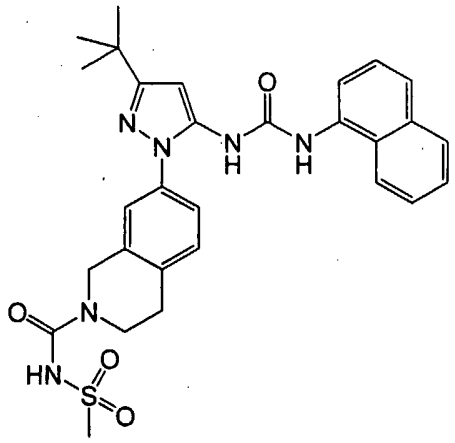
dimethylaminolsulphonyl)amino]carbonyl]-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazol-5-yl)- 3-(4-chlorophenyl)urea.

Example 255



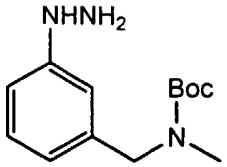
Example 252, CDI, and methanesulfonamide are reacted under standard conditions to yield 1-(3-t-butyl-1-[[1-N-[[(methanesulphonyl)amino]carbonyl]-1-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-pyrazol-5-yl)- 3-(4-chlorophenyl)urea.

Example 256



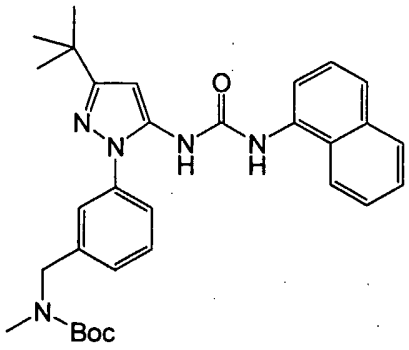
Example 251, CDI, and methanesulfonamide are reacted under standard conditions to yield 1-(3-t-butyl-1-[[1-N-[[(methanesulphonyl)amino]carbonyl]-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazol-5-yl)- 3-(1-naphthyl)urea.

Example FFF



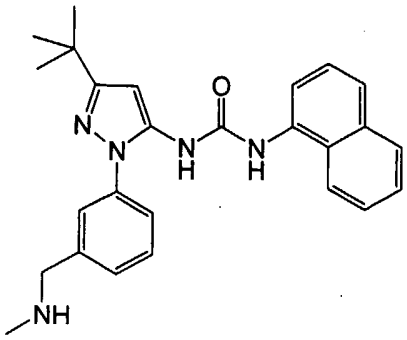
Commercially available 3-nitrobenzoic acid is reacted with methylamine and EDC under standard conditions to afford N-methyl-3-nitrobenzamide, which is reduced with LAH under standard conditions to afford N-methyl(3-nitrophenyl)methanamine, which is protected with benzylchloroformate under standard conditions to yield t-butyl 3-nitrobenzylmethylcarbamate. This material is nitrosated and reduced to yield t-butyl 3-hydrzazinobenzylmethylcarbamate.

Example 257



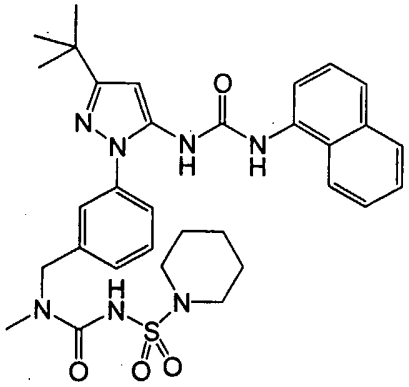
Utilizing the same synthetic procedure as for Example 164, Example FFF (10 mmol) and Example PP (10.5 mmol) are combined to afford t-butyl 3-(3-t-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)benzylmethylcarbamate.

Example 258



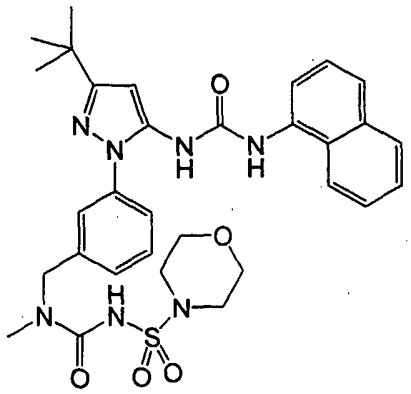
Example 257 is deprotected with trifluoroacetic acid under standard conditions to afford 1-(3-t-butyl-1-(3-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 259



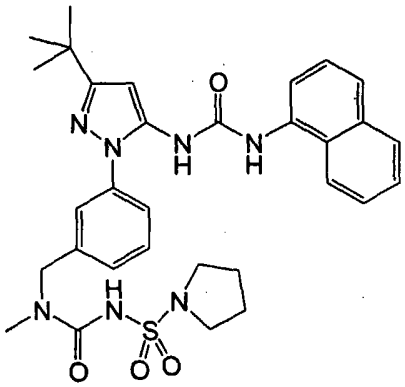
Example 258 is reacted with chlorosulfonyl isocyanate then piperdine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-piperdinylsulphonyl)amino]carbonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 260



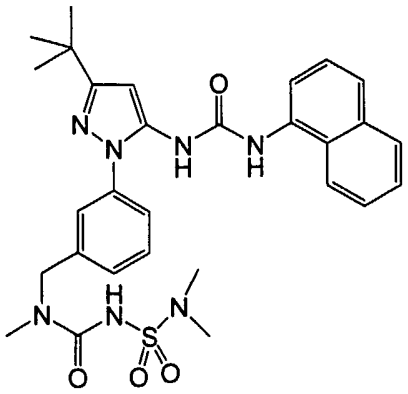
Example 258 is reacted with chlorosulfonyl isocyanate then morpholine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-morpholinyl-sulphonyl)amino]carbonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 261



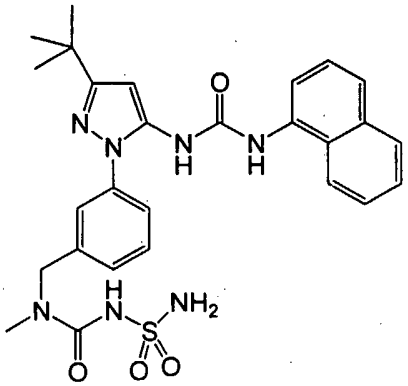
Example 258 is reacted with chlorosulfonyl isocyanate then pyrrolidine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-piperdinyl-sulphonyl)amino]carbonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 262



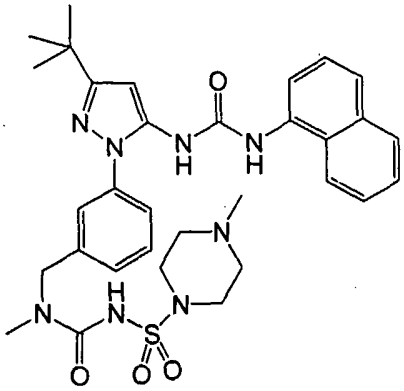
Example 258 is reacted with chlorosulfonyl isocyanate then dimethylamine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-dimethylamino-sulphonyl)amino]carbonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 263



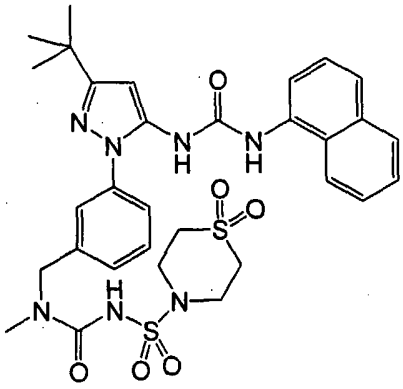
Example 258 is reacted with chlorosulfonyl isocyanate then ammonia according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-aminosulphonyl)amino]carbonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 264



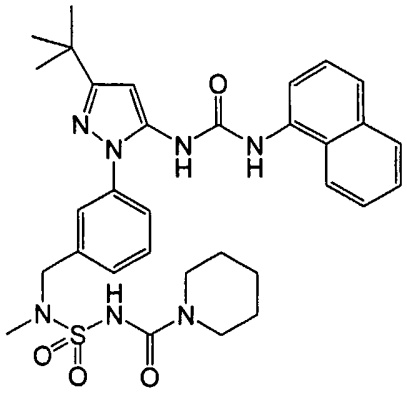
Example 258 is reacted with chlorosulfonyl isocyanate then N-methyl piperzine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-(N-methylpiperzinyl)sulphonyl)amino]carbonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 265



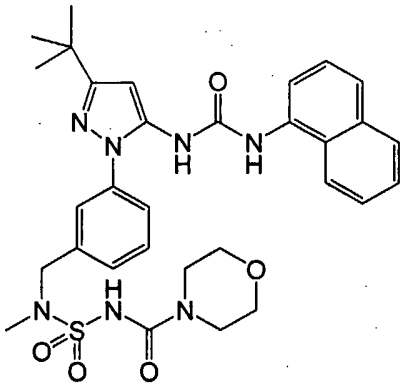
Example 258 is reacted with chlorosulfonyl isocyanate then 4,4-dioxo-4-thiomorpholine according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-(4,4-dioxo-4-thiomorpholinyl)sulphonyl)amino]carbonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 266



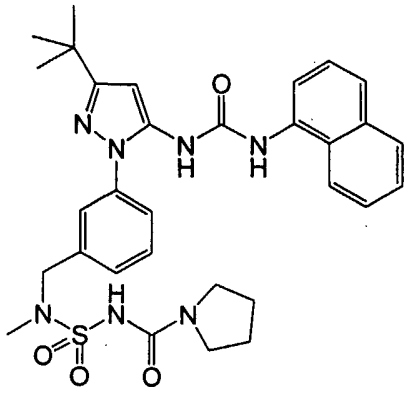
Cchlorosulfonyl isocyanate, piperdine, then Example 258 are reacted according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-piperdinylcarbonyl)amino]sulphonyll]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 267



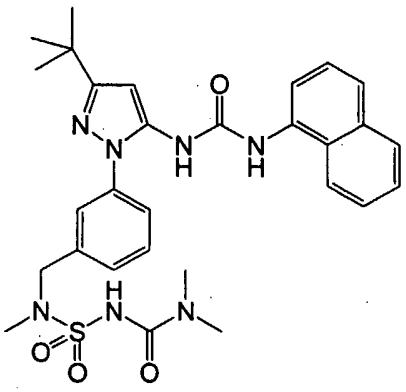
Chlorosulfonyl isocyanate, morpholine and then Example 258 are reacted according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-morpholinyl-carbonyl)amino] sulphonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 268



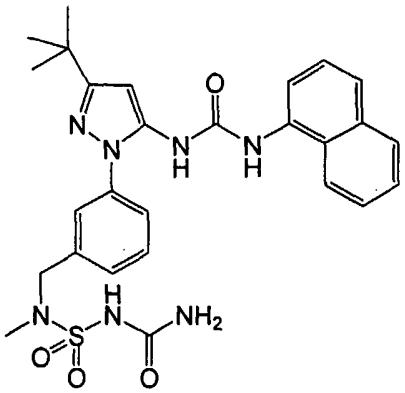
Chlorosulfonyl isocyanate, pyrrolidine and then Example 258 are reacted according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-piperdinyl-carbonyl)amino] sulphonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 269



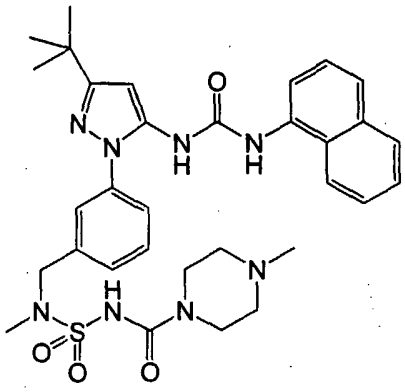
Chlorosulfonyl isocyanate, dimethylamine, then Example 258 are reacted according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-dimethylamino-carbonyl)amino] sulphonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 270



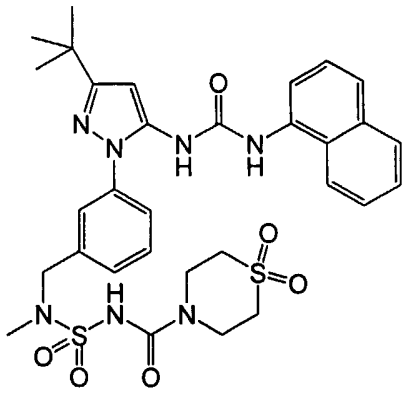
Chlorosulfonyl isocyanate, ammonia and then Example 258 are reacted according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-aminocarbonyl)amino]sulphony]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 271



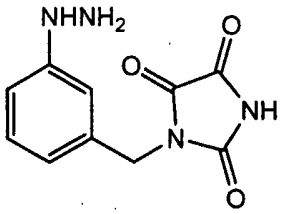
Chlorosulfonyl isocyanate, N-methyl piperzine and then Example 258 are reacted according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-(N-methylpiperzinyl)carbonyl)amino]sulphonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 272



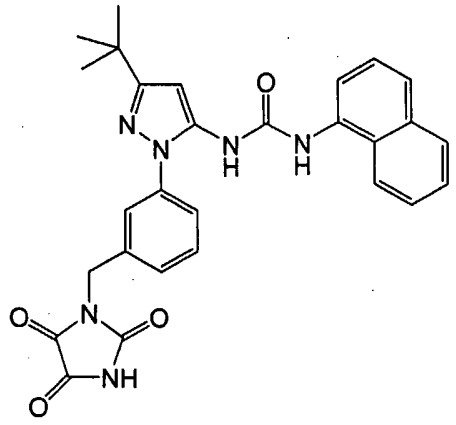
Chlorosulfonyl isocyanate, 4,4-dioxo-4-thiomorpholine and then Example 258 are reacted according to the procedure for Example 7 to afford 1-(3-t-butyl-1-[[3-[[(1-(4,4-dioxo-4-thiomorpholinyl)carbonyl)amino]sulphonyl]-((methylamino)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example GGG



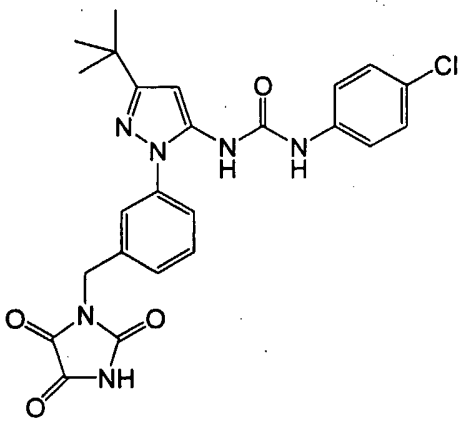
Commercially available 3-nitrobenzamide is reduced with LAH under standard conditions to afford (3-nitrophenyl)methanamine, which is reacted with 4-methoxybenzylisocyanate to afford 1-(3-nitrobenzyl)-3-(4-methoxybenzyl)urea. This material is subsequently reacted with oxalyl chloride to afford 1-(3-nitrobenzyl)-3-(4-methoxybenzyl)imidazolidine-2,4,5-trione whose nitro group is reduced and oxidized to afford 1-(3-hydrazinylbenzyl)-3-(4-methoxybenzyl)imidazolidine-2,4,5-trione. This material is deprotected with TFA under standard conditions to afford the title compound 1-(3-hydrazinylbenzyl)imidazolidine-2,4,5-trione.

Example 273



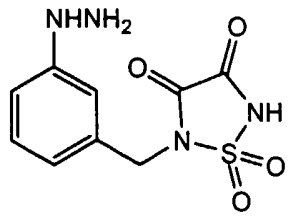
Utilizing the same synthetic procedure as for Example 164, Example GGG (10 mmol) and Example PP (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,4,5-trioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea

Example 274



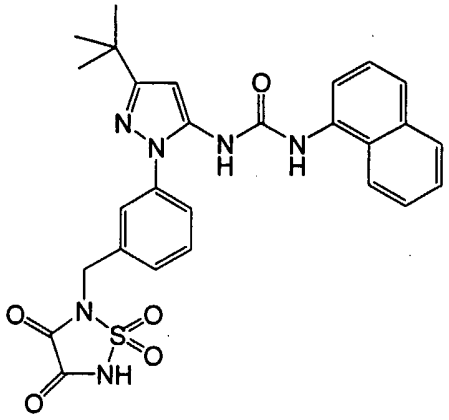
Utilizing the same synthetic procedure as for Example 164, Example GGG (10 mmol) and Example QQ (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,4,5-trioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example HHH



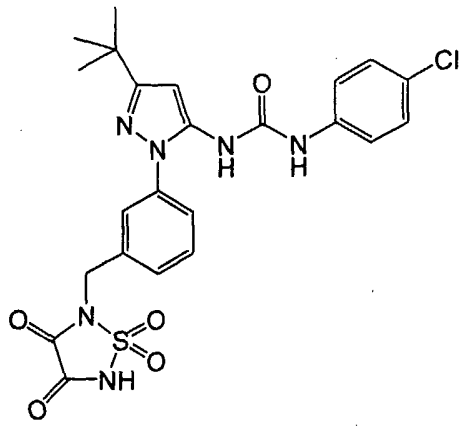
Commercially available 3-nitrobenzamide is reduced with LAH under standard conditions to afford (3-nitrophenyl)methanamine, which is reacted with N-4-methoxybenzylsulfamic acid and EDC to afford 1-(4-methoxybenzyl)-3-benzylsulfonylurea. This material is reacted with oxalyl chloride to afford 1-(3-nitrobenzyl)-3-(4-methoxybenzyl)imidazolidine-2,2-dioxo-2-thio-4,5-trione whose nitro group is reduced and oxidized to afford 1-(3-hydrazinylbenzyl)-3-(4-methoxybenzyl)imidazolidine-2,2-dioxo-2-thio-4,5-trione. This material is deprotected with TFA under standard conditions to afford the title compound 1-(3-hydrazinylbenzyl)imidazolidine-2,2-dioxo-2-thio-4,5-trione.

Example 275



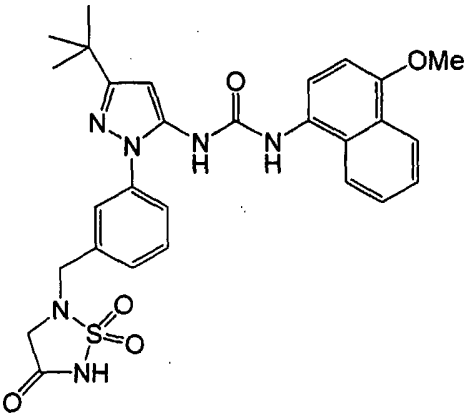
Utilizing the same synthetic procedure as for Example 164, Example HHH (10 mmol) and Example PP (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,2-dioxo-2-thio-4,5-diioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 276



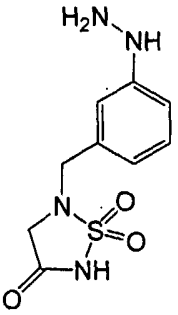
Utilizing the same synthetic procedure as for Example 164, Example HHH (10 mmol) and Example QQ (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,2-dioxo-2-thio-4,5-diioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example 277



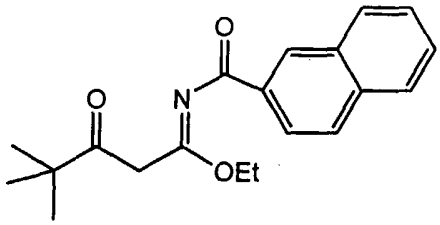
Example CC, 4-methoxy-1-aminonaphthalene and Example E are reacted using the procedure for Example 162 to afford 1-(5-t-butyl-2-{3-[1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-3-(4-methoxynaphth-1-yl)-urea.

Example III



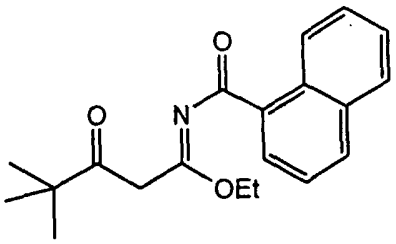
A solution of 1-(chloromethyl)-3-nitrobenzene and Example DD are combined using the procedure for Example 77 to yield 2-(4-methoxybenzyl)-5-(3-nitrophenylmethyl)-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one. This material is reduced under standard condition to yield 2-(4-methoxybenzyl)-5-(3-aminophenylmethyl)-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one, which was nitrosated and acidified to yield 5-(3-hydrazinophenylmethyl)-1,1-dioxo-1λ^6-[1,2,5]thiadiazolidin-3-one.

Example JJJ



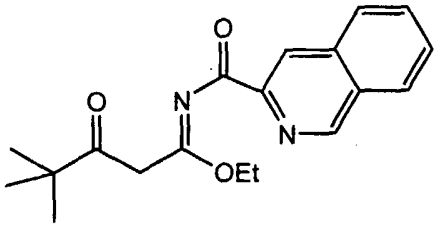
Intermediate HH (5 g, 0.0241 mol) is added to pyridine (5 mL) in CH_2Cl_2 (25 mL) and cooled in an ice bath. The suspension is stirred for 5 min and 2-naphthoic acid chloride is added dropwise over 5 min. The reaction mixture is stirred an additional 5 min at 0 °C, and the reaction is warmed and stirred at RT for 1 h. The reaction is pour into ethyl acetate (100 mL) and water (100 ml). After shaking, the aqueous layer is removed, the organic layer washed with water, dried ($MgSO_4$) and concentrated to afford (Z)-N-(1-ethoxy-4,4-dimethyl-3-oxopentylidene)-2-naphthamide.

Example KKK



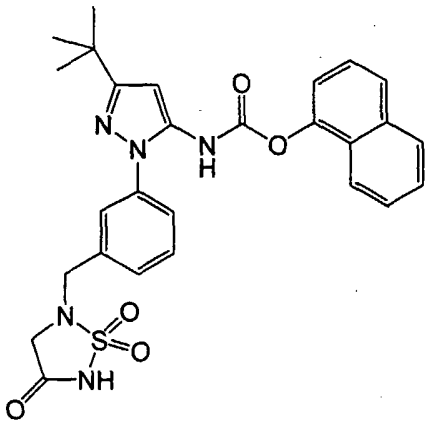
Intermediate HH (5 g, 0.0241 mol) is added to pyridine (5 mL) in CH_2Cl_2 (25 mL) and cooled in an ice bath. The suspension is stirred for 5 min and 1-naphthoic acid chloride is added dropwise over 5 min. The reaction mixture is stirred an additional 5 min at 0 °C, and the reaction is warmed and stirred at RT for 1 h. The reaction is pour into ethyl acetate (100 mL) and water (100 ml). After shaking, the aqueous layer is removed, the organic layer washed with water, dried ($MgSO_4$) and concentrated to afford (Z)-N-(1-ethoxy-4,4-dimethyl-3-oxopentylidene)-1-naphthamide

Example LLL



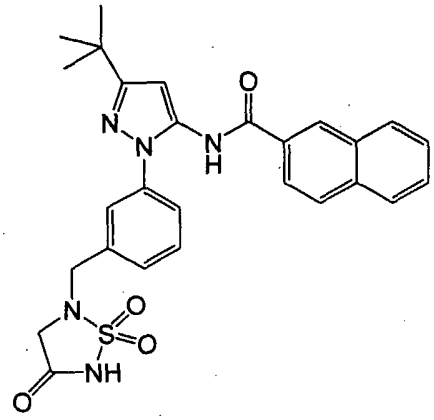
Intermediate HH (5 g, 0.0241 mol) is added to pyridine (5 mL) in CH_2Cl_2 (25 mL) and cooled in an ice bath. The suspension is stirred for 5 min and isoquinoloic acid chloride is added dropwise over 5 min. The reaction mixture is stirred an additional 5 min at 0 °C, and the reaction is warmed and stirred at RT for 1 h. The reaction is pour into ethyl acetate (100 mL) and water (100 ml). After shaking, the aqueous layer is removed, the organic layer washed with water, dried ($MgSO_4$) and concentrated to afford (Z)-N-(1-ethoxy-4,4-dimethyl-3-oxopentylidene)isoquinoline-3-carboxamide.

Example 278



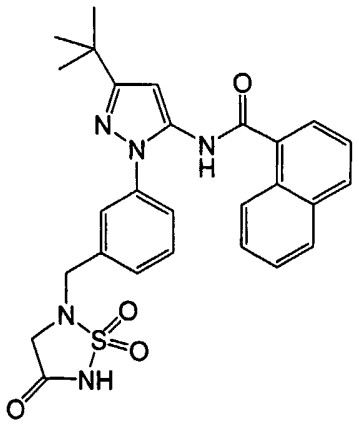
Utilizing the same synthetic procedure as for Example 164, Example III (10 mmol) and Example II (10.5 mmol) are combined to afford 1-naphtyl 1-(3-t-butyl-1-(3-((2,4,5-trioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)carbmate.

Example 279



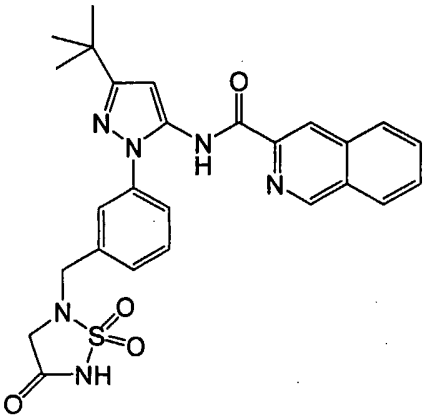
Utilizing the same synthetic procedure as for Example 164, Example III (10 mmol) and Example JJJ (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,4,5-trioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-2-naphthamide.

Example 280



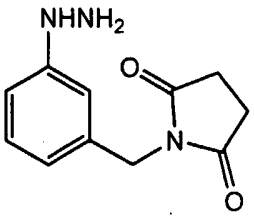
Utilizing the same synthetic procedure as for Example 164 Example III (10 mmol) and Example KKK (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,4,5-trioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-1-naphthamide.

Example 281



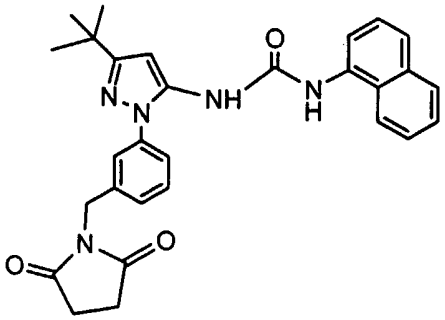
Utilizing the same synthetic procedure as for Example 149, Example III (10 mmol) and Example KKK (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,4,5-trioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)isoquinoline-3-carboxamide.

Example MMM



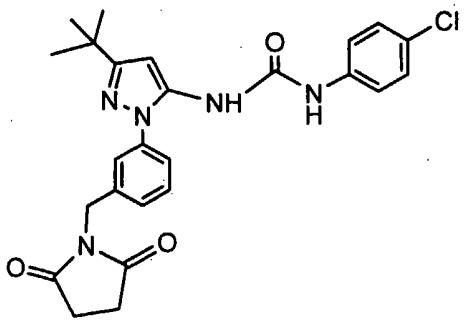
Commercially available 3-nitrobenzamide is reduced with LAH under standard conditions to afford (3-nitrophenyl)methanamine, which is reacted with succinic anhydride under standard conditions to afford 1-(3-nitrobenzyl)pyrrolidine-2,5-dione. This material is reduced at the nitro group and oxidized to afford 1-(3-hydrazinobenzyl)pyrrolidine-2,5-dione.

Example 282



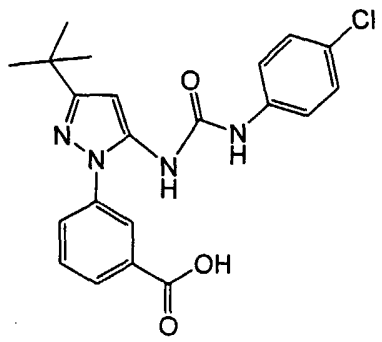
Utilizing the same synthetic procedure as for Example 164, Example MMM (10 mmol) and Example PP (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,5-dioxopyrrolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea.

Example 283



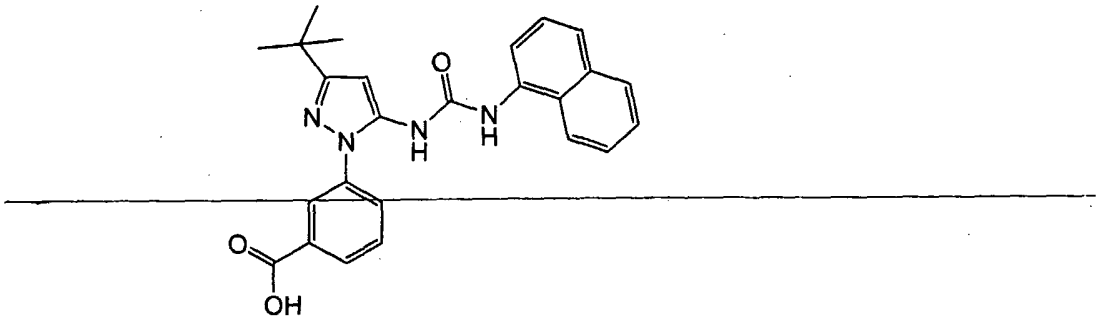
Utilizing the same synthetic procedure as for Example 164, Example MMM (10 mmol) and Example QQ (10.5 mmol) are combined to afford 1-(3-t-butyl-1-(3-((2,5-dioxopyrrolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea.

Example 284



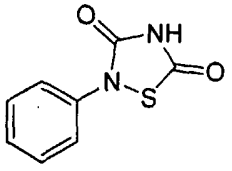
Example C was reacted with LiOH utilizing the procedure for Example 146 to yield 3-(3-t-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)benzoic acid in 90% overall yield. ^{1}H NMR (DMSO-d_6): 9.00 (s, 1 H), 8.83 (s, 1 H), 8.25 – 7.42 (m, 11 H), 6.42 (s, 1 H), 1.26 (s, 9 H); MS(ESI): Expected: 412.88 Found: 413.00.

Example 285



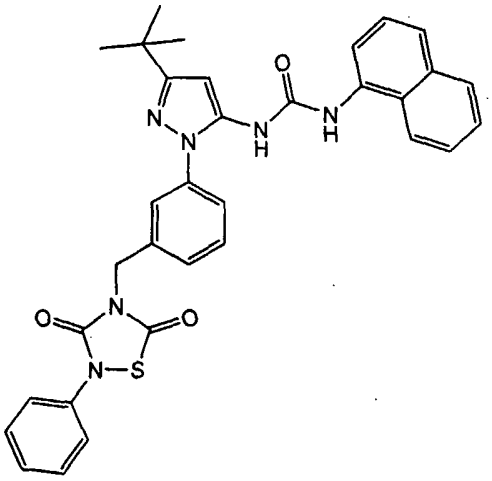
Example B was reacted with LiOH utilizing the procedure for Example 146 to yield 3-(3-t-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)benzoic acid in 90% overall yield. ^{1}H NMR (DMSO- d_6): δ 9.11 (s, 1H), 8.47 (s, 1H), 8.06 (m, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 8.0, 7.6 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.34 (s, 1H), 1.27 (s, 9H); MS (ESI) Expected: 428.49 Found: 429.2 (M+1).

Example NNN



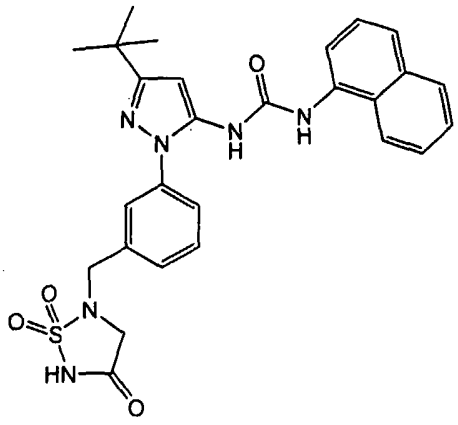
To the solution of phenyl-urea (13.0 g, 95.48 mol) in THF (100 mL) was slowly added chlorocarbonyl sulfenylchloride (13 mL, 148.85 mmol) at RT. The reaction mixture was refluxed overnight, the volatiles removed in vacuo yielded 2-phenyl-1,2,4-thiadiazolidine-3,5-dione as a white solid (4.0 g, 20%). ^{1}H NMR (DMSO-d_6): δ 12.49 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.43(t, J = 7.6 Hz, 2H), 7.27 (t, J = 7.2 Hz, 1 H).

Example 286



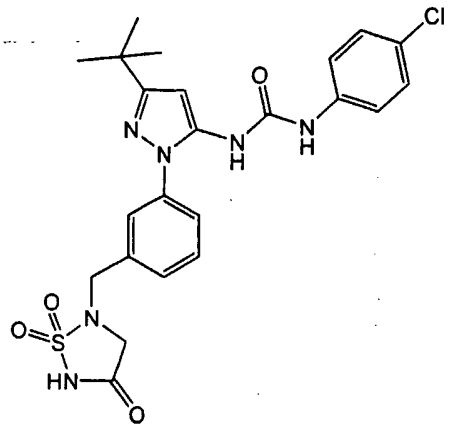
Example E and Example NNN were reacted together utilizing the same general approach as for Example 160 to afford 1-(3-t-butyl-1-(3-((3,5-dioxo-2-phenyl-1,2,4-thiadiazolidin-4-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea. ^{1}H NMR (DMSO- d_6): δ8.96 (s, 1 H), 8.01 - 7.21 (m, 16 H), 6.40 (s, 1 H), 4.85 (s, 2 H), 1.28 (s, 9 H); MS (ESI): Expected: 590.21, Found 591.26 (M+1).

Example 287



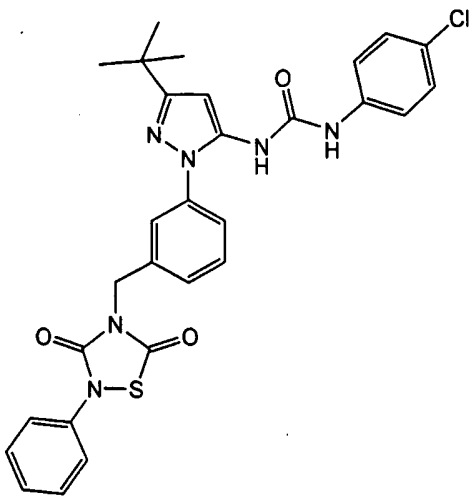
Example CC, 1-naphthylisocyanate and Example DD were combined utilizing the same general approach for Example 162 to yield 1-(5-t-butyl-2-{3-[5-1,1,4-trioxo-1λ^6-[1,2,5]thiadia- zolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-1-naphthylurea. ^{1}H NMR (DMSO- d_6): δ 9.0 (s, 1H), 8.81 (s, 1H), 7.99 – 7.42 (m, 11H), 6.41 (s, 1H), 4.33 (s, 2H), 1.27 (s, 9H); MS (ESI) Exact Mass: 532.19 Found: = 533.24

Example 288



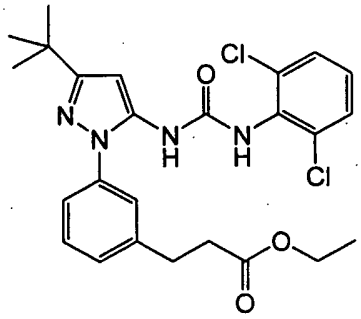
Example CC, p-chlorophenylisocyanate and Example DD were combined utilizing the same general approach for Example 162 to yield 1-(5-t-butyl-2-{3-[5-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-3-(4-chloro-phenyl)-urea. ^{1}H NMR (DMSO- d_6): δ 9.07 (s, 1H), 8.42 (s, 1H), 7.52 – 7.272 (m, 8H), 6.36 (s, 1H), 4.60 (s, 2H), 1.26 (s, 9H); MS (ESI) Exact Mass: 516.13 Found: = 517.1

Example 289



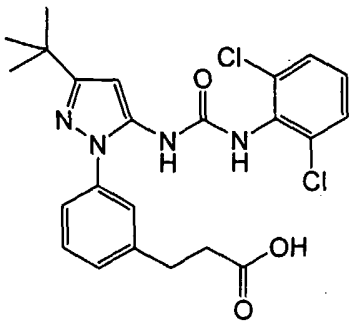
Example G and Example NNN were reacted together utilizing the same general approach as for Example 160 to afford 1-(3-t-butyl-1-(3-((3,5-dioxo-2-phenyl-1,2,4-thiadiazolidin-4-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(4-chlorophenyl)urea. ^{1}H NMR (DMSO- d_6): δ9.02 (s, 1H), 8.51 (s, 1H), 7.52 - 7.24 (m, 13H), 6.36 (s, 1H), 4.90 (s, 2H), 1.27 (s, 9H); MS (ESI): Expected: 574.16 Found: 575.26 (M+1)

Example 290



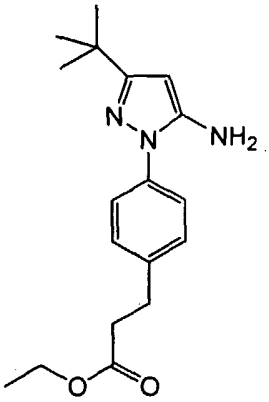
Example Z and 2,6-dichlorophenylisocyanate were reacted utilizing the same conditions as for Example 145 to yield ethyl 3-(3-(3-t-butyl-5-(3-(2,6-dichlorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)propanoate. ^{1}H NMR (DMSO- d_6): δ 7.46 - 7.26 (m, 7H), 6.35 (s, 1H), 4.11 (q, J = 7.2Hz, 2H), 3.31 (t, J = 5.2 Hz, 2H), 2.68 (t, J = 5.6 Hz, 2H), 1.32 (s, 9H), 1.24 (t, J = 7.2Hz, 3H); MS(ESI): Expected:: 502.15 Found: = 503.1 (M+1).

Example 291



Example 290 was reacted utilizing the same condition as for Example 146 to yield 3-(3-(3-t-butyl-5-(3-(2,6-dichlorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)propanoic acid in >90% yield. ^{1}H NMR (DMSO- d_6): δ 8.70 (s, 1H), 8.60 (s, 1H) 7.50 - 7.24 (m, 7H), 6.26 (s, 1H), 2.87 (t, J = 5.2 Hz, 2H), 2.57 (t, J = 5.6 Hz, 2H), 1.25 (s, 9H); MS(ESI): Expected: 474.12 Found: 475.18 (M+1).

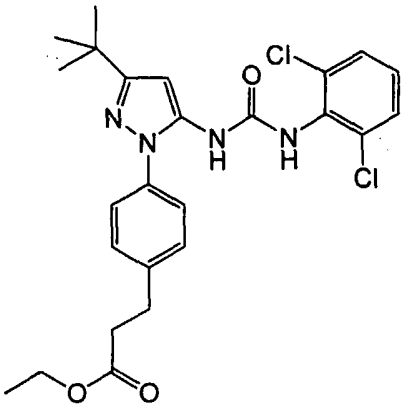
Example OOO



A mixture of ethyl 3-(4-aminophenyl)acrylate(1.5 g) and 10 % Pd on activated carbon (0.3 g) in ethanol (20 ml) was hydrogenated at 30 psi for 18h and filtered over Celite. Removal of the volatiles in vacuo provided ethyl 3-(4-aminophenyl)propionate (1.5 g).

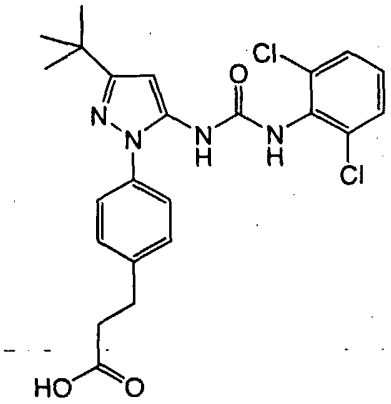
A solution of the crude material from the previous reaction (1.5 g, 8.4 mmol) was dissolved in 6 N HCl (9 ml), cooled to 0 °C, and vigorously stirred. Sodium nitrite (0.58 g) in water (7 ml) was added. After 1h, tin (II) chloride dihydrate (5 g) in 6 N HCl (10 ml) was added. The reaction mixture was stirred at 0 °C for 3h. The pH was adjusted to pH 7 to yield ethyl 3-(4-(3-t-butyl-5-amino-1H-pyrazol-1-yl)phenyl)propanoate.

Example 292



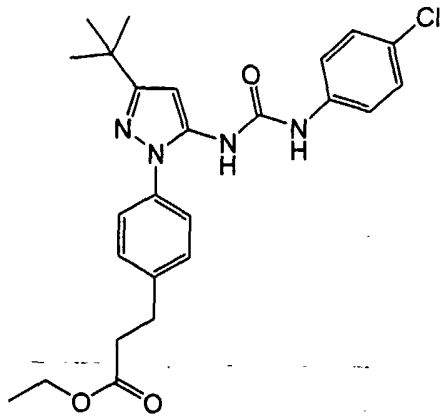
Example OOO and 2,6-dichlorophenylisocyanate were reacted utilizing the same conditions as for Example 145 to yield ethyl 3-(4-(3-t-butyl-5-(3-(2,6-dichlorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)propanoate. ^{1}H NMR (DMSO- d_6): δ 7.45 - 7.24 (m, 7H), 6.36 (s, 1H), 4.10 (q, J = 7.2Hz, 2H), 3.02 (t, J = 5.2 Hz, 2H), 2.70 (t, J = 5.6 Hz, 2H), 1.33 (s, 9H), 1.22 (t, J = 7.2Hz, 3H); MS(ESI): Expected:: 502.15 Found: = 503.1 (M+1).

Example 293



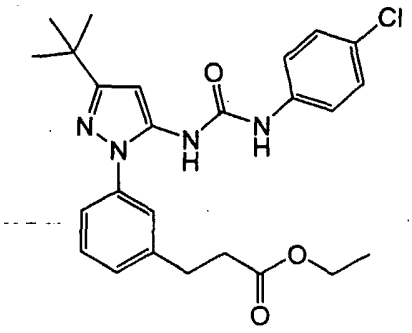
Example 292 was reacted utilizing the same condition as for Example 146 to yield 3-(3-(3-t-butyl-5-(3-(2,6-dichlorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)propanoic acid in >90% yield. ^{1}H NMR (DMSO- d_6): δ 8.66 (s, 1H), 8.58 (s, 1H) 7.50 - 7.28 (m, 7H), 6.27 (s, 1H), 2.85 (t, J = 5.2 Hz, 2H), 2.48 (t, J = 5.6 Hz, 2H), 1.24 (s, 9H); MS(ESI): Expected: 474.12 Found: 475.18 (M+1).

Example 294



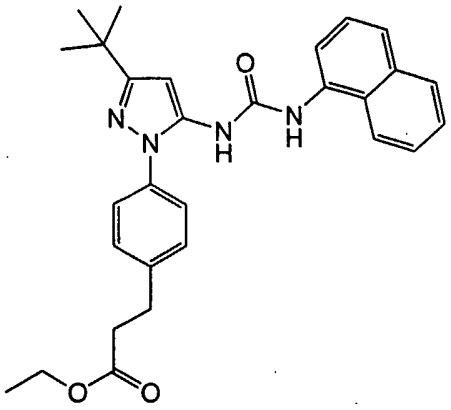
Example OOO and p-chlorophenylisocyanate were reacted utilizing the same conditions as for Example 145 to yield ethyl 3-(4-(3-tert-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)propanoate. ^{1}H NMR (DMSO- d_6): δ 7.34 - 7.19 (m, 9H), 6.36 (s, 1H), 4.10 (q, J = 7.2Hz, 2H), 2.92 (t, J = 5.2 Hz, 2H), 2.58 (t, J = 5.6 Hz, 2H), 1.32 (s, 9H), 1.25 (t, J = 7.2Hz, 3H); MS(ESI): Exact Mass: 468.19 Found: = 469.21 (M+1).

Example 295



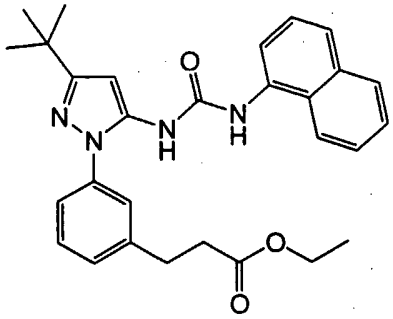
Example Z and p-chlorophenylisocyanate were reacted utilizing the same conditions as for Example 145 to yield ethyl 3-(3-(3-tert-butyl-5-(3-(4-chlorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)propanoate. ^{1}H NMR (DMSO- d_6): δ 9.12 (s, 1H), 8.37 (s, 1H), 7.41 - 7.27 (m, 8H), 6.34 (s, 1H), 5.73 (s, 1H), 4.01 (q, J = 7.2Hz, 2H), 2.90 (t, J = 5.2 Hz, 2H), 2.62 (t, J = 5.6 Hz, 2H), 1.25 (s, 9H), 1.125 (t, J = 7.2Hz, 3H); MS(ESI): Exact Mass: 468.19 Found: = 469.21 (M+1).

Example 296



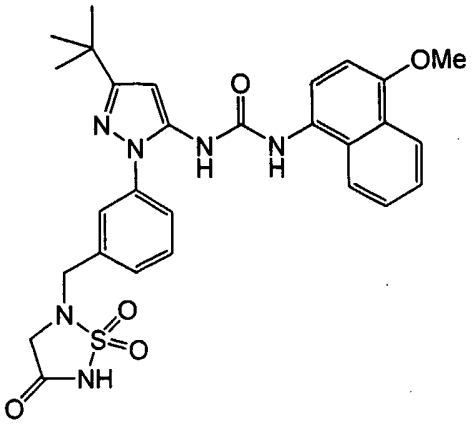
Example OOO and 1-naphthylisocyanate were reacted utilizing the same conditions as for Example 145 to yield ethyl 3-(4-(3-tert-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)phenyl)propanoate. δ 7.88 – 9.95 (m, 13H), 6.27 (s, 1H), 4.04 (q, J = 7.2Hz, 2H), 2.75 (t, J = 5.2 Hz, 2H), 2.42 (t, J = 5.6 Hz, 2H), 1.27 (s, 9H), 1.20 (t, J = 7.2Hz, 3H); MS(ESI): Exact Mass: 484.25 Found: = 485.26 (M+1).

Example 297



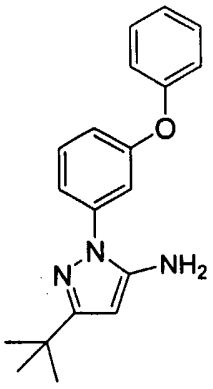
Example Z and 1-naphthylisocyanate were reacted utilizing the same conditions as for Example 145 to yield ethyl 3-(3-(3-tert-butyl-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)phenyl)propanoate. ^{1}H NMR (DMSO- d_6): δ 9.01 (s, 1H), 8.80 (s, 1H), 8.0 - 7.27 (m, 11H), 6.41 (s, 1H), 4.01 (q, J = 7.2Hz, 2H), 2.95 (t, J = 5.2 Hz, 2H), 2.72 (t, J = 5.6 Hz, 2H), 1.27 (s, 9H), 1.15 (t, J = 7.2Hz, 3H); MS(ESI): Exact Mass: 484.25 Found: = 485.26 (M+1).

Example 298



Example CC, 1-(4-methoxynaphthyl)isocyanate and Example DD were combined utilizing the same general approach for Example 162 to yield 1-(5-t-butyl-2-{3-[5-1,1,4-trioxo-1λ^6-[1,2,5]thiadiazolidin-2-ylmethyl]-phenyl}-2H-pyrazol-3-yl)-1-(4-methoxynaphthyl)urea. ^{1}H NMR (DMSO- d_6): δ 8.69 (s, 1H), 8.61 (s, 1H), 8.15 – 6.90 (m, 10H), 6.36 (s, 1H), 4.37 (s, 2H), 3.93 (s, 3H), 1.22 (s, 9H); MS (ESI) Exact Mass: 562.20 Found: = 563.2.

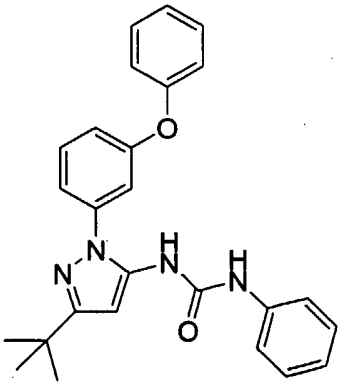
Example PPP



In a 250 mL Erlenmeyer flask with a magnetic stir bar, 3-phenoxyphenylamine (4.81 g, 0.026 mol) was added to 6 N HCl (40 mL) and cooled with an ice bath to 0 °C. A solution of $NaNO_2$ (2.11 g, 0.0306 mol, 1.18 eq.) in water (5 mL) was added drop wise. After 30 min, $SnCl_2 2H_2O$ (52.0 g, 0.23 mol, 8.86 eq.) in 6 N HCl (100 mL) was added and the reaction mixture was allowed to stir for 3 h, and then subsequently transferred to a 500 mL round bottom flask. To this, 4,4-dimethyl-3-oxopentanenitrile (3.25 g, 0.026 mol) and EtOH (100 ml) were added and the mixture refluxed for 4h,

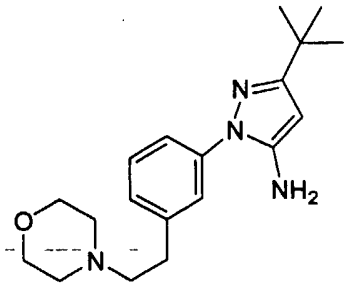
concentrated in vacuo and the residue extracted with EtOAc (2 X 100 mL) and purified by column chromatography using hexane/EtOAc/Et_3N (8:2:0.2) to yield 3-*tert*-butyl-1-(3-phenoxyphenyl)-1*H*-pyrazol-5-amine (1.40g, 17%). mp: 108 – 110 °C; ^1H NMR ($CDCl_3$): δ 7.3 (m, 10H), 5.7 (s, 1H), 4.9 (brs, 2H), 1.3 (s, 9H).

Example 299



In a dry vial with a magnetic stir bar, Example PPP (0.184 g; 0.60 mmol) was dissolved in 2 mL CH_2Cl_2 (anhydrous) followed by the addition of phenylisocyanate (0.0653 mL; 0.60 mmol; 1 eq.). The reaction was kept under Ar and stirred for 18h. Evaporation of solvent gave a crystalline mass that was recrystallized from EtOAc/hexane and then filtered washing with hexane/EtOAc (4:1) to yield 1-[3-*tert*-butyl-1-(3-phenoxyphenyl)-1*H*-pyrazol-5-yl]-3-phenylurea (0.150 g, 50%). HPLC purity: 96%; ^1H NMR ($CDCl_3$): δ 7.5 (m, 16H), 6.8 (s, 1H), 6.5 (s, 1H), 1.4 (s, 9H).

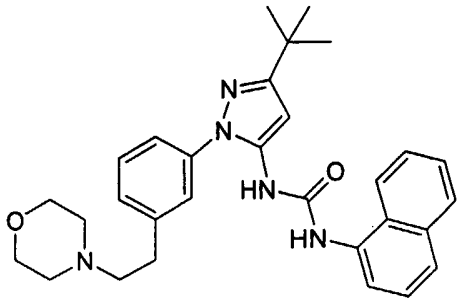
Example QQQ



To a stirred solution of Example L (1.2 g, 3.5 mmol) in THF (6 ml) was added borane-methylsulfide (9 mmol). The mixture was heated to reflux for 90 min and cooled to RT, and 6 N HCl was added and heated to reflux for 10 min. The mixture was basified

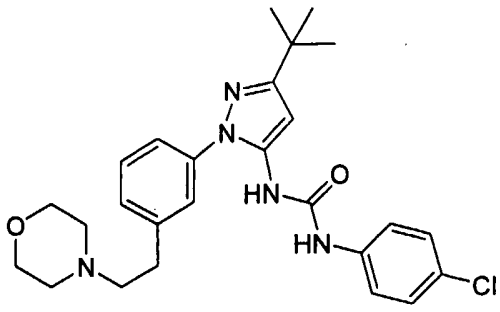
by adding sodium hydroxide, followed by extraction with ethyl acetate. The organic layer was dried (Na_2SO_4) filtered and concentrated in vacuo to yield 3-*tert*-butyl-1-[3-(2-morpholinoethyl)phenyl]-1*H*-pyrazol-5-amine (0.78 g), which was used without further purification.

Example 300



A mixture of Example QQQ (0.35 g, 1.07 mmol) and 1-naphthylisocyanate (0.18 g, 1.05 mmol) in dry CH_2Cl_2 (4 ml) was stirred at RT under N_2 for 18 h. The solvent was removed in vacuo and the crude product was purified by column chromatography using 5 % methanol in CH_2Cl_2 (with a small amount of TEA) as the eluent (0.18 g, off-white solid) to yield 1-{3-*tert*-butyl-1-[3-(2-morpholinoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-naphthalen-1-yl)urea. mp: 88 – 90 °C; ^{1}H NMR (200MHz, DMSO- d_6): δ 9.07 (s, 1H), 8.80 (s, 1H), 8.06-7.92 (m, 3H), 7.69 - 7.44 (m, 7H), 7.40 - 7.29 (m, 1H), 6.44 (s, 1H), 3.57 - 3.55 (m, 4H), 3.33 - 3.11 (m, 4H), 2.40 - 2.38 (m, 4H), 1.32 (s, 9H); MS

Example 301



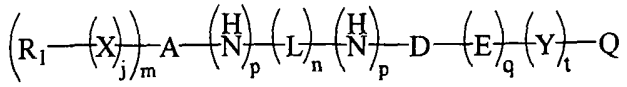
The title compound was synthesized in a manner analogous to Example 23 utilizing Example QQQ (0.35 g, 1.07 mmol) and 4-chlorophenylisocyanate (0.165 g, 1.05 mmol) to yield 1-{3-*tert*-butyl-1-[3-(2-morpholinoethyl)phenyl]-1*H*-pyrazol-5-yl}-3-(4-

chlorophenyl)urea. mp: 82 – 84 °C; ^{1}H NMR (200MHz, DMSO- d_6): δ 9.18 (s, 1H, s), 8.40 (s, 1H), 7.53 - 7.26 (m, 8H), 6.37 (s, 1H), 3.62 - 3.54 (m, 4H), 2.82-2.78 (m, 4H), 2.41-2.39 (m, 4H), 1.30 (s, 9H); MS

All of the references above identified are incorporated by reference herein. In addition, two simultaneously applications are also incorporated by reference, namely Modulation of Protein Functionalities, S/N 10/746,545, filed December 24, 2003, and Anti-Cancer Medicaments, S/N 10/746,607, filed December 24, 2003.

We Claim:

1. A compound having the formula



(IA)

wherein:

R^1 is selected from the group consisting of aryls and heteroaryls;

each X and Y is individually selected from the group consisting of -O-, -S-, $-NR_6-$, $-NR_6SO_2-$, $-NR_6CO-$, alkynyls, alkenyls, alkylenes, $-O(CH_2)_h-$, and $-NR_6(CH_2)_h-$, where each h is individually selected from the group consisting of 1, 2, 3, or 4, and where for each of alkylenes, $-O(CH_2)_h-$, and $-NR_6(CH_2)_h-$, one of the methylene groups present therein may be optionally double-bonded to a side-chain oxo group except that where $-O(CH_2)_h-$ the introduction of the side-chain oxo group does not form an ester moiety;

A is selected from the group consisting of aromatic, monocycloheterocyclic, and bicycloheterocyclic rings;

D is phenyl or a five- or six-membered heterocyclic ring selected from the group consisting of pyrazolyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, thienyl, pyridyl, and pyrimidyl;

E is selected from the group consisting of phenyl, pyridinyl, and pyrimidinyl;

L is selected from the group consisting of -C(O)- and $-S(O)_2-$;

j is 0 or 1;

m is 0 or 1;

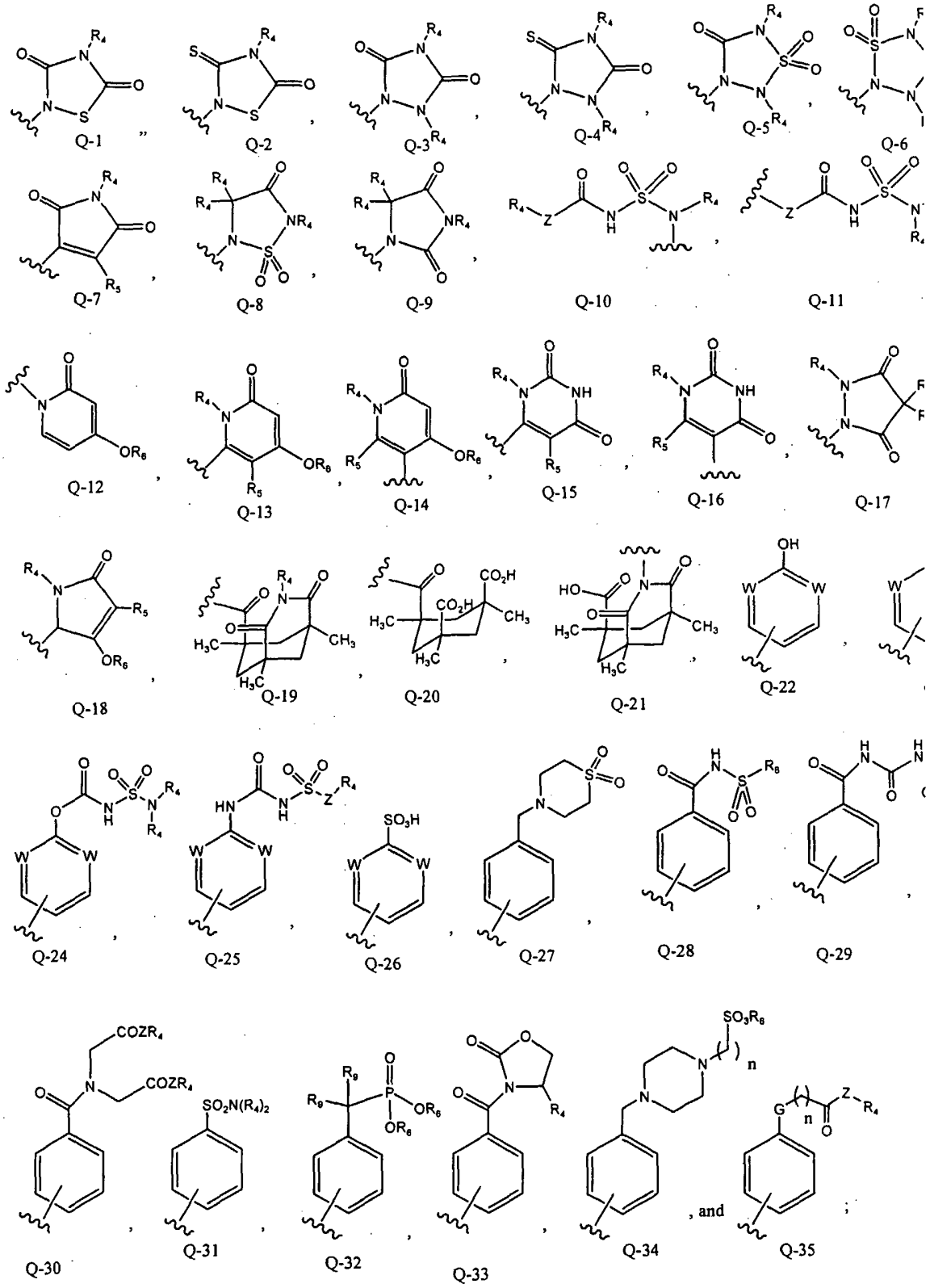
n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

t is 0 or 1;

Q is selected from the group consisting of



each R_4 group is individually selected from the group consisting of -H, alkyls, aminoalkyls, alkoxyalkyls, aryls, aralkyls, heterocyclyls, and heterocyclylalkyls except when the R_4 substituent places a heteroatom on an *alpha*-carbon directly attached to a ring nitrogen on Q;

when two R_4 groups are bonded with the same atom, the two R_4 groups optionally form an alicyclic or heterocyclic 4-7 membered ring;

each R_5 is individually selected from the group consisting of -H, alkyls, aryls, heterocyclyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, hydroxys, alkoxys, aryloxys, alkylthios, arylthios, cyanos, halogens, perfluoroalkyls, alkylcarbonyls, and nitros;

each R_6 is individually selected from the group consisting of -H, alkyls, allyls, and β-trimethylsilylethyl;

each R_8 is individually selected from the group consisting of alkyls, aralkyls, heterocyclyls, and heterocyclylalkyls;

each R_9 group is individually selected from the group consisting of -H, -F, and alkyls, wherein when two R_9 groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring; and

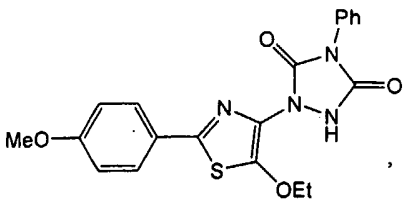
G is alkylene, $N(R_6)$, O;

each Z is individually selected from the group consisting of -O- and $-N(R_4)-$;

each ring of formula (IA) optionally includes one or more of R_7, where R_7 is a noninterfering substituent individually selected from the group consisting of -H, alkyls, aryls, heterocyclyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, hydroxys, alkoxys, aryloxys, alkylthios, arthylthios, cyanos, halogens, nitrilos, nitros, alkylsulfinyls, alkylsulfonyls, aminosulfonyls, and perfluoroalkyls;

except that:

when Q is Q-3 or Q-4, then the compound of formula (I) is not



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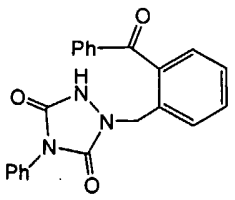

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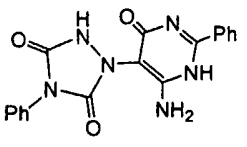


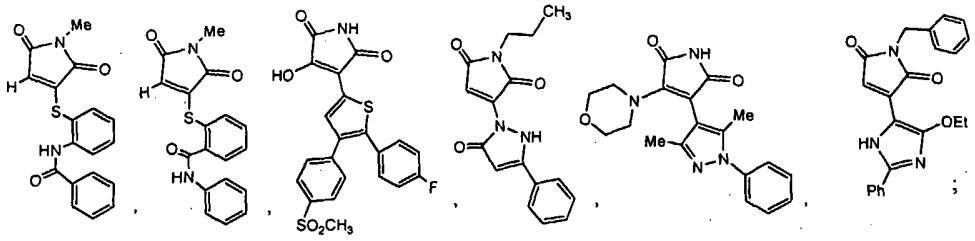
;

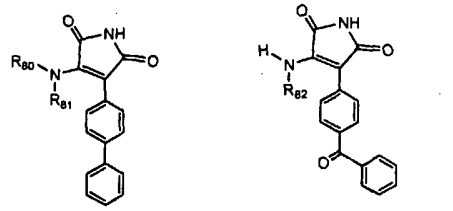
when Q is Q-7, q is 0, and R_5 and D are phenyl, then A is not phenyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, or imidazolyl;

when Q is Q-7, R_5 is -OH, Y is -O-, -S-, or -CO-, m is 0, n is 0, p is 0, and A is phenyl, pyridyl, or thiazolyl, then D is not thienyl, thiazolyl, or phenyl;

when Q is Q-7, R_5 is -OH, m is 0, n is 0, p is 0, t is 0, and A is phenyl, pyridyl, or thiazolyl, then D is not thienyl, thiazolyl, or phenyl;

when Q is Q-7, then the compound of formula (I) is not



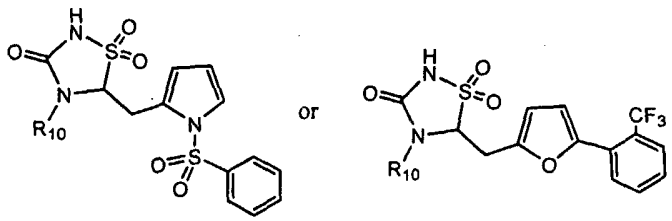


R80 is H, Me
R81 is substituted phenyl

R82 is substituted phenyl

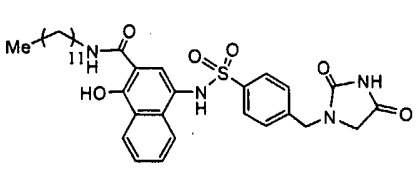
when Q is Q-8, then Y is not $-CH_2O-$;

when Q is Q-8, the compound of formula (I) is not



R_{10} = alkyl, aryl, arylalkoxyalkyl, or arylalkyls

when Q is Q-9, then the compound of formula (I) is not



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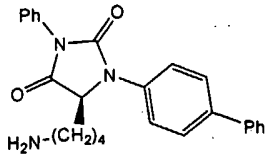

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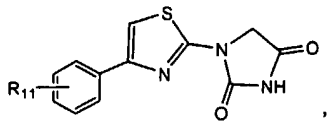
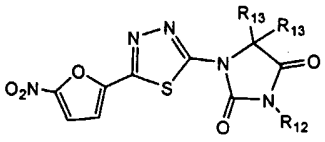


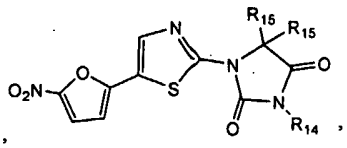
,

R11 = H, alkyl, alkoxy, nitro, halogen



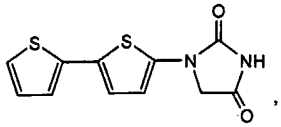
,

R12, R13 = H, alkyl



,

R14= H, alkyl, allyl, propargyl
R15 = H, alkyl,



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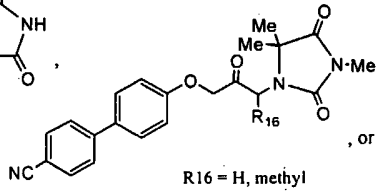
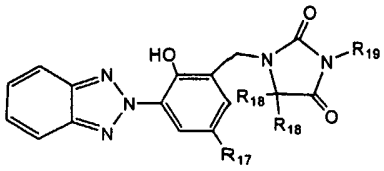


, or

R16 = H, methyl

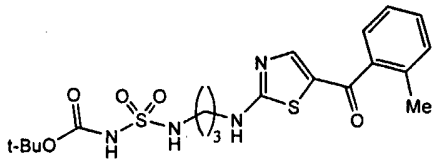


;

R17, R18 = alkyl
R19 = H, alkyl

when Q is Q-10, t is 0, and E is phenyl, then any R_7 on E is not an *o*-alkoxy;

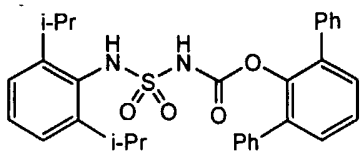
when Q is Q-10, then the compound of formula (I) is not



;

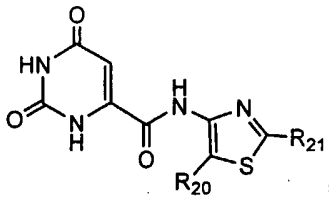
when Q is Q-11, t is 0, and E is phenyl, then any R_7 on E is not an *o*-alkoxy;

when Q is Q-11, then the compound of formula (I) is not



;

when Q is Q-15, then the compound of formula (I) is not



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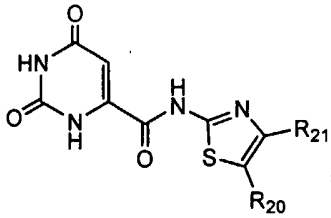

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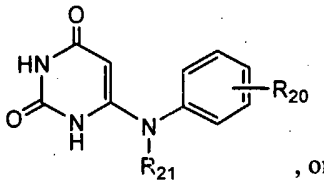

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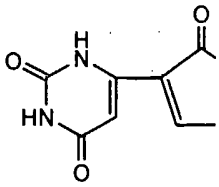
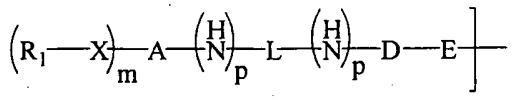


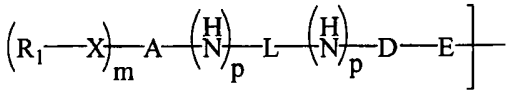
R_{20} = substituted phenyl, R_{21} = H, alkyl

when Q is Q-16 and Y is -NH-, then



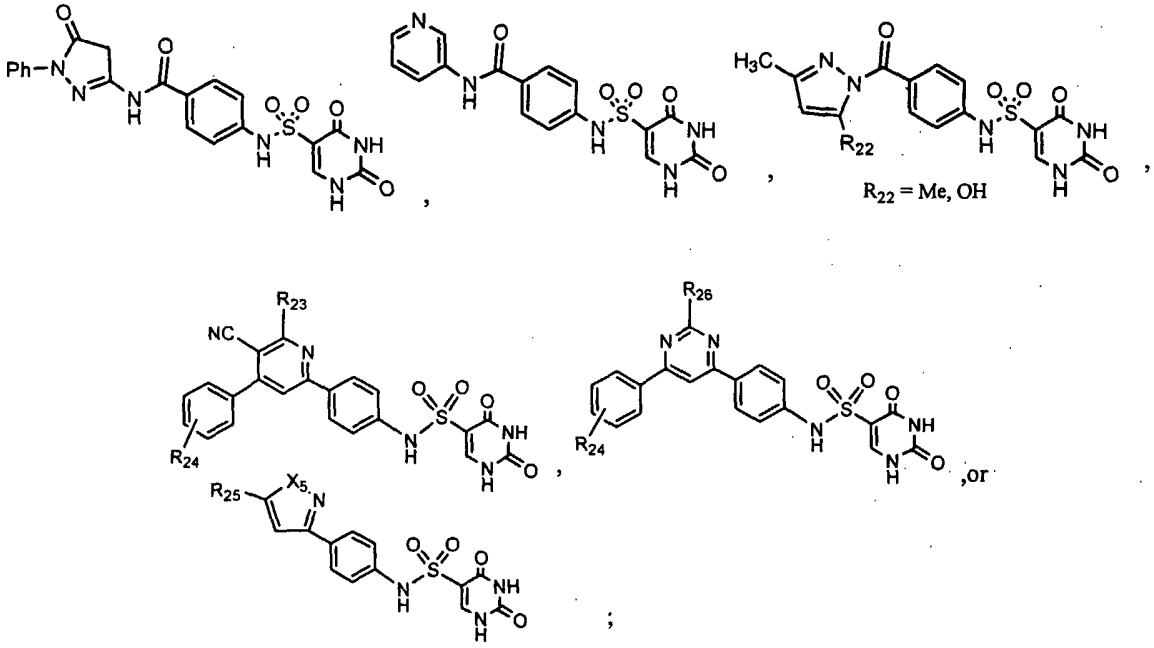
of formula (I) is not biphenyl;

when Q is Q-16 and Y is -S-, then



of formula (I) is not phenylsulfonylaminophenyl or phenylcarbonylaminophenyl;

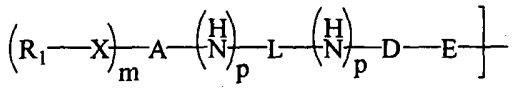
when Q is Q-16 and Y is $-SO_2NH-$, then the compound of formula (I) is not



R_{22} = Me, OH

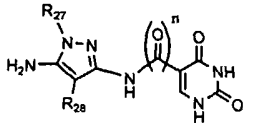
R_{23} = OH, SH, NH2
R_{24} = hydrogen or one or more methoxy, hydroxy, fluoro, chloro, nitro, dimethylamino, or furanyl
R_{25} = substituted phenyl, furanyl
R_{26} = OH or Cl
X_5 = O, NH;

when Q is Q-16 and Y is -CONH-, then



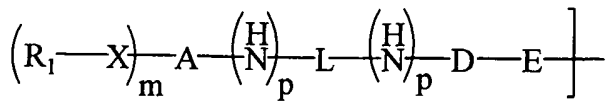
of formula (I) is not imidazophenyl;

when Q is Q-16 and Y is -CONH-, then the compound of formula (I) is not



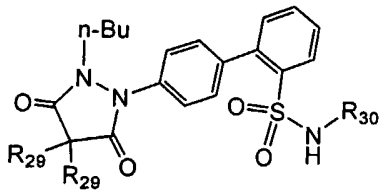
R_{27} = substituted phenyl, pyridylcarbonyl
R_{28} = CN, methoxycarbonyl
n = 0 or 1

when Q is Q-16 and t is 0, then



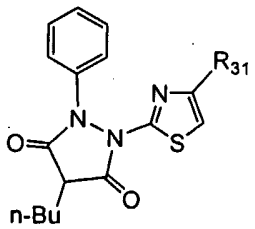
of formula (I) is not phenylcarbonylphenyl, pyrimidophenyl, phenylpyrimidyl, pyrimidyl, or N-pyrolyl;

when Q is Q-17, then the compound of formula (I) is not



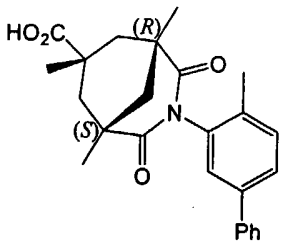
R_{29} = alkyl
R_{30} = H, t-Bu, benzoyl

or



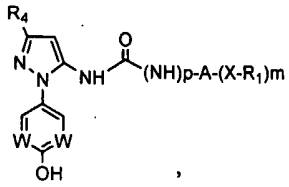
R_{31} = substituted phenyl ;

when Q is Q-21, then the compound of formula (I) is not



;

when Q is Q-22, then the compound of formula (I) is selected from the group consisting of



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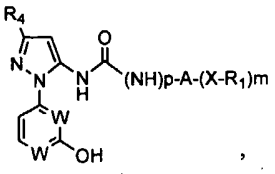

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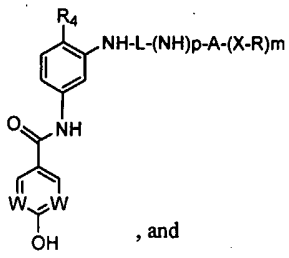
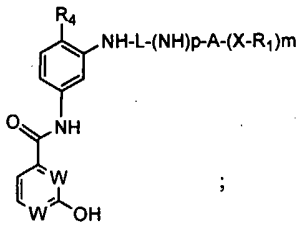
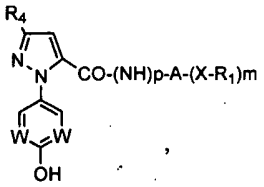


, and



;

when Q is Q-22 and q is 0, then the compound of formula (I) is selected from the group consisting of



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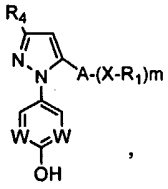

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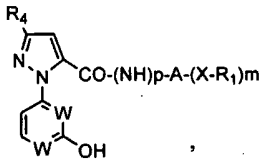

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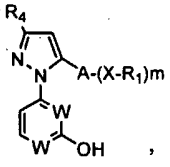

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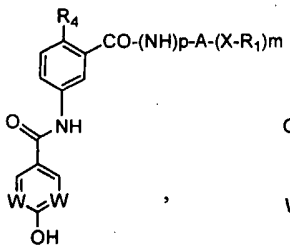

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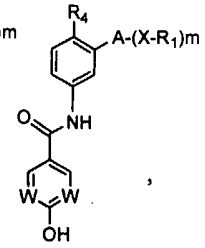

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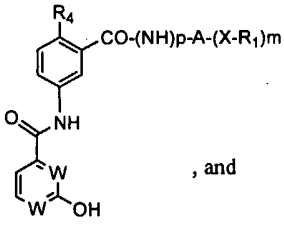

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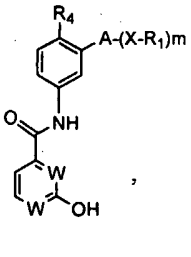
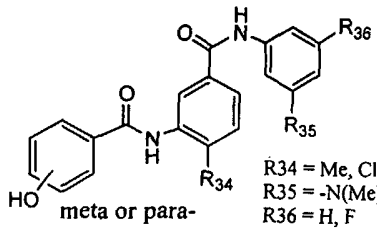
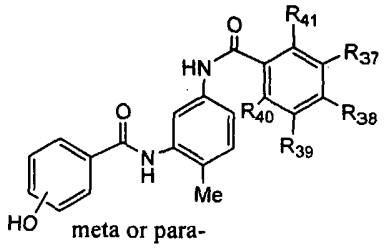
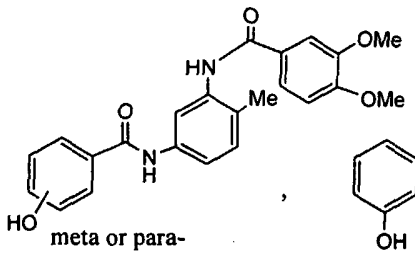


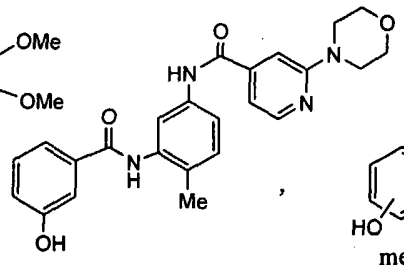
,

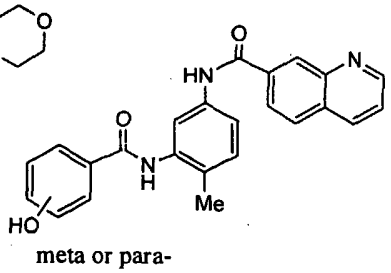
but excluding











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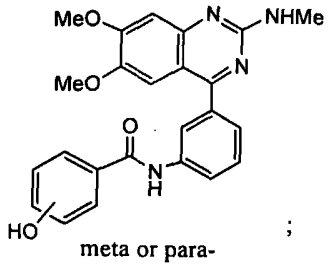
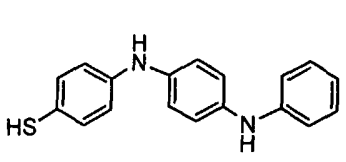


;

when Q is Q-23, then the compound of formula (I) is not



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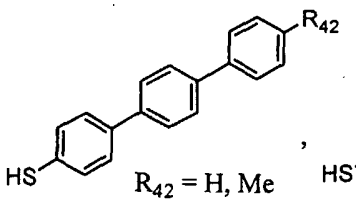

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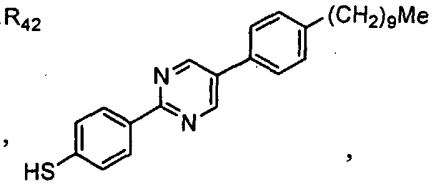

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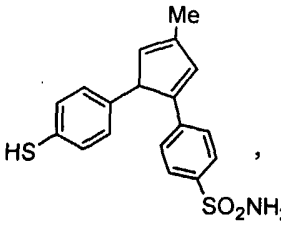

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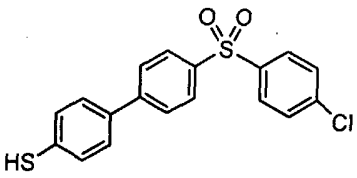

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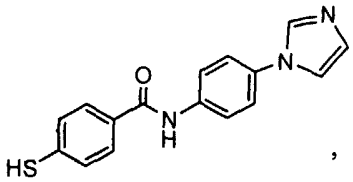

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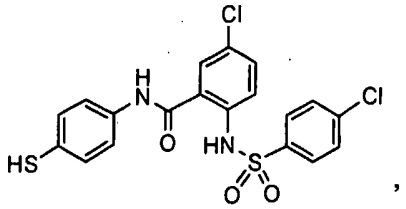
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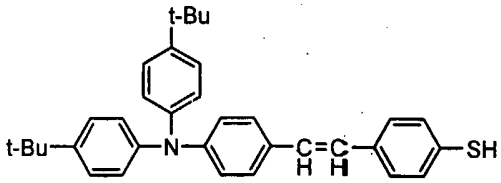
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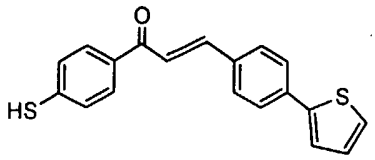
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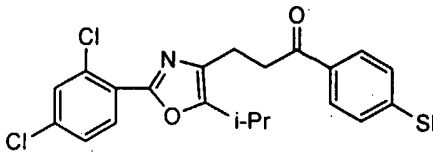
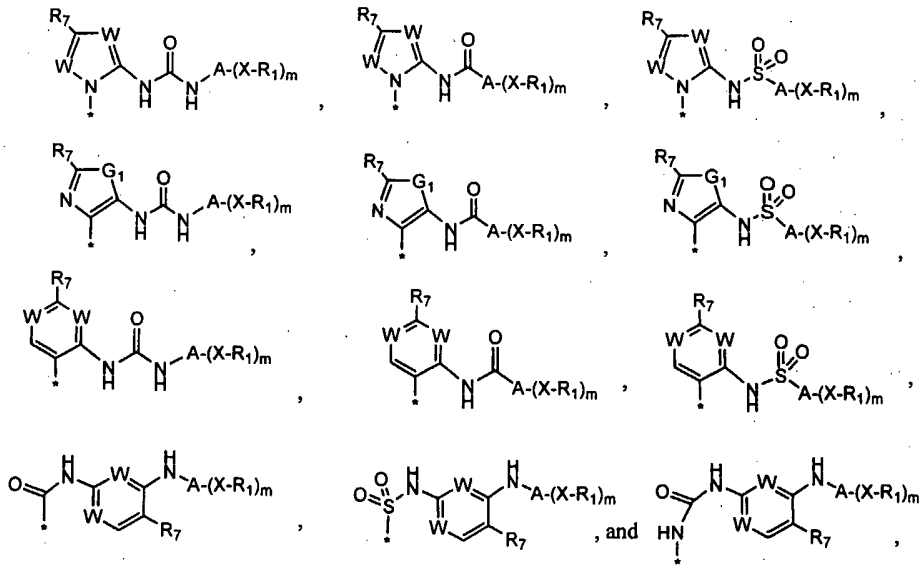

;

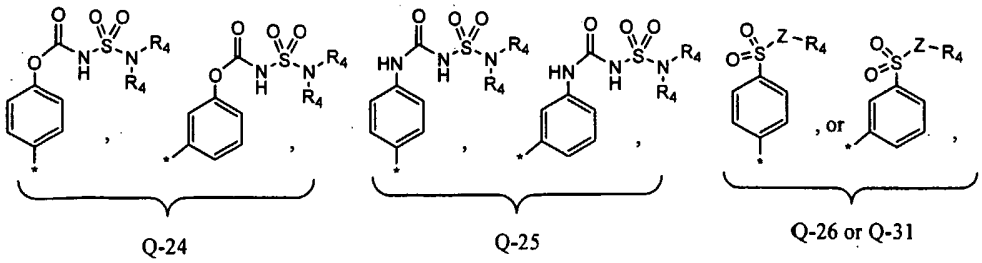
when Q is Q-24, Q-25, Q-26, or Q-31, then the compound of formula (I) is selected from the group consisting of


, and

wherein each W is individually selected from the group consisting of -CH- and -N-;

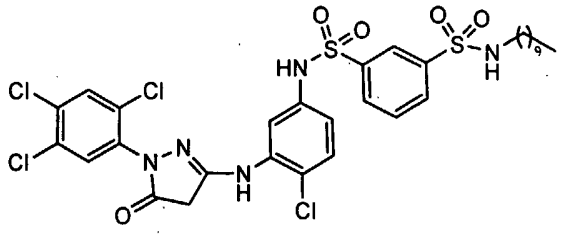
each G_1 is individually selected from the group consisting of -O-, -S-, and -N(R_4)-; and

* denotes the point of attachment to Q-24, Q-25, Q-26, or Q-31 as follows:



wherein each Z is individually selected from the group consisting of -O- and -N(R_4)-;

when Q is Q-31, then the compound of formula (I) is not



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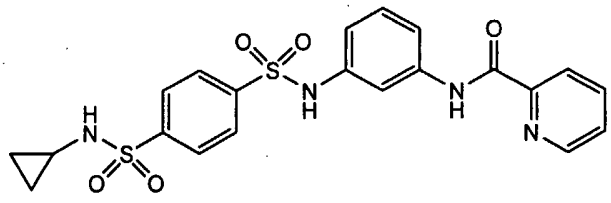
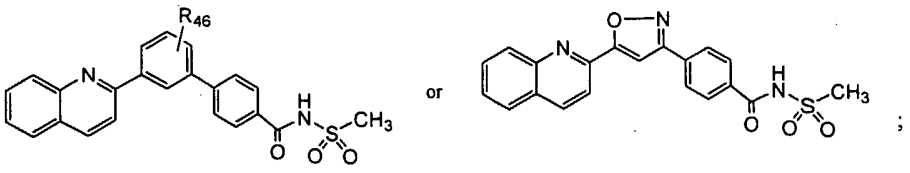


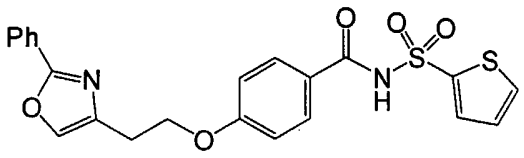
;

when Q is Q-28 or Q-29 and t is 0, then the compound of formula (I) is not



R_{46} = hydrogen, hydroxyalkyl, alkoxyalkyloxy, hydroxy

when Q is Q-28 or Q-29 and Y is an ether linkage, then the compound of formula (I) is not



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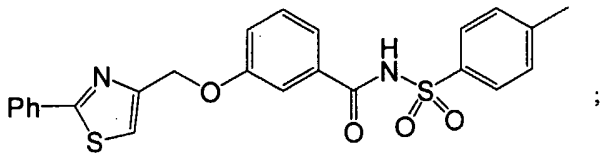
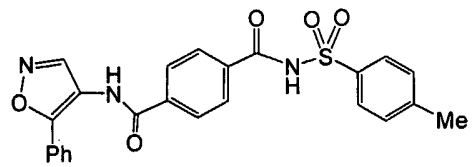


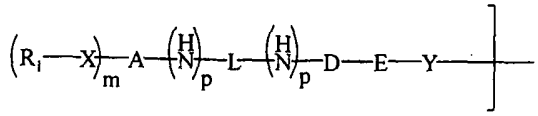
;

when Q is Q-28 or Q-29 and Y is -CONH-, then the compound of formula (I) is not



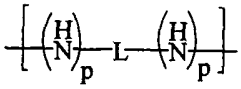
;

when Q is Q-32, then



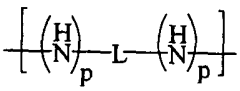
is not biphenyl, benzoxazolylphenyl, pyridylphenyl or bipyridyl;

when Q is Q-32, Y is -CONH-, q is 0, m is 0, and

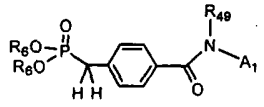


of formula (I) is -CONH-, then A is not phenyl;

when Q is Q-32, q is 0, m is 0, and



is -CONH-, then the compound of formula (I) is not



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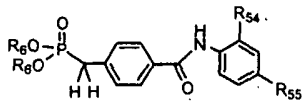

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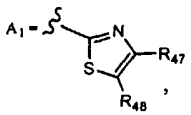

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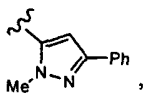

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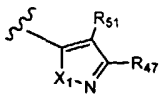

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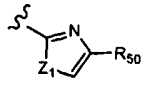


,

R_{47} = alkyl, substituted phenyl, thienyl, phenacetyl naphthyl

R_{48} = H, alkyl, Br, substituted phenyl, benzoyl, phenylsulfonyl

R_{49} = H, alkyl, phenyl

R_{50} = substituted phenyl

R_{54} = benzoyl, phenylalkylaminocarbonyl, substituted phenylaminocarbonyl H, Br

R_{55} = Cl, Br, SPh, benzoyl, phenylsulfonyl

R_{51} = H, phenylsulfonyl, phenyl, benzyl

R_6 = Et, i-Pr

R_{53} = substituted phenyl, substituted benzyl

X_1 = O, N-Ph, N-alkyl, N-carbamoyl

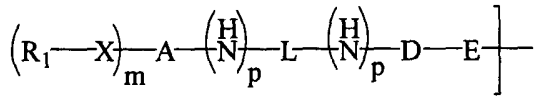
Z_1 = N(R50), O

when Q is Q-32, D is thiazolyl, q is 0, t is 0, p is 0, n is 0, and m is 0, then A is not phenyl or 2-pyridone;

when Q is Q-32, D is oxazolyl or isoxazolyl, q is 0, t is 0, p is 0, n is 0, and m is 0, then A is not phenyl;

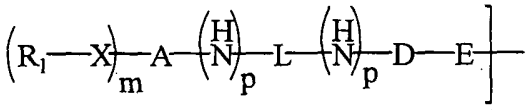
when Q is Q-32, D is pyrimidyl q is 0, t is 0, p is 0, n is 0, and m is 0, then A is not phenyl;

when Q is Q-32 and Y is an ether linkage, then



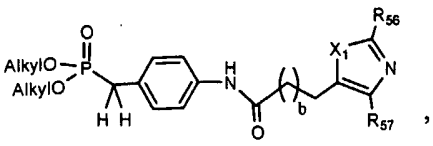
of formula (I) is not biphenyl or phenyloxazolyl;

when Q is Q-32 and Y is -CH=CH-, then



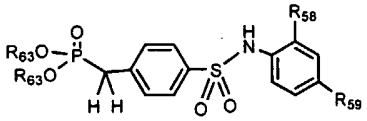
of formula (I) is not phenylaminophenyl;

when Q is Q-32, then the compound of formula (I) is not



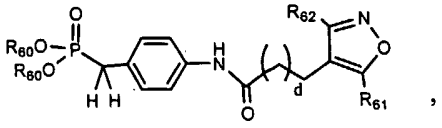
,

b = 0-1
X_1 = O, S
R56 = H, CF3, Cl, imidazolyl, amino, morpholino, phenylthio, cycloalkyl, benzyl, phenyl, phenoxy, thienyl, substituted alkyl, pyridylthio, pyrimidyl, benzylamino, N-benimidazolyl, pyridylcarbonylamino, ureido,N- thiourea, substituted alkanoylamino, phenylsulfonyl, substituted benzoyl, phenylalkenoyl, furanoyl, thienoyl, pyridinoyl,
R57 = substituted phenyl, substituted biphenyl

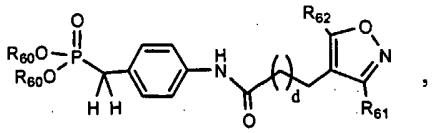


, or

R58 = substituted alkylaminocarbonyl, phenylaminocarbonyl
R59 = H, Cl



,



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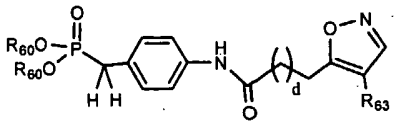

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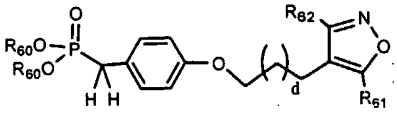
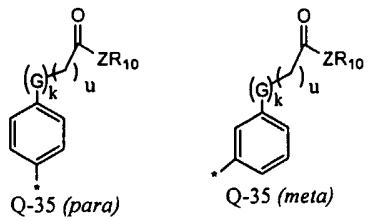


; and

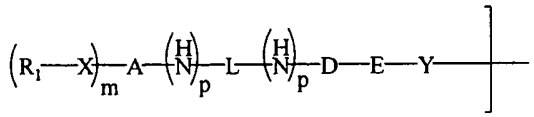
d = 0-2
R60 = H, alkyl
R61 = substituted phenyl, thienyl, Br
R62= H, alkyl, phenyl
R63 = substituted phenyl

when Q is Q-35 as shown

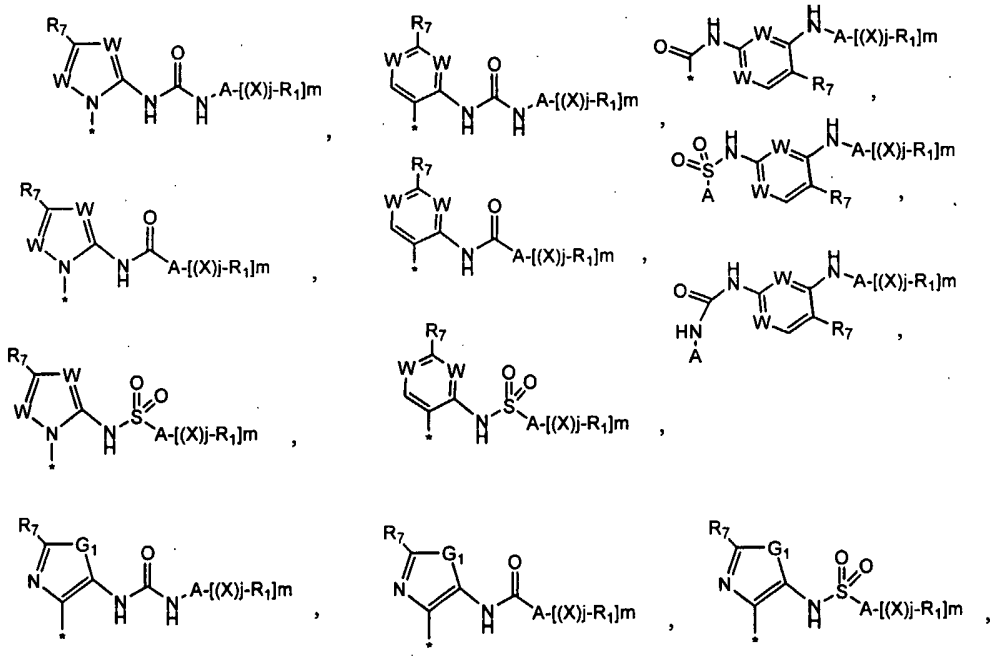


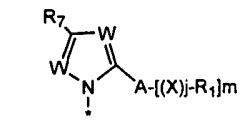
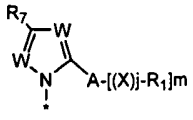
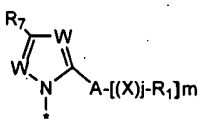
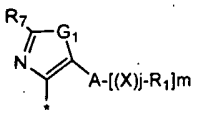
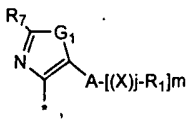
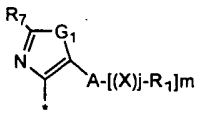
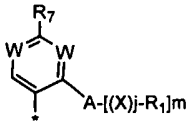
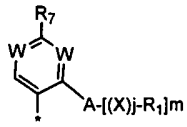
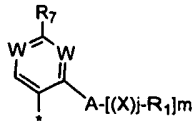
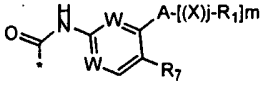
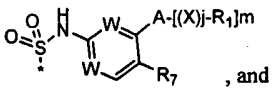
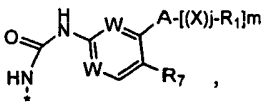
Q-35 *(para)* Q-35 *(meta)*

wherein G is selected from the group consisting of -O-, -S-, -NR_4-, and -CH_2-, k is 0 or 1, and u is 1, 2, 3, or 4, then

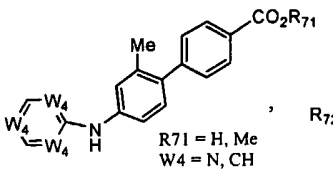


is selected from the group consisting of

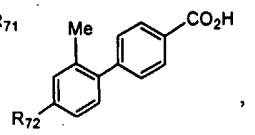



R7
W
W
N
A-[(X)j-R1]m
,

R7
W
W
N
A-[(X)j-R1]m
,

R7
W
W
N
A-[(X)j-R1]m
,

R7
G1
N
A-[(X)j-R1]m
,

R7
G1
N
A-[(X)j-R1]m
,

R7
G1
N
A-[(X)j-R1]m
,

R7
W
W
A-[(X)j-R1]m
,

R7
W
W
A-[(X)j-R1]m
,

R7
W
W
A-[(X)j-R1]m
,

O
H
N
W
W
A-[(X)j-R1]m
R7
,

O
O
S
H
N
W
W
A-[(X)j-R1]m
R7
, and

O
H
N
HN
W
W
A-[(X)j-R1]m
R7
,

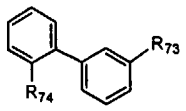
except that the compound of formula (I) is not



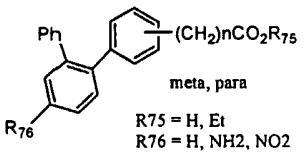
R71 = H, Me
W4 = N, CH



R72 = thiazolyl, isoxazolyl imidazolyl, furyl

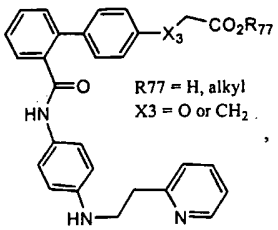


28.1 R73 = -OCH2CO2H
R74 = oxazolyl, imidazolyl
28.2 R73= CO2Me
R74= chlorophenyl

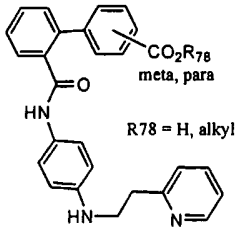


meta, para

R75 = H, Et
R76 = H, NH2, NO2
n = 0-1

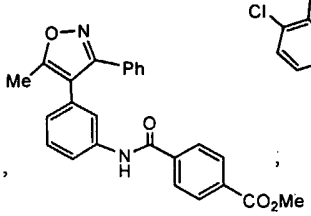


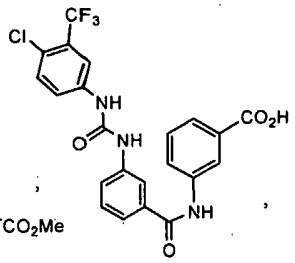
R77 = H, alkyl
X3 = O or CH_2

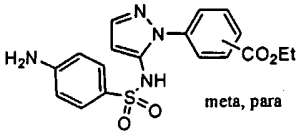


meta, para

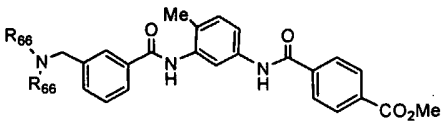
R78 = H, alkyl

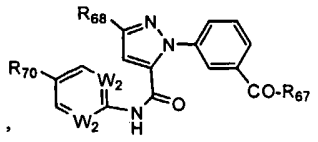




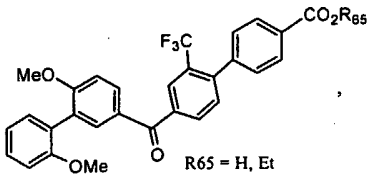


meta, para

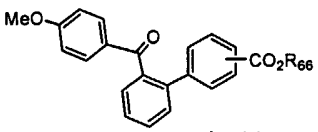




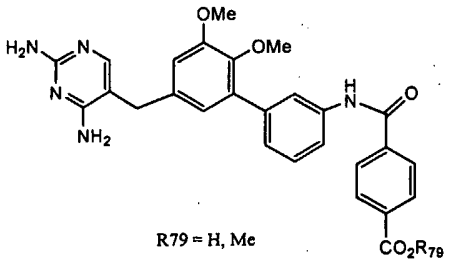
R67 = OH, NH_2
R68 = CF_3, Me
R70 = 2-$MeSO_2$-phen-1-yl,
2-NH_2SO_2-phen-1-yl,
morpholino, imidazolyl, $N(Et)_2$
W2 = CR_{69} or N



R65 = H, Et

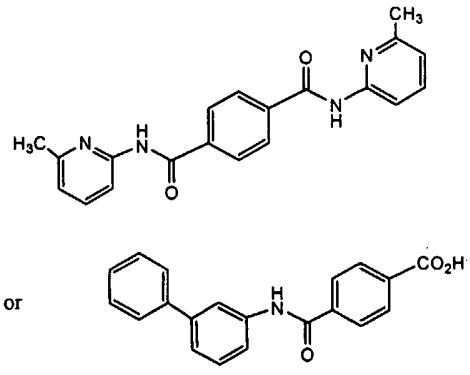


meta, para
R66 = alkyl



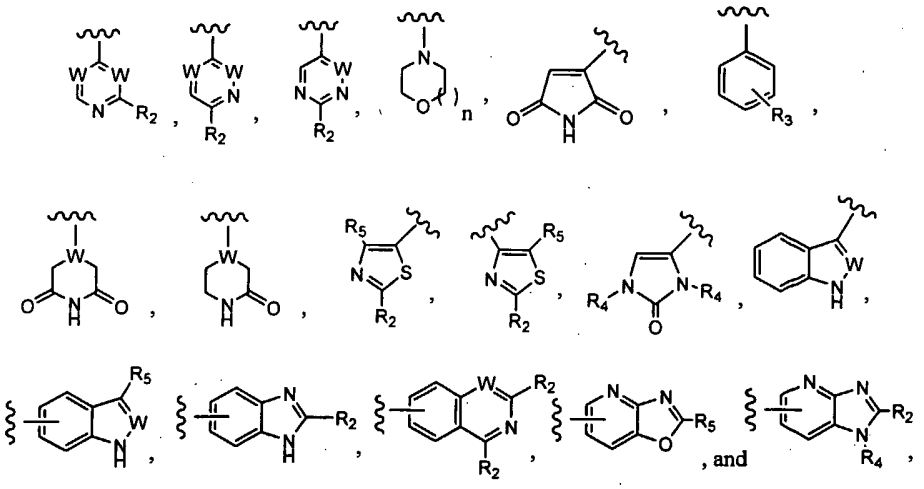
R79 = H, Me

, or



2. The compound of claim 1, wherein R_1 is selected from the group consisting of 6-5 fused heteroaryls, 6-5 fused heterocyclyls, 5-6 fused heteroaryls, and 5-6 fused heterocyclyls.

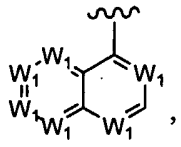
3. The compound of claim 2, where R_1 is selected from the group consisting of



each R_2 is individually selected from the group consisting of -H, alkyls, aminos, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, halogens, alkoxys, and hydroxys; and

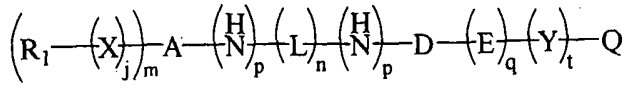
each R_3 is individually selected from the group consisting of -H, alkyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, alkoxys, hydroxys, cyanos, halogens, perfluoroalkyls, alkylsulfinyls, alkylsulfonyls, R_4NHSO_2-, and $-NHSO_2R_4$.

4. The compound of claim 1, wherein A is selected from the group consisting of aromatic, monocycloheterocyclic, and bicycloheterocyclic rings; and most preferably phenyl, naphthyl, pyridyl, pyrimidyl, thienyl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, benzothienyl, pyrazolylpyrimidinyl, imidazopyrimidinyl, purinyl, and



where each W_1 is individually selected from the group consisting of -CH- and -N-.

5. A method of modulating the activation state of p38 α-kinase comprising the step of contacting said kinase with a molecule having the formula



(II)

wherein:

R^1 is selected from the group consisting of aryls and heteroaryls;

each X and Y is individually selected from the group consisting of -O-, -S-, $-NR_6-$, $-NR_6SO_2-$, $-NR_6CO-$, alkynyls, alkenyls, alkylenes, $-O(CH_2)_h-$, and $-NR_6(CH_2)_h-$, where each h is individually selected from the group consisting of 1, 2, 3, or 4, and where for each of alkylenes, $-O(CH_2)_h-$, and $-NR_6(CH_2)_h-$, one of the methylene groups present therein may be optionally double-bonded to a side-chain oxo group except that where $-O(CH_2)_h-$ the introduction of the side-chain oxo group does not form an ester moiety;

A is selected from the group consisting of aromatic, monocycloheterocyclic, and bicycloheterocyclic rings;

D is phenyl or a five- or six-membered heterocyclic ring selected from the group consisting of pyrazolyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, thienyl, pyridyl, and pyrimidyl;

E is selected from the group consisting of phenyl, pyridinyl, and pyrimidinyl;

L is selected from the group consisting of -C(O)- and $-S(O)_2-$;

j is 0 or 1;

m is 0 or 1;

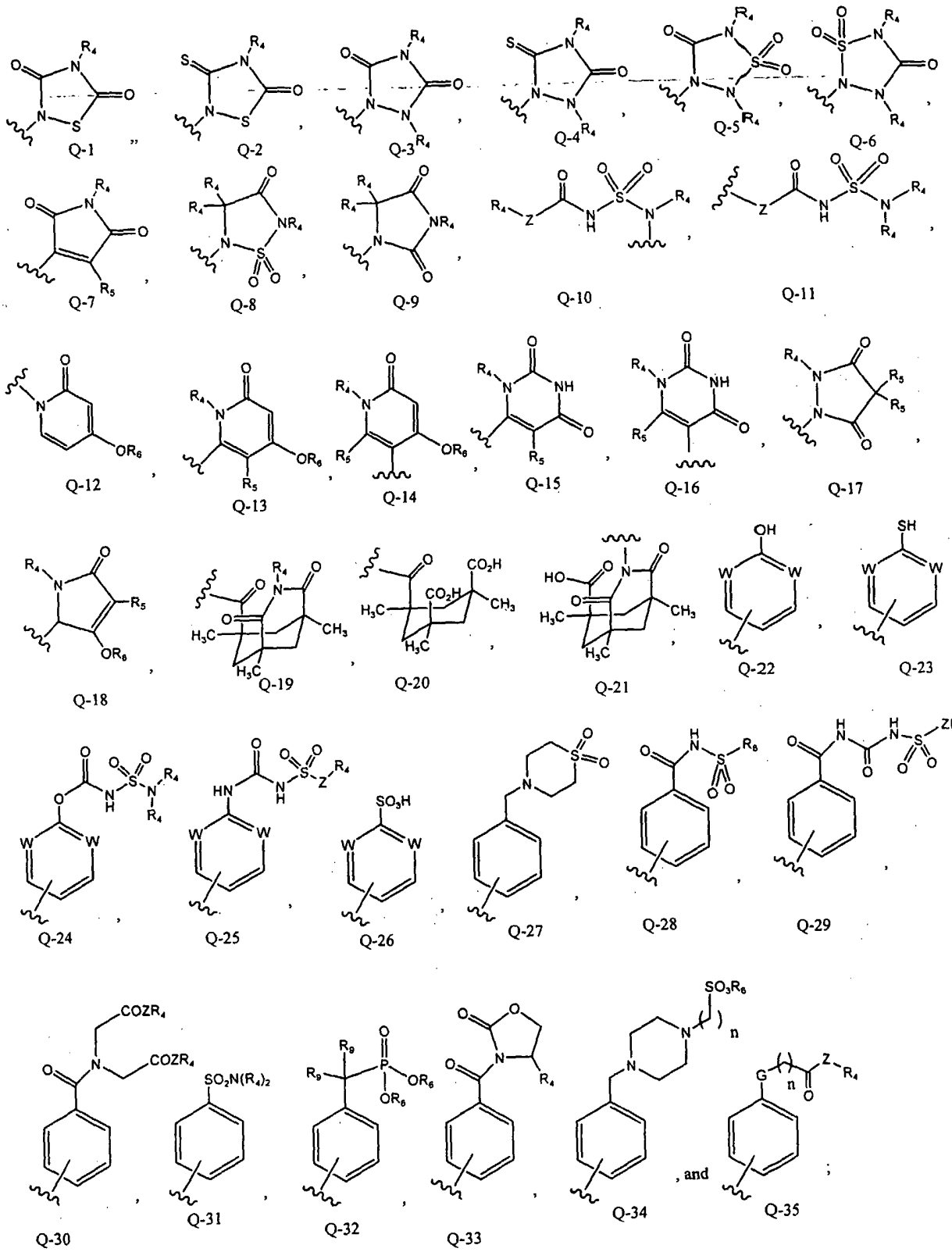
n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

t is 0 or 1;

Q is selected from the group consisting of


Q-1
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, and ;

each R_4 group is individually selected from the group consisting of -H, alkyls, aminoalkyls, alkoxyalkyls, aryls, aralkyls, heterocyclyls, and heterocyclylalkyls except when the R_4 substituent places a heteroatom on an *alpha*-carbon directly attached to a ring nitrogen on Q;

when two R_4 groups are bonded with the same atom, the two R_4 groups optionally form an alicyclic or heterocyclic 4-7 membered ring;

each R_5 is individually selected from the group consisting of -H, alkyls, aryls, heterocyclyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, hydroxys, alkoxys, aryloxys, alkylthios, arylthios, cyanos, halogens, perfluoroalkyls, alkylcarbonyls, and nitros;

each R_6 is individually selected from the group consisting of -H, alkyls, allyls, and β-trimethylsilylethyl;

each R_8 is individually selected from the group consisting of alkyls, aralkyls, heterocyclyls, and heterocyclylalkyls;

each R_9 group is individually selected from the group consisting of -H, -F, and alkyls, wherein when two R_9 groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring;

G is alkylene, $N(R_6)$, O;

each Z is individually selected from the group consisting of -O- and $-N(R_4)-$; and

each ring of formula (II) optionally includes one or more of R_7, where R_7 is a noninterfering substituent individually selected from the group consisting of -H, alkyls, aryls, heterocyclyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, hydroxys, alkoxys, aryloxys, alkylthios, arthylthios, cyanos, halogens, nitrilos, nitros, alkylsulfinyls, alkylsulfonyls, aminosulfonyls, and perfluoroalkyls,

and thereby causing modulation of said activation state.

6. The method of claim 5, said contacting step occurring at the region of a switch control pocket of said kinase.

7. The method of claim 6, said switch control pocket of said kinase comprising an amino acid residue sequence operable for binding to said Formula (II) molecule.

8. The method of claim 6, said switch control pocket selected from the group consisting of simple, composite and combined switch control pockets.

9. The method of claim 8, said region being selected from the group consisting of the α-C helix, the α-D helix, the catalytic loop, the switch control ligand sequence, the C-lobe residues, the glycine rich loop residues, and combinations thereof.

10. The method of claim 9, said α-C helix including SEQ ID NO. 2.

11. The method of claim 9, said catalytic loop including SEQ ID NO. 3.

12. The method of claim 9, said switch control ligand sequence being selected from the group consisting of SEQ ID NO. 4, SEQ ID NO. 5, and combinations thereof.

13. The method of claim 9, said C-lobe residues including SEQ ID NO. 6.

14. The method of claim 9, said glycine rich loop residues including SEQ ID NO. 7.

15. The method of claim 5, said kinase selected from the group consisting of the consensus wild type sequence and disease polymorphs thereof.

16. The method of claim 5, said activation state being selected from the group consisting of the upregulated and downregulated states.

17. The method of claim 5, said molecule being an antagonist of the on switch control pocket for said kinase.

18. The method of claim 5, said molecule being an agonist of the off switch control

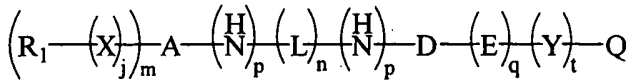
pocket for said kinase.

19. The method of claim 5, said method including the step of administering said molecule to an individual undergoing treatment for a condition selected from the group consisting of human inflammation, rheumatoid arthritis, rheumatoid spondylitis, ostero-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof.

20. The method of claim 19, said molecule being administered by a method selected from the group consisting of oral, parenteral, inhalation, and subcutaneous.

21. The method of claim 5, said molecule having the structure of the compound of claim 1.

22. An adduct comprising a molecule binding with a kinase, said molecule having the formula



(III)

wherein:

R^1 is selected from the group consisting of aryls and heteroaryls;

each X and Y is individually selected from the group consisting of -O-, -S-, $-NR_6-$, $-NR_6SO_2-$, $-NR_6CO-$, alkynyls, alkenyls, alkylenes, $-O(CH_2)_h-$, and $-NR_6(CH_2)_h-$, where each h is individually selected from the group consisting of 1, 2, 3, or 4, and where for each of alkylenes, $-O(CH_2)_h-$, and $-NR_6(CH_2)_h-$, one of the methylene groups present therein may be optionally double-bonded to a side-

chain oxo group except that where $-O(CH_2)_h-$ the introduction of the side-chain oxo group does not form an ester moiety;

A is selected from the group consisting of aromatic, monocycloheterocyclic, and bicycloheterocyclic rings;

D is phenyl or a five- or six-membered heterocyclic ring selected from the group consisting of pyrazolyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, thienyl, pyridyl, and pyrimidyl;

E is selected from the group consisting of phenyl, pyridinyl, and pyrimidinyl;

L is selected from the group consisting of $-C(O)-$ and $-S(O)_2-$;

j is 0 or 1;

m is 0 or 1;

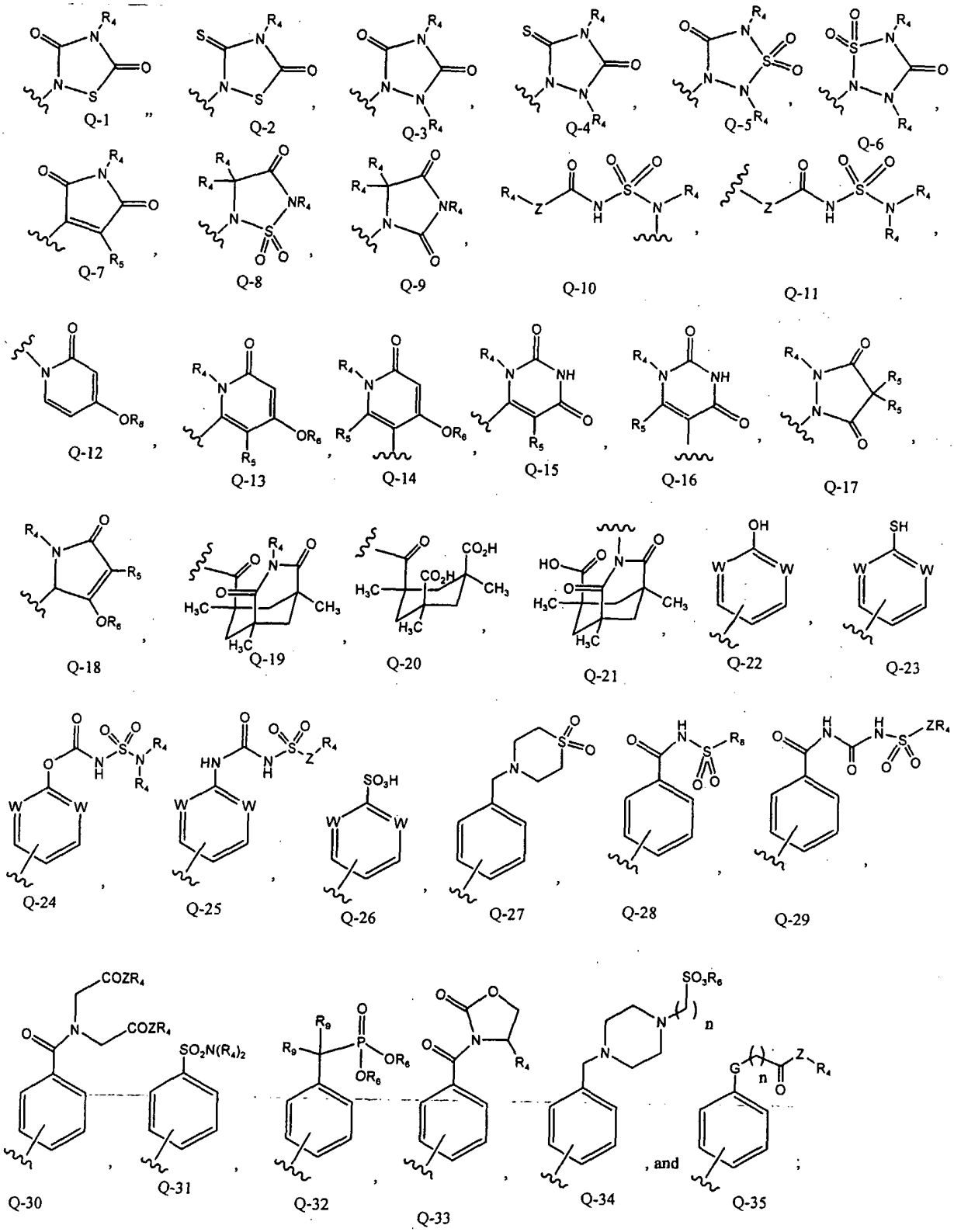
n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

t is 0 or 1;

Q is selected from the group consisting of



each R_4 group is individually selected from the group consisting of -H, alkyls, aminoalkyls, alkoxyalkyls, aryls, aralkyls, heterocyclyls, and heterocyclylalkyls except when the R_4 substituent places a heteroatom on an *alpha*-carbon directly attached to a ring nitrogen on Q;

when two R_4 groups are bonded with the same atom, the two R_4 groups optionally form an alicyclic or heterocyclic 4-7 membered ring;

each R_5 is individually selected from the group consisting of -H, alkyls, aryls, heterocyclyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, hydroxys, alkoxys, aryloxys, alkylthios, arylthios, cyanos, halogens, perfluoroalkyls, alkylcarbonyls, and nitros;

each R_6 is individually selected from the group consisting of -H, alkyls, allyls, and β-trimethylsilylethyl;

each R_8 is individually selected from the group consisting of alkyls, aralkyls, heterocyclyls, and heterocyclylalkyls;

each R_9 group is individually selected from the group consisting of -H, -F, and alkyls, wherein when two R_9 groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring;

G is alkylene, $N(R_6)$, O;

each Z is individually selected from the group consisting of -O- and $-N(R_4)-$; and

each ring of formula (III) optionally includes one or more of R_7, where R_7 is a noninterfering substituent individually selected from the group consisting of -H, alkyls, aryls, heterocyclyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, hydroxys, alkoxys, aryloxys, alkylthios, arthylthios, cyanos, halogens, nitrilos, nitros, alkylsulfinyls, alkylsulfonyls, aminosulfonyls, and perfluoroalkyls.

23. The adduct of claim 22, said molecule binding at the region of a switch control pocket of said kinase.

24. The adduct of claim 23, said switch control pocket of said kinase comprising an

amino acid residue sequence operable for binding to said Formula (III) molecule.

25. The adduct of claim 23, said switch control pocket selected from the group consisting of simple, composite and combined switch control pockets.

26. The adduct of claim 25, said region being selected from the group consisting of the α-C helix, the α-D helix, the catalytic loop, the switch control ligand sequence, the C-terminal residues, the glycine rich loop residues, and combinations thereof.

27. The adduct of claim 26, said α-C helix including SEQ ID NO. 2.

28. The adduct of claim 26, said catalytic loop including SEQ ID NO. 3.

29. The adduct of claim 26, said switch control ligand sequence being selected from the group consisting of SEQ ID NO. 4, SEQ ID NO. 5, and combinations thereof.

30. The adduct of claim 26, said C-lobe residues selected from SEQ ID NO. 6.

31. The adduct of claim 26, said glycine rich loop residues taken from SEQ ID NO. 7.

32. The adduct of claim 22, said kinase selected from the group consisting of the consensus wild type sequence and disease polymorphs thereof.

33. The adduct of claim 22, said molecule having the structure of the compound of claim 1.

34. A compound having the formula

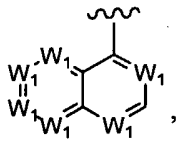
$$\mathbf{A\text{-}T\text{-}(L)_n\text{-}(NH)_p\text{-}D\text{-}(E)_q\text{-}(Y)_t\text{-}Q}$$

(IB)

wherein:

Y is selected from the group consisting of -O-, -S-, -NR_6-, -NR_6SO_2-, -NR_6CO-, alkynyls, alkenyls, alkylenes, -$O(CH_2)_h$-, and -$NR_6(CH_2)_h$-, where each h is individually selected from the group consisting of 1, 2, 3, or 4, and where for each of alkylenes, -$O(CH_2)_h$-, and -$NR_6(CH_2)_h$-, one of the methylene groups present therein may be optionally double-bonded to a side-chain oxo group except that where -$O(CH_2)_h$- the introduction of the side-chain oxo group does not form an ester moiety;

A is selected from the group consisting of aromatic, monocycloheterocyclic, and bicycloheterocyclic rings; and most preferably phenyl, naphthyl, pyridyl, pyrimidyl, thienyl, furyl, pyrrolyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, benzothienyl, pyrazolylpyrimidinyl, imidazopyrimidinyl, purinyl, and



where each W1 is individually selected form the group consisting of –CH- and –N-.

D is phenyl or a five- or six-membered heterocyclic ring selected from the group consisting of pyrazolyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, thienyl, pyridyl, and pyrimidyl;

E is selected from the group consisting of phenyl, pyridinyl, and pyrimidinyl;

L is selected from the group consisting of -C(O)- and -$S(O)_2$-;

T is NR_6, O, alkylene, -$O(CH_2)_h$-, or -$NR_6(CH_2)_h$-, where each h is individually selected from the group consisting of 1, 2, 3, or 4, or T is absent wherein A is directly bonded to –$(L)_n(NH)_p$-D-$(E)_q$-$(Y)_t$-Q;

n is 0 or 1;

p is 0 or 1;

q is 0 or 1;

t is 0 or 1;

v is 1,2, or 3;

x is 1 or 2;

Q is selected from the group consisting of formulae Q36 – Q59 , inclusive,

each R_4 group is individually selected from the group consisting of -H, alkyls , aminoalkyls, alkoxyalkyls, aryls, aralkyls, heterocyclyls, and heterocyclylalkyls except when the R_4 substituent places a heteroatom on an *alpha*-carbon directly attached to a ring nitrogen on Q;

when two R_4 groups are bonded with the same atom, the two R_4 groups optionally form an alicyclic or heterocyclic 4-7 membered ring;

each R_6 is individually selected from the group consisting of -H, alkyls , allyls, and B-trimethylsilylethyl;

each R_8 is individually selected from the group consisting of alkyls, phenyl, naphthyl, aralkyls, heterocyclyls, and heterocyclylalkyls;

each R_9 group is individually selected from the group consisting of -H, -F, and alkyls, wherein when two R_9 groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring;

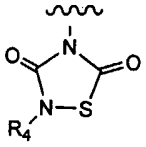
each $R_{9'}$ group is individually selected from the group consisting of -F, and alkyls, wherein when two $R_{9'}$ groups are geminal alkyl groups, said geminal alkyl groups may be cyclized to form a 3-6 membered ring;

each R_{10} is alkyl or perfluoroalkyl;

G is alkylene, $N(R_6)$, O;

each Z is individually selected from the group consisting of -O- and $-N(R_4)-$; and each ring of formula (I) optionally includes one or more of $R_{7'}$, where $R_{7'}$ is a substituent individually selected from the group consisting of -H, alkyls , aryls , heterocyclyls, alkylaminos, arylaminos, cycloalkylaminos, heterocyclylaminos, hydroxys, alkoxys, perfluoroalkoxys, aryloxys, alkylthios, arthylthios, cyanos, halogens, nitrilos, nitros, alkylsulfinyls, alkylsulfonyls, aminosulfonyls, perfluoroalkyls; aminooxaloylamino; alkylaminooxaloylamino; dialkylaminooxaloylamino; morpholinooxaloylamino; piperazinooxaloylamino; alkoxycarbonylamino; heterocyclyloxycarbonylamino;

heterocyclylalkyloxycarbonylamino; heterocyclylcarbonylamino; heterocyclylalkylcarbonylamino; aminoalkyloxycarbonylamino; alkylaminoalkyloxycarbonylamino; or dialkylaminoalkyloxycarbonylamino, said Q36-Q59 groups being



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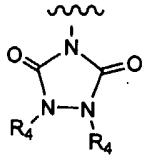

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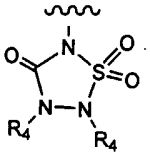

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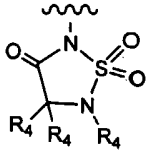

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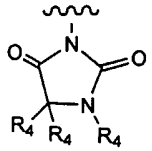

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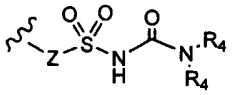

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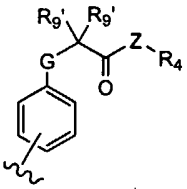

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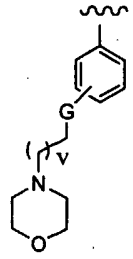

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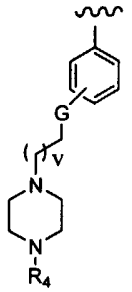

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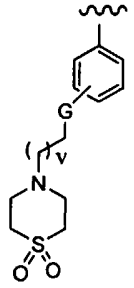

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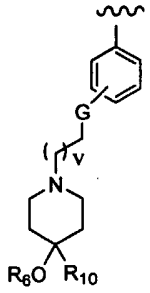

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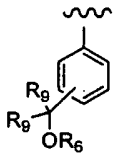

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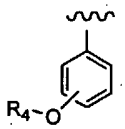

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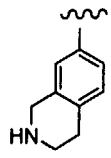

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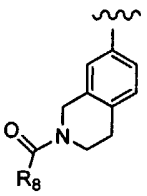

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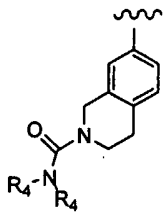
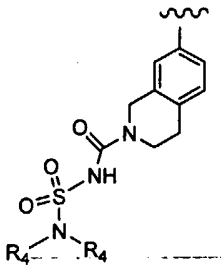
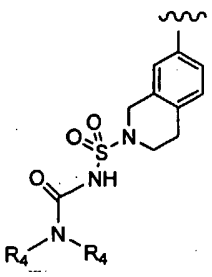


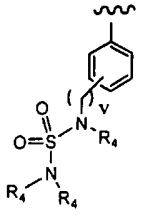
Q-51



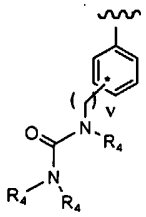
Q-52



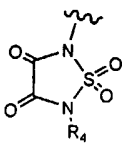
Q-53



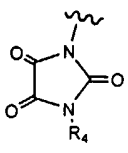
Q-54



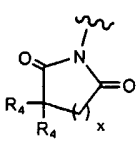
Q-55



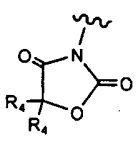
Q-56



Q-57



Q-58



Q-59

35. A method of modulating the activation state of p38 α-kinase comprising the step of contacting said kinase with a molecule having the formula of claim 34.

36. The method of claim 35, said contacting step occurring at the region of a switch control pocket of said kinase.

37. The method of claim 36, said switch control pocket of said kinase comprising an amino acid residue sequence operable for binding to said Formula (IB) molecule.

38. The method of claim 36, said switch control pocket selected from the group consisting of simple, composite and combined switch control pockets.

39. The method of claim 38, said region being selected from the group consisting of the α-C helix, the α-D helix, the catalytic loop, the switch control ligand sequence, the C-lobe residues, the glycine rich loop residues, and combinations thereof.

40. The method of claim 39, said α-C helix including SEQ ID NO. 2.

41. The method of claim 39, said catalytic loop including SEQ ID NO. 3.

42. The method of claim 39, said switch control ligand sequence being selected from the group consisting of SEQ ID NO. 4, SEQ ID NO. 5, and combinations thereof.

43. The method of claim 39, said C-lobe residues including SEQ ID NO. 6.

44. The method of claim 39, said glycine rich loop residues including SEQ ID NO. 7.

45. The method of claim 35, said kinase selected from the group consisting of the consensus wild type sequence and disease polymorphs thereof.

46. The method of claim 35, said activation state being selected from the group consisting of the upregulated and downregulated states.

47. The method of claim 35, said molecule being an antagonist of the on switch control pocket for said kinase.

48. The method of claim 35, said molecule being an agonist of the off switch control pocket for said kinase.

49. The method of claim 35, said method including the step of administering said molecule to an individual undergoing treatment for a condition selected from the group consisting of human inflammation, rheumatoid arthritis, rheumatoid spondylitis, ostero-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof.

50. The method of claim 49, said molecule being administered by a method selected from the group consisting of oral, parenteral, inhalation, and subcutaneous.

51. An adduct comprising a molecule binding with a p 38-alpha kinase, said molecule having the formula of claim 34.

52. The adduct of claim 51, said molecule binding at the region of a switch control pocket of said kinase.

53. The adduct of claim 52, said switch control pocket of said kinase comprising an amino acid residue sequence operable for binding to said molecule.

54. The adduct of claim 52, said switch control pocket selected from the group consisting of simple, composite and combined switch control pockets.

55. The adduct of claim 52, said region being selected from the group consisting of the α-C helix, the α-D helix, the catalytic loop, the switch control ligand sequence, the C-terminal residues, the glycine rich loop residues, and combinations thereof.

56. The adduct of claim 55, said α-C helix including SEQ ID NO. 2.

57. The adduct of claim 55, said catalytic loop including SEQ ID NO. 3.

58. The adduct of claim 55, said switch control sequence being selected from the group consisting of SEQ ID NO. 4, SEQ ID NO. 5, and combinations thereof.

59. The adduct of claim 55, said C-lobe residues selected from the group consisting of SEQ ID NO. 6.

60. The adduct of claim 55, said glycine rich loop residues including SEQ ID NO. 7.

61. The adduct of claim 51, said kinase selected from the group consisting of the consensus wild type P 38-alpha kinase sequence and disease polymorphs thereof.

62. A kinase-modulator adduct comprising a p38-alpha kinase having a switch control pocket with a non-naturally occurring molecule bound to the kinase at the region of said switch control pocket, said molecule serving to at least partially regulate the biological activity of said protein by inducing or restricting the conformation of the protein.

63. The adduct of claim 62, said molecule serving to induce a conformation change in said kinase.

64. The adduct of claim 62, said molecule serving to restrict a conformation change in said kinase.

65. The adduct of claim 62, said region of the switch control pocket being selected from the group consisting of the α-C helix, the α-D helix, the catalytic loop, the switch control ligand sequence, the C-terminal residues, the glycine rich loop residues, and combinations thereof.

66. The adduct of claim 65, said α-C helix including SEQ ID NO. 2.

67. The adduct of claim 65, said catalytic loop including SEQ ID NO. 3.

68. The adduct of claim 65, said switch control sequence being selected from the group consisting of SEQ ID NO. 4, SEQ ID NO. 5, and combinations thereof.

69. The adduct of claim 65, said C-lobe residues selected from the group consisting of SEQ ID NO. 6.

70. The adduct of claim 65, said glycine rich loop residues including SEQ ID NO. 7.

71. The adduct of claim 62, said kinase also having a switch control ligand, said ligand interacting *in vivo* with said pocket to regulate the conformation and biological activity of said kinase such that the kinase will assume a first conformation and a first biological activity upon said ligand-pocket interaction, and will assume a second, different conformation and biological activity in the absence of said ligand-pocket interaction.

72. The adduct of claim 62, said pocket being an on-pocket, said molecule binding with said kinase at the region of said on-pocket as an agonist.

73. The adduct of claim 62, said pocket being an on-pocket, said molecule binding with said kinase at the region of said on-pocket as an antagonist.

74. The adduct of claim 62, said pocket being an off-pocket, said molecule binding with said kinase at the region of said off-pocket as an agonist.

75. The adduct of claim 62, said pocket being an off-pocket, said molecule binding with said kinase at the region of said off-pocket as an antagonist.

76. A method of altering the biological activity of a p38 kinase comprising the steps of:

providing a p38-alpha kinase having a switch control pocket;

contacting said kinase with a non-naturally occurring molecule modulator; and

causing said modulator to bind with said kinase at the region of said pocket in order to at least partially regulate the biological activity of the kinase by inducing or restricting the conformation of the kinase.

77. The method of claim 76, said molecule serving to induce a conformation change in said kinase.

78. The method of claim 76, said molecule serving to restrict a conformation change in said kinase.

79. The method of claim 76, said kinase also having a switch control ligand, said ligand interacting *in vivo* with said pocket to regulate the conformation and biological activity of said kinase such that the kinase will assume a first conformation and a first biological activity upon said ligand-pocket interaction, and will assume a second, different conformation and biological activity in the absence of said ligand-pocket interaction.

80. The method of claim 76, said pocket being an on-pocket, said molecule binding with said kinase at the region of said on-pocket as an agonist.

81. The method of claim 76, said pocket being an on-pocket, said molecule binding with said kinase at the region of said on-pocket as an antagonist.

82. The method of claim 76, said pocket being an off-pocket, said molecule binding with said kinase at the region of said off-pocket as an agonist.

83. The method of claim 76, said pocket being an off-pocket, said molecule binding with said kinase at the region of said off-pocket as an antagonist.