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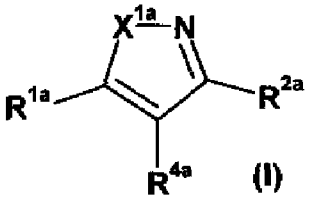
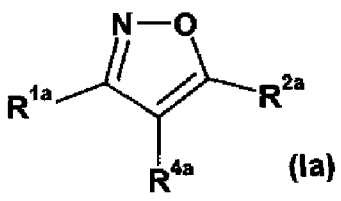
(54) **Title**: ARYLPYRAZOLES AND ARYLISOXAZOLES AND THEIR USE AS PKD MODULATORS



(I)



(Ia)

(57) **Abstract**: The present invention provides novel organic compounds of formula (I) or (Ia): which may be inhibitors of a selective subset of kinases belonging to the AGC or calmodulin kinase family, such as for example PKD-1/2/3, inhibitors of histone deacetylase (HDAC) phosphorylation, or inhibitors of other kinases. The selectivity of which would depend on the structural variation thereof, and for treatment of a disorder or disease mediated by those selected AGC or calmodulin family kinases. These organic compounds can be used to treat various PKD associated states such as heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, or hyperproliferative skin disorders.

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ARYLPYRAZOLES AND ARYLISOXAZOLES AND THEIR USE AS PKD MODULATORS

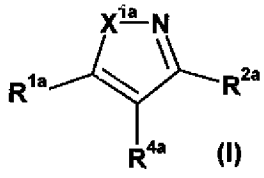
The role of protein kinase C (PKC) in cell signaling has been known for almost two decades and since then a whole family of PKC-like enzymes has been identified. In 1994, a novel PKC-related enzyme, PKCmu, otherwise known as protein kinase D (PKD), was identified. This widely expressed cytosolic serine-threonine kinase can be recruited to the trans-Golgi network and is, therefore, considered a modulator of cell trafficking. This was followed in 1999, by the identification of PKCnu (PKD3), and in 2001 by the identification of PKD2, the constitutive expression of which was largely restricted to the pancreas, heart, lung, smooth muscle, brain and rapidly proliferating tissues such as testis and colonic crypts. PKD, PKCnu and PKD2 are now accepted as a distinct PKC-related family of protein kinases, called the PKD family.

The three isoforms of the PKD family, PKD1/PKCmu PKD2 and PKD3/PKCnu, share a similar architecture with regulatory sub-domains that play specific roles in the activation, translocation and function of the enzymes. The PKD enzymes have been implicated in diverse cellular functions, including Golgi organization and plasma membrane directed transport, metastasis, immune responses, apoptosis and cell proliferation. FEBS Lett. 2003 Jul 3;546(1):81-6.

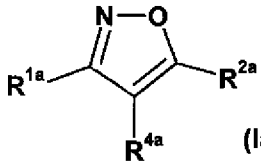
The PKD enzymes represent a new family of second messenger stimulated kinases, with diacylglycerol as a prime, but not the sole, mediator of activation. Their molecular architecture features a catalytic domain, unrelated to that of PKC family members; a large inhibitory, regulatory domain, comprised of two zinc fingers; and a pleckstrin homology domain. These different sub-domains play distinctive roles in the activation, translocation and biological functions of the kinase. The enzymes have been implicated in signaling mechanisms controlling cell proliferation and programmed cell death and in metastasis, immune responses, and Golgi restructuring and function. A variety of proteins specifically interact with the different sub-domains of the enzymes and directs their wide range of cellular functions. Int J Biochem Cell Biol. 2002 Jun;34(6):577-81.

The invention pertains, at least in part, to PKD modulating compounds and methods for using them to treat PKD associated disorders. Examples of PKD modulating compounds include compounds of formulae I-VI or a compound otherwise described herein .

In another embodiment, the invention pertains, at least in part, to compounds of Formula (I) or (Ia):


(I)

or

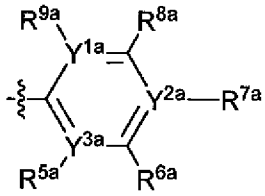

(Ia)

wherein:

X^{1a} is NR^{10a} or O;

R^{1a} is a substituted or unsubstituted aryl;

R^{2a} is: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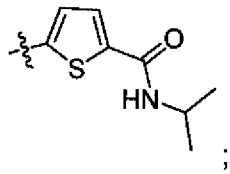

;

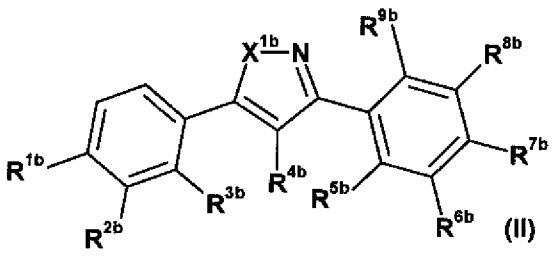
R^{5a}, R^{6a}, R^{7a}, R^{8a} and R^{9a} are each, independently, absent, hydrogen, halogen, alkyl, aminocarbonyl, carbonyl, heterocyclyl, hydroxyl, alkoxyl, amido or imino; R^{5a} and R^{6a} may be linked to form an aryl or heterocyclyl ring; R^{6a} and R^{7a} may be linked to form an aryl ring; R^{8a} and R^{9a} may be linked to form a lactam;

Y^{1a}, Y^{2a} and Y^{3a} are each, independently, N or C;

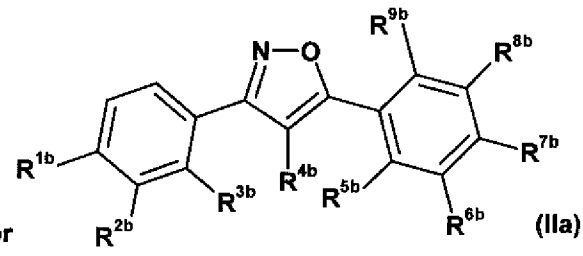
R^{10a} and R^{4a} are each, idependently, hydrogen, halogen or alkyl; and

pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In another embodiment, the invention also pertains, at least in part, to compounds of Formula (II) or (IIa):


(II)

or


(IIa)

wherein

X^{1b} is NR^{10b} or O;

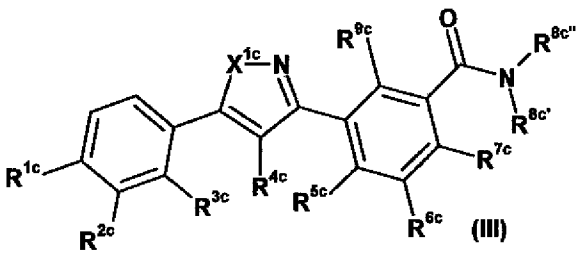
R^{1b} and R^{2b} are each independently hydrogen, alkyl, alkenyl, halogen, amino, amido, heterocyclyl or carbonyl;

R^{3b} is hydrogen or alkoxy;

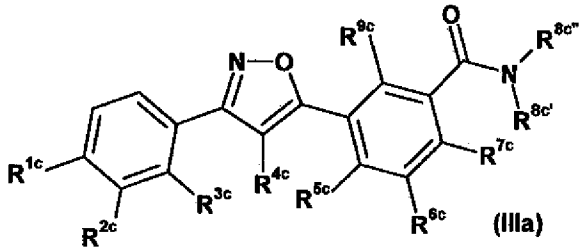
R^{5b} and R^{6b} are each hydrogen or R^{5b} and R^{6b} may be linked together to form an aryl or heterocyclyl ring;

R^{7b} and R^{8b} are each, independently, a hydrogen, aminocarbonyl, carbonyl or heterocyclyl or R^{6b} and R^{7b} may be linked together to form an aryl ring; R^{4b}, R^{9b} and R^{10b} are each, idependently, hydrogen, halogen, alkyl or alkoxy; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In yet another embodiment, the invention pertains, at least in part, to compounds of Formula (III) or (IIIa):


(III)

or


(IIIa)

wherein

X^{1c} is NR^{10c} or O;

R^{1c} is heterocyclyl;

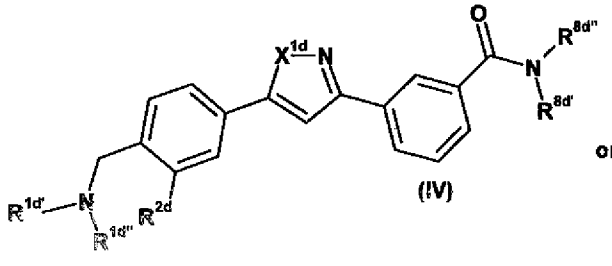
R^{2c}, R^{3c}, R^{4c}, R^{9c} and R^{10c} are each, independently, hydrogen, alkyl, halogen or alkoxy;

R^{5c}, R^{6c} and R^{7c} are each, independently, hydrogen, halogen or alkyl;

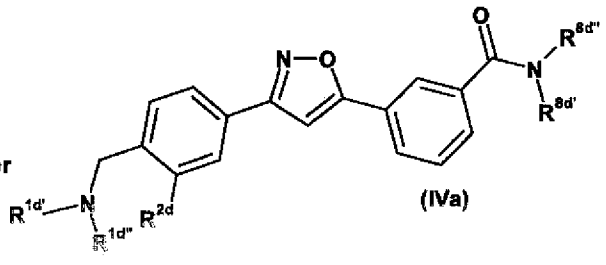
$R^{8c'}$ and $R^{8c''}$ are each, independently, a hydrogen, hydroxyl, alkyl, alkoxyl, amido or heterocyclyl;

R^{5c} and R^{6c} can be linked together to form an aryl or heterocyclyl ring; R^{6c} and R^{7c} can be linked together to form an aryl ring; $R^{8c''}$ and R^{9c} may be linked together to form a lactam; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In another embodiment, the invention pertains, at least in part, to compounds of Formula (IV) or (IVa):


(IV)

or


(IVa)

wherein:

X^{1d} is NH or O;

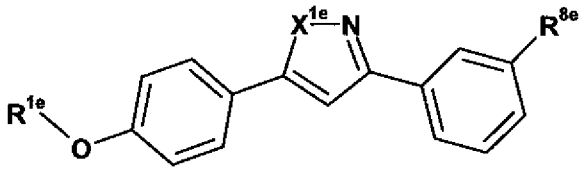
$R^{1d'}$ and $R^{1d''}$ are each, independently, hydrogen, alkyl, acyl, amido, amino or heterocyclyl;

R^{2d} is hydrogen or halogen;

$R^{8d'}$ and $R^{8d''}$ are each, independently, hydrogen, alkyl, amido or imino; and

$R^{1d'}$ and $R^{1d''}$ may be linked to form a heterocyclyl ring; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In another embodiment, the invention pertains, at least in part, to compounds of Formula (V):



(V)

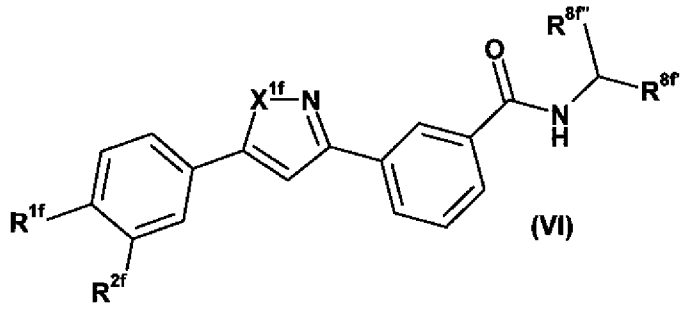
wherein:

X^{1e} is NH or O;

R^{1e} is hydrogen, alkyl, amino, amido, heterocyclyl or alkoxycarbonylalkyl;

R^{8e} is carbonyl or amido; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In another embodiment, the invention pertains, at least in part, to compounds of Formula (VI):



(VI)

wherein:

X^{1f} is NH or O;

R^{1f} is alkyl or heterocyclyl;

R^{2f} is hydrogen or halogen;

R^{8f} is alkyl or cyano;

$R^{8f'}$ is hydrogen or alkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In one embodiment, the invention pertains, at least in part, to methods for treating a subject for a PKD associated state by administering to the subject an effective amount of a compound of the invention (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein).

In another embodiment, the invention pertains, at least in part, to pharmaceutical compositions comprising a compound of the invention (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein), and a pharmaceutically acceptable carrier.

In yet another embodiment, the invention pertains to compounds of the present invention, (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein), for use as a medicament.

In another embodiment of the invention also pertains to kits comprising, compounds of the present invention, (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein).

The invention pertains, at least in part, to compounds, pharmacuectical compositions containing the compounds and methods of use thereof. The present invention also relates to to the use of these compounds as modulators of PKD-1/2/3, and inhibitors of histone deacetylase (HDAC) phosphorylation. The compounds of the invention may also be used, for example, to treat various PKD associated states such as heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, hyperproliferative skin disorders, etc.

PKD is believed to be implicated in a number of clinical conditions including infectious/inflammatory disease, cancer, metabolic disease, and cardiovascular disorders. PKD has been shown to be involved in the down-stream response to receptor-antigen binding in T and B cells, neutrophils, and mast cells, and mediation of the mast cell response to a variety of cytokines. Moreover, PKD may mediate the mitogenic response to a variety of biological mediators and molecules, such as for example, the biological responses elicited by PKC activation in small cell lung cancer cells, and responses that sensitize cells for apoptosis induced by genotoxic chemotherapeutics. PKD may be involved in metabolic control. PKD plays a role in pre-adipocyte differentiation, and the cellular location of PKD in skeletal muscle changes upon transition between the fasted and the fed state. Moreover, PKD is expressed in the myocardium and vascular smooth muscle and activated by oxidative stress. PKD is activated by key cardiovascular mediators such as angiotensin II, endothelin and PDGF. Modulation of PKD thus has the potential to modulate immune cell regulation, tumor progression, metabolic disorders, cardiovascular disease as well as treating PKD associated disorders.

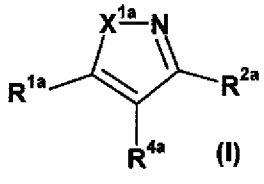
In particular, PKD1 may play a role in development of central tolerance in thymus gland, proliferation of pancreatic cancer cells, cardiac myocyte contraction, endothelial cell proliferation, osteoblasts differentiation, and prostate cancer cells adhesion and invasion. Furthermore, compounds that specifically modulate PKD1 may be used to limit cardiac hypertrophy.

Since its identification, PKD has been shown to play a role in growth factor signaling as well as in stress-induced signaling. It enhances expression of anti-apoptotic genes through the activation of NFkB and is activated upon treatment of cells with genotoxic chemotherapeutics. Moreover, PKD has emerged as an important regulator of plasma membrane enzymes and receptors. In some cases, it mediates cross-talk between different signaling systems.

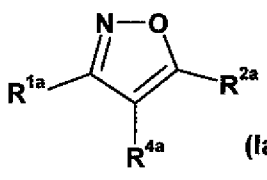
PKD1 has been shown to play a role in proliferation of keratinocytes in skin, B and T lymphocytes and mast cells signaling. Transcriptional regulation of gene expression is tightly coupled to histone deacetylases (HDAC) and histone acetyltransferase (HAT) that modify the access of transcription factors to DNA binding sites. PKD1 has been shown to participate in nuclear export of HDAC5. HDAC5 is phosphorylated by PKD1 in cardiac myocytes, which results in the binding of 14-3-3 protein to the phosphoserine motif on HDAC5, thus leading to nuclear export through a CRM1-dependent mechanism. This results in increased transcriptional activity of hypertrophy mediating genes in myocytes. Cardiac failure is usually preceded by cardiac hypertrophy that is mediated by altered gene expression involved in myocyte contraction, calcium handling and metabolism.

Compounds of the Invention

The present invention also pertains, at least in part, to compounds of formula (I) or (Ia):



(I) or



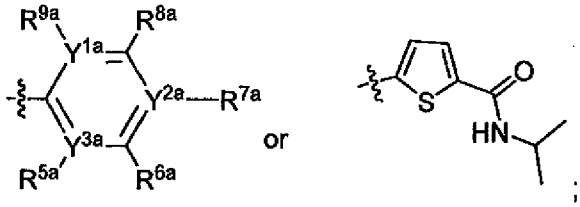
(Ia)

wherein:

X^{1a} is NR^{11a} or O;

R^{1a} is a substituted or unsubstituted aryl;

R^{2a} is:



R^{5a}, R^{6a}, R^{7a}, R^{8a} and R^{9a} are each, independently, absent, hydrogen, halogen, alkyl, aminocarbonyl, carbonyl, heterocyclyl, hydroxyl, alkoxyl, amido or imino; R^{5a} and R^{6a} may be linked to form an aryl or heterocyclyl ring; R^{6a} and R^{7a} may be linked to form an aryl ring; R^{8a} and R^{9a} may be linked to form a lactam;

Y^{1a}, Y^{2a} and Y^{3a} are each, independently, N or C;

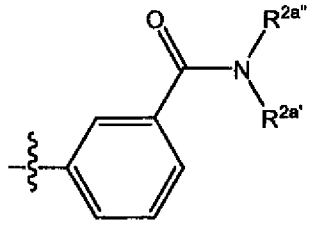
R^{11a} and R^{4a} are each, idependently, hydrogen, halogen or alkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugsand enantiomers thereof.

In one embodiment, R^{11a} is hydrogen, halogen or unsubstituted or substituted alkyl (*e.g.*, cyano substituted alkyl).

In another embodiment, X^{1a} is NH. Other examples of X^{1a} is O.

In one embodiment, R^{4a} is hydrogen.

In another embodiment R^{2a} is:



In certain embodiments, $R^{2a'}$ is a hydrogen and $R^{2a''}$ is alkyl. Examples of alkyl $R^{2a''}$ groups include unsubstituted alkyl groups (*e.g.* methyl or isopropyl), cycloalkyl groups (*e.g.* cyclopropyl or cyclohexyl) and nitrile substituted alkyl (*e.g.* cyanomethyl or 1-cyanoethyl).

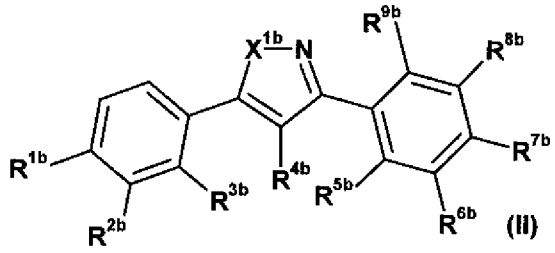
In another embodiment, R^{2a} is meta amido substituted heterocycle (*e.g.* 2, 4 or 6 pyridyl). Examples of amide substituents include optionally substituted alkyl amides of formula: -C(=O)NH-alkyl, examples of which are methylamide or isopropyl amide.

In yet another embodiment, R^{2a} is substituted with a cycloalkyl amide (*e.g.* cyclopropylamide or cyclopropylmethylamide). The alkyl amides may be substituted with any substituent which allows the compound of the invention to perform its intended function. Examples of such substituents include cyano (*e.g.* cyanomethyl or 1-cyanoethyl).

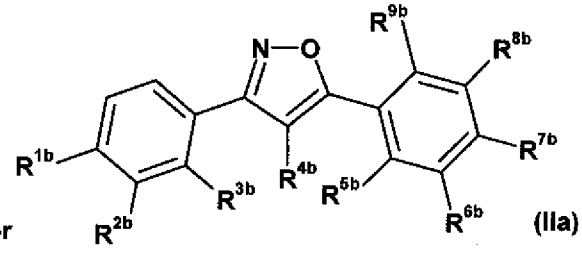
In another embodiment, R^{1a} is substituted or unsubstituted phenyl. Examples of substituents on R^{1a} include, for example, tertiary amines such as N-methyl piperazine.

Other examples of R^{1a} include heterocycles (*e.g.*, nitrogen containing heterocycles, e.g., pyridine). The heterocycle may be substituted or unsubstituted. In a further embodiment, the substituted heterocycle is substituted with a tertiary amine (*e.g.* N-methyl piperazine).

The present invention also pertains, at least in part, to compounds of formula (II) or (IIa):


(II)

or


(IIa)

wherein

X^{1b} is NR^{10b} or O;

R^{1b} and R^{2b} are each independently hydrogen, alkyl, alkenyl, halogen, amino, amido, heterocyclyl or carbonyl;

R^{3b} is hydrogen or alkoxy;

R^{5b} and R^{6b} are each hydrogen or R^{5b} and R^{6b} may be linked together to form an aryl or heterocyclyl ring;

R^{7b} and R^{8b} are each, independently, a hydrogen, aminocarbonyl, carbonyl or heterocyclyl or R^{6b} and R^{7b} may be linked together to form an aryl ring; R^{4b}, R^{9b} and R^{10b} are each, idependently, hydrogen, halogen, alkyl or alkoxy; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In certain embodiments, X^{1b} is O. Other options for X^{1b} is NH.

In another embodiment, R^{1b} is hydrogen, or substituted or unsubstituted alkyl. Examples of substituted alkyl include hydroxy substituted alkyl such as hydroxymethyl.

Other examples of R^{1b} include moieties of the formula:

$$-(CR^{11b}R^{12b})_jNR^{13b}(CR^{14b}R^{15b})_kR^{16b}$$

wherein:

j and k are each, independently, an integer selected from 0, 1, 2, 3, 4, 5 or 6;

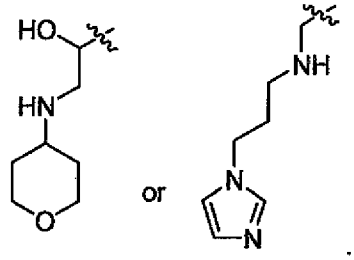
R^{11b} and R^{12b} are each independently, hydrogen or hydroxyl;

R^{13b}, R^{14b}, R^{15b} and R^{16b} are each, independently, hydrogen, hydroxyl, halogen, alkyl or a heterocycle.

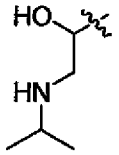
In a further embodiment, j is 2 and $(CR^{11b}R^{12b})_2$ is $-CHOH-CH_2-$. In another embodiment, j is 1 and $CR^{11b}R^{12b}$ is CH_2. Examples of R^{13b} include hydrogen. In another

further embodiment, k is 0, 1 or 3. In a further embodiment, $(CR^{14b}R^{15b})_3$ is $(CH_2)_3$. In another embodiment, $CR^{14b}R^{15b}$ is $CH(CH_3)$-. Examples of R^{13b} include heterocycles, such as pyrazinyl or morpholinyl.

In another embodiment R^{1b} is:



Other examples of R^{16b} include alkyl, e.g., methyl. Examples of R^{1b} when R^{13b} is alkyl include:



In another embodiment, R^{1b} is of the formula:

$$-(C=O)_tNR^{17b}(CR^{18b}R^{19b})_mNR^{20b}(CR^{21b}R^{22b})_nR^{23b}$$

wherein

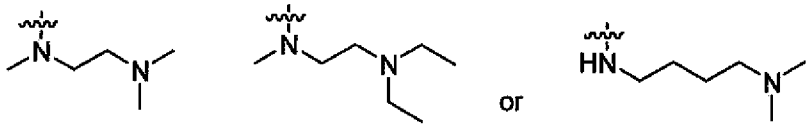
m and n are each, independently, 0, 1, 2, 3, 4, 5, or 6;

t is 0 or 1;

R^{17b} and R^{20b} are each independently, hydrogen, alkyl or aryl;

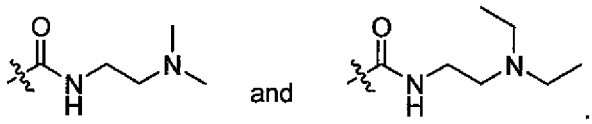
R^{18b}, R^{19b}, R^{20b}, R^{21b} and R^{22b} are each, independently, hydrogen, hydroxyl, alkyl or halogen. In a further embodiment, t is 0. In another embodiment, R^{17b} is alkyl, e.g., methyl. In yet another embodiment, m is 2 or 3. Examples of $(CR^{18b}R^{19b})_m$ include $(CH_2)_3$ and $(CH_2)_2$. Examples of R^{20b} include alkyl, such as methyl or ethyl. Examples of R^{21b} and R^{22b} include hydrogen. Examples of R^{23b} include alkyl (e.g., methyl) and hydrogen.

In a further embodiment R^{1b} is:

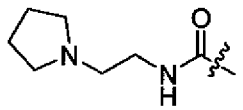


Other examples of R^{1b} groups include halogens (*e.g.* fluorine, bromine, chlorine, or iodine), alkenyl (*e.g.*, ethenyl or propenyl), amide groups (e.g., wherein t is 1), substituted carbonyl groups (e.g., alkoxy substituted carbonyl, *e.g.* methyl ester) and heterocyclic groups. Examples of heterocyclic R^{1b} groups include nitrogen containing heterocycles, such

as morpholinyl, piperazinyl, N-methyl piperazine and pyridinyl. Amide R^{1b} groups may be substituted or unsubstituted . For example, the amide R^{1b} groups may be alkyl substituted and the alkyl group may further be substituted with other groups which allow the compound to perform its intended function. Examples of substituents on the alkyl amide R^{1b} group include amino, alkylamino, dialkylamino, and heterocycles (*e.g.* wherein R^{1b} is a pyrrolidino ethyl amide). Examples of alkyl substituted amide R^{1b} groups include:



In another embodiment R^{1b} is heterocyclyl substituted alkyl amide. An example of a heterocyclyl substituted alkyl amide of R^{1b} is:



In another embodiment, R^{2b} is hydrogen, alkyl (e.g., substituted or unsubstituted), or an amine of the formula:

$$-(NR^{24b})_p(CR^{25b}R^{26b})_qNR^{27b}(CR^{28b}R^{29b})_rQ$$

wherein:

p is 0 or 1;

q and r are each, independently, an integer selected from 0, 1, 2, 3, 4, 5, or 6;

R^{24b}, R^{25b}, R^{26b} R^{27b}, R^{28b}, and R^{29b} are each, independently, hydrogen, hydroxyl or halogen; and

Q is a heterocycle (e.g., pyranyl, imidazolyl, or pyridinyl), hydrogen, hydroxyl, alkyl or halogen . In one embodiment, p is 0. Examples of R^{2b} include compounds wherein $(CR^{22b}R^{23b})_q$ is CH_2. Examples of NR^{27b} include hydrogen. Examples of r include 0, 2, and 3. R^{2b} is $-CH_2$-NH-pyranyl, $-CH_2$-NH-$(CH_2)_3$-imidazolyl or $-CH_2$-NH-$(CH_2)_2$-pyridinyl.

In another embodiment, p is 1 and NR^{24b} is NH or NCH_3. An example of R^{2b} when p is 1 is $-N(CH_3)(CH_2)_2N(CH_3)_2$.

Other examples of R^{2b} include cyclic amines (*e.g.* pyridine, N-methyl piperazine or N-(tert-butoxycarbonyloxy)hexylamine) and halogens (*e.g.* fluorine, bromine, chlorine, or iodine).

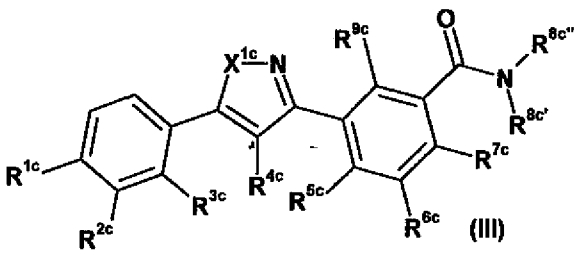
Examples of R^{3b} include hydrogen or alkoxy (*e.g.* methoxy).

In another embodiment, R^{5b} and/or R^{6b} is hydrogen. In certain embodiments, R^{5b} and R^{5b} may be linked to form a ring (*e.g.* a fused pyridinyl ring).

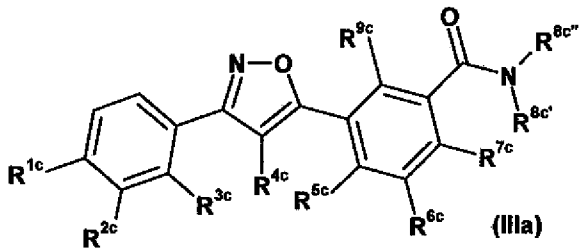
In another embodiment, R^{7b} is hydrogen or an aminocarbonyl (e.g., a substituted or unsubstituted aminocarbonyl). Examples of alkyl substituted aminocarbonyls include methyl amide, isopropyl amide and cyclopropylmethyl amide. In another embodiment, R^{7b} comprises a carbonyl or an alkoxy substituted carbonyl (*e.g.* methyl or ethyl ester). In certain embodiments, the invention also pertains to compounds wherein R^{6b} and R^{7b} are linked to form a ring (*e.g.* a fused phenyl ring).

In another embodiment, R^{8b} is hydrogen, a substituted or unsubstituted aminocarbonyl, substituted or unsubstituted amino, substituted or unsubstituted heterocyclyl (*e.g.* pyrimidinyl, pyrazinyl or oxazolyl), or comprises a carbonyl (e.g., a carboxylic acid, methyl ester or ethyl ester). Examples of amide R^{8b} groups include alkyl aminocarbonyls (*e.g.* methyl, ethyl or isopropyl amide). The alkyl aminocarbonyls may further be substituted with substituents which allow the compound of the invention to perform its intended function. Examples of such substituents include cyano. Examples of such R^{8b} groups include cyanomethyl amide, 1-cyanoethyl amide or 1-cyanopropyl amide. Examples of substituents of heterocyclic R^{8b} groups include alkyl and halogenated alkyl, e.g., 2,2,2-trifluoro-N-(4-methyloxazol-5-yl)acetamide.

The present invention also pertains, at least in part, to compounds of formula (III) or (IIIa):


(III)

or


(IIIa)

wherein

X^{1c} is NR^{10c} or O;

R^{1c} is heterocyclyl;

R^{2c}, R^{3c}, R^{4c}, R^{9c} and R^{10c} are each, independently, hydrogen, alkyl, halogen or alkoxy;

R^{5c}, R^{6c} and R^{7c} are each, independently, hydrogen, halogen or alkyl;

$R^{8c'}$ and $R^{8c''}$ are each, independently, a hydrogen, hydroxyl, alkyl, alkoxyl, amido or heterocyclyl;

R^{5c} and R^{6c} can be linked together to form an aryl or heterocyclyl ring; R^{6c} and R^{7c} can be linked together to form an aryl ring; $R^{8c''}$ and R^{9c} may be linked together to form a

lactam; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In certain embodiments, X^{1c} is NH. Other options for X^{1c} is O. In a further embodiment, X^{1c} is NR^{10c}. Examples of R^{10c} include substituted or unsubstituted alkyl (*e.g.* methyl, ethyl, or 2-cyanoethyl).

In one embodiment, R^{1c} is a heterocycle. The heterocycle may be either unsubstituted or substituted, e.g., with an alkyl , *e.g.* N-methyl piperazinyl.

In yet another embodiment, R^{4c} is hydrogen, alkyl (*e.g.* methyl) or halogen (*e.g.* fluorine, chlorine, bromine or iodine). Examples of R^{5c} include hydrogen and halogen (*e.g.* fluorine, chlorine, bromine, etc.).

In yet another embodiment, R^{5c} and R^{6c} are linked to form a heterocycle, *e.g.* a fused pyridinyl ring. Other examples of R^{6c} and R^{7c} include, but are not limited to, hydrogen, alkyl (*e.g.* methyl, ethyl, propyl, etc.) or halogen (*e.g.* fluorine, chlorine, or bromine). Optionally, R^{6c} and R^{7c} may be linked to form an aryl ring, for example, a fused phenyl ring. Examples of R^{3c} include hydrogen, substituted or unsubstituted alkyl (e.g., methyl, ethyl, trifluoromethyl) and alkoxy (e.g., methoxy, ethoxy, etc.).

In another embodiment, R^{2c} is hydrogen, substituted or unsubstituted alkyl (*e.g.* methyl, ethyl, propyl, butyl, trifluoromethyl, etc.), halogen (*e.g.* fluorine, chlorine, bromine, or iodine), alkoxy (*e.g.* methoxy, ethoxy, propoxy, etc.), substituted or unsubstituted phenyl or a heterocycle (*e.g.* pyridinyl). Examples of substituents on the phenyl include halogens (e.g., fluorine, bromine, chlorine, or iodine) and aminocarbonyls.

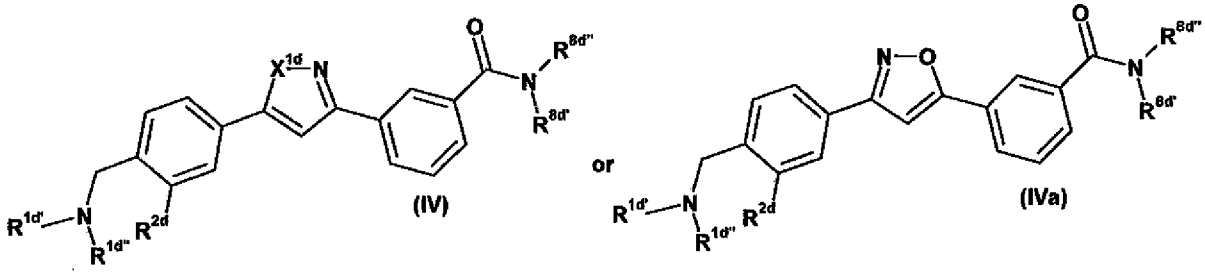
In one embodiment, $R^{8c'}$ is hydrogen.

In another embodiment, R^{9c} is hydrogen or alkoxy (*e.g.* methoxy).

In yet another embodiment, $R^{8c'}$ and R^{9c} are linked to form a lactam *e.g.* a piperidonyl ring.

Other examples of $R^{8c'}$ include substituted or unsubstituted alkyl (*e.g.* methyl, ethyl, propyl, butyl, isopropyl, isobutyl, sec-butyl, etc.), substituted or unsubstituted amidyl (*e.g.* acetamide or propanamide), heterocyclic (*e.g.* pyranyl), alkyl ester (*e.g.* CH_3-O-C=O-$(CH_2)_2$-), and amino (e.g., alkyl amino, dialkyl amino, and aminoalkylaminoalkyl (*e.g.*–NH-$(CH_2)_2N(CH_3)_2$)). Examples of substituents on substituted alkyl $R^{8c'}$ groups include hydroxy, halogen, cyano, and other groups. Examples of alkyl $R^{8c'}$ groups include, but are not limited to cyclopropylmethyl, 1-cyclopropylethyl, 2,2,2-triflouroethyl, 2-hydroxyisopropyl, 2-hydroxyethyl or 2-methoxyethyl, cyanomethyl, 1-cyanoethyl, 1-cyanopropyl, 1-caynobutyl, 2-cyanoethyl, cyclohexyl and cyclopropyl.

The present invention also pertains, at least in part, to compounds of formula (IV) or (IVa):



wherein:

X^{1d} is NH or O;

$R^{1d'}$ and $R^{1d''}$ are each, independently, hydrogen, alkyl, acyl, amido, amino or heterocyclyl;

R^{2d} is hydrogen or halogen;

$R^{8d'}$ and $R^{8d''}$ are each, independently, hydrogen, alkyl, amido or imino; and

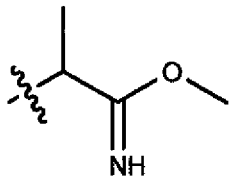
$R^{1d'}$ and $R^{1d''}$ may be linked to form a heterocyclyl ring; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In certain embodiments, X^{1d} is NH. Other options for X^{1d} is O.

In one embodiment, R^{2d} is hydrogen or halogen *e.g.* fluorine or chlorine.

Examples of $R^{8d''}$ include hydrogen and alkyl *e.g.* methyl.

In one embodiment, $R^{8d'}$ is hydrogen, alkyl *e.g.* (methyl, ethyl or isopropyl), substituted alkyl (*e.g.* cyanomethyl, 1-cyanoethyl, 1-cyanopropyl, cyanoisopropyl, 1, 1-dicyanomethyl, cyanophenylmethyl or 1-cyclopropylethyl), cycloalkyl, substituted cycloalkyl (*e.g.* 1-cyanocyclopropyl or 1-cyanocyclohexyl), an amide, a substituted amide (*e.g.* cyanoacetamide) or a substituted or unsubstituted imine, *e.g.*

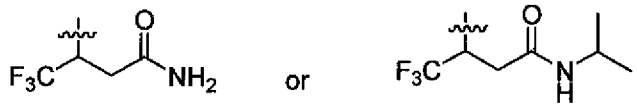


In another embodiment, $R^{1d''}$ is hydrogen or alkyl (*e.g.* methyl or ethyl).

In yet another embodiment, $R^{1d'}$ and $R^{1d''}$ are linked to form a substituted or unsubstituted heterocyclic ring. Examples of $R^{1d'}$ and $R^{1d''}$ linked to form a substituted or unsubstituted heterocyclic ring are piperazine, piperadine, morpholine, aminopiperadine, piperazine-3-one, N-methyl piperazine or N-tert-butoxycarbonyl piperazine.

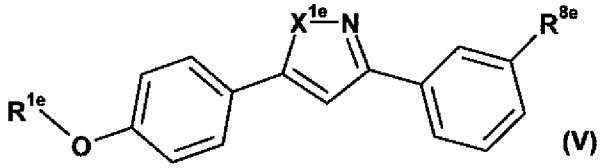
In one embodiment, $R^{1d'}$ is hydrogen, alkyl (*e.g.* methyl, ethyl, isopropyl, isobutyl or sec-butyl), cycloalkyl (*e.g.* cyclopropyl or cyclohexyl), substituted alkyl, halogen substituted

alkyl (*e.g.* 2-fluoromethyl, 2,2-difluoromethyl or 2,2,2-trifluoromethyl), alkoxy substituted alkyl (*e.g.* 2-methoxyethyl, 3-methoxypropyl or methoxyisopropyl), hydroxy substituted alkyl (*e.g.* hydroxyisopropyl or hydroxymethylbutyl), heterocyclyl substituted alkyl (*e.g.* pyranylmethyl, pyridinylethyl, imidazolylethyl or imidazolylpropyl), an amide (*e.g.* acetamide or propanamide), a substituted amide or a halogen substituted alkyl amide. Examples of a halogen substituted alkyl amide of $R^{1d'}$ are:



Other examples of $R^{1d'}$ include unsubstituted or substituted heterocycles (*e.g.* pyranyl), acyl, amines, alkyl amines and substituted alkyl amines *e.g.*–$(CH_2)_2N(CH_3)_2$.

The present invention also pertains, at least in part, to compounds of formula (V):



(V)

wherein:

X^{1e} is NH or O;

R^{1e} is hydrogen, alkyl, amino, amido, heterocyclyl or alkoxycarbonylalkyl;

R^{8e} is carbonyl or amido; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In oner embodiment, X^{1e} is NH. In another embodiment X^{1e} is O.

Examples of R^{8e} include moieties which comprise a carbonyl *e.g.* a carboxylic acid. In another example R^{8e} is a substituted or unsubstituted amide *e.g.* isopropylamide.

In one embodiment, R^{1e} is hydrogen, substituted or unsubstituted alkyl (*e.g.* 2-hydroxyethyl) or a substituted or unsubstituted amine.

In another embodiment, R^{1e} is:

$$-(CH_2)_{0-4}-Q$$

wherein Q is hydrogen, halogen, hydroxy, alkoxy, alkyl, acyl, alkylaminocarbonyl, heterocyclyl, haloalkylaminocarbonyl, carbamoyl, hydroxycarboxy, alkoxycarboxy or amino.

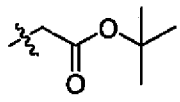
In one example Q is a substituted or unsubstituted heterocycle *e.g.* pyrrolidinylethyl, imidazolylethyl, morpholinylethyl or morpholinylpropyl.

In yet another embodiment, R^{1e} is a dialkylamino alkyl amine (*e.g.* -$(CH_2)_2N(CH_3)_2$ or –$(CH_2)_3N(CH_3)_2$), or a substituted or unsubstituted heterocycle. Examples of nitrogen

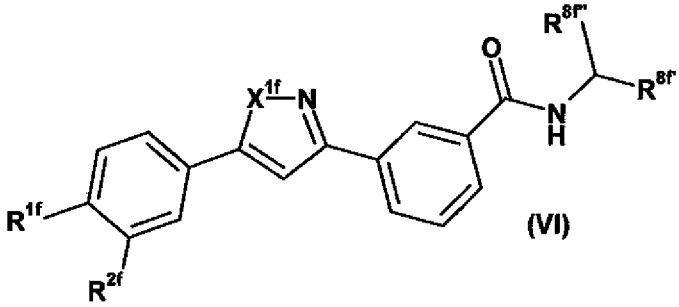
containing heterocycles include pyrrolidinyl and piperadinyl. Examples of an oxycarbonyl substituted nitrogen containing heterocycle include N-tert-butoxycarbonyl pyrrolidine and N-tert-butoxycarbonyl piperadine).

In another embodiment, R^{1e} is a substituted or unsubstituted amide, for example N-isopropyl acetamide or N-phenyl acetamide.

In yet another embodiment, R^{1e} is carbonyl alkyl or an alkoxycarbonylalkyl, for example:



The present invention also pertains, at least in part, to compounds of formula (VI):



(VI)

wherein:

X^{1f} is NH or O;

R^{1f} is alkyl or heterocyclyl;

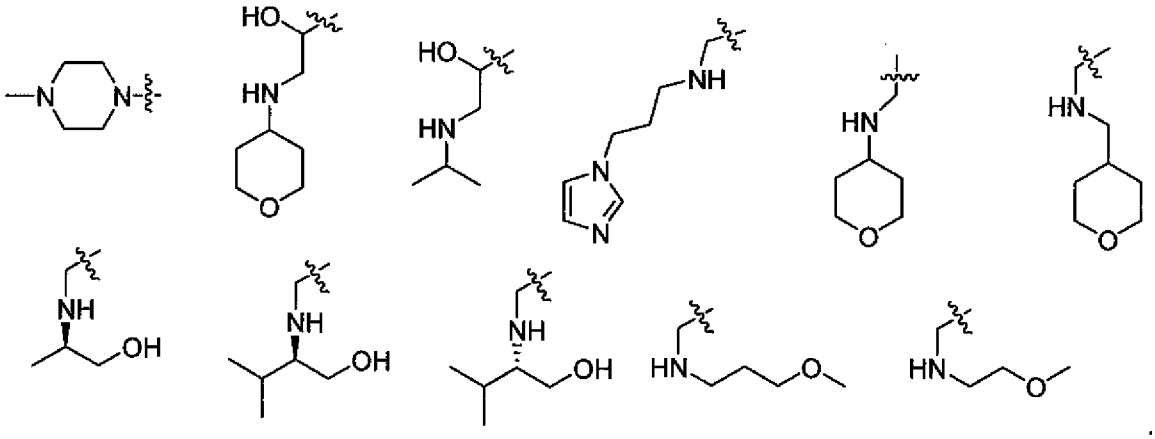
R^{2f} is hydrogen or halogen;

R^{8f} is alkyl or cyano;

$R^{8f'}$ is hydrogen or alkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

In one embodiment, R^{1f}, R^{2f}, R^{8f} and $R^{8f'}$ may each be optionally further substituted. Examples of substituents on these variables include, but are not limited to, hydrogen, halogen, hydroxy, alkoxy, alkyl, acyl, alkylaminocarbonyl, heterocyclyl, haloalkylaminocarbonyl, carbamoyl, hydroxycarboxy, alkoxycarboxy and amino.

Examples of R^{1f} include:



Examples of R^{2f} include hydrogen and halogen *e.g.*, chloro.

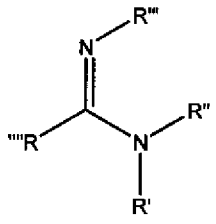
Examples of R^{8f} include alkyl *e.g.*, isopropyl and cyano.

Examples $R^{8f'}$ include hydrogen and alkyl, *e.g.* methyl.

Further examples of compounds of Formulae I-VI and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugsand enantiomers thereof.

In one embodiment, the compounds of the present invention have a molecular weight of less than about 650 g/mol.

The term amidine is a class of oxoacid derivatives. The oxoacid from which an amidine is derived must be of the form $R_nE(=O)OH$, where R is a substituent. The −OH group is replaced by an $-NH_2$ group and the =O group is replaced by =NR, giving amidines the general structure $R_nE(=NR)NR_2$. When the parent oxoacid is a carboxylic acid, the resulting amidine is a carboxamidine, and has the following general structure:



Carboxamidines are frequently referred to simply as amidines, as they are the most commonly-encountered type of amidine in organic chemistry. The simplest amidine is formamidine, $HC(=NH)NH_2$.

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or

more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, *e.g.*, with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids.

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, etc. Furthermore, the term "aryl" includes multicyclic aryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles," "heterocycles," "heteroaryls" or "heteroaromatics."

Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5- pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2, 3-triazolyl, tetrazolyl, 2-,

3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl. A heteroaryl group may be mono-, bi-, tri-, or polycyclic.

The term "heteroaryl" also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include but are not limited to 1-, 2-, 3-, 5-, 6-, 7-, or 8- indolizinyl, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7-, or 8- purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl, 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl, 2-, 3-, 4-, 5-, or 6-naphthyridinyl, 2-, 3- , 5-, 6-, 7-, or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl, 2-, 4-, 6-, or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbzaolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 8-, 9-, or 10-phenathrolinyl, 1-, 2- , 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl, 2-, 3-, 4-, 5-, 6-, or l-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- benzisoqinolinyl, 2-, 3-, 4-, or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, or 11-7H-pyrazino[2,3-c]carbazolyl,2-, 3-, 5-, 6-, or 7-2H- furo[3,2-b]-pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 54H-imidazo[4,5-d] thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6- imidazo[2,1-b] thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 4-, 5-, 6-, or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9- benzoxapinyl, 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-1H-pyrrolo[1,2-b][2]benzazapinyl. Typical fused heteroary groups include, but are not limited to 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl.

The aromatic ring of an "aryl" or "heteroaryl" group can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxy, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and

alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (*e.g.*, tetralin).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 or straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls," the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls," the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, the term "lower alkyl" means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl,

alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "acyl" includes compounds and moieties which contain the acyl radical (CH_3CO-) or a carbonyl group. It includes substituted acyl moieties. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "aroyl" includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc. It includes substituted aroyl moieties. The term "substituted aroyl" includes aroyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido,

nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The terms "alkoxyalkyl," "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, *e.g.*, oxygen, nitrogen or sulfur atoms.

The term "carbamoyl" includes $H_2NC(O)$-, alkyl-NHC(O)-, $(alkyl)_2NC(O)$-, aryl-NHC(O)-, alkyl(aryl)-NC(O)-, heteroaryl-NHC(O)-, alkyl(heteroaryl)-NC(O)-, aryl-alkyl-NHC(O)-, alkyl(aryl-alkyl)-NC(O)-, etc. The term includes substituted carbamoyl moieties.

The term "sulfonyl" includes R-SO_2--, wherein R is hydrogen, alkyl, aryl, heteroaryl, aryl-alkyl, heteroaryl-alkyl, alkoxy, aryloxy, cycloalkyl, or heterocyclyl.

The term "sulfonamido" includes alkyl-$S(O)_2$-NH-, aryl-$S(O)_2$-NH-, aryl-alkyl-$S(O)_2$-NH-, heteroaryl-$S(O)_2$-NH-, heteroaryl-alkyl-$S(O)_2$-NH-, alkyl-$S(O)_2$-N(alkyl)-, aryl-$S(O)_2$-N(alkyl)-, aryl-alkyl-$S(O)_2$-N(alkyl)-, heteroaryl-$S(O)_2$-N(alkyl)-, heteroaryl-alkyl-$S(O)_2$-N(alkyl)-, etc. The term includes substituted carbamoyl moieties

The term "heterocyclyl" or "heterocyclo" includes an optionally substituted, saturated or unsaturated non-aromatic ring or ring system, *e.g.*, which is a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocyclyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1, 4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, I,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, etc.

The term "heterocyclyl" includes heterocyclic groups as defined herein substituted with 1, 2 or 3 substituents such as alkyl, hydroxy (or protected hydroxy), halo, oxo (*e.g.*, =O), amino, alkylamino or dialkylamino, alkoxy, cycloalkyl, carboxyl, heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge, alkyl-O-C(O)--, mercapto, nitro, cyano, sulfamoyl or sulfonamide, aryl, alkyl-C(O)-O--, aryl-C(O)-O--, aryl-S--, aryloxy, alkyl-S--, formyl (*e.g.*, HC(O)--), carbamoyl, aryl-alkyl--, and aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH--, alkylamino, dialkylamino or halogen.

The term "sulfamoyl" includes $H_2NS(O)_2$-, alkyl-$NHS(O)_2$-, $(alkyl)_2NS(O)_2$-, aryl-$NHS(O)_2$-, alkyl(aryl)-$NS(O)_2$-, $(aryl)_2NS(O)_2$-, heteroaryl-$NHS(O)_2$-, (aryl-alkyl)-$NHS(O)_2$-, (heteroaryl-alkyl)-$NHS(O)_2$- , etc. The term includes substituted sulfamoyl moieties.

The term "aryloxy" includes both an --O-aryl and an --O-heteroaryl group, wherein aryl and heteroaryl are defined herein. The term includes substituted aryloxy moieties.

The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term includes "alkyl amino" which comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group. The term "amine" or "amino" also includes substituted moieties.

The term "amide," "amido" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino). The term "amide," "amido" or "aminocarbonyl" also includes substituted moieties.

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. The carbonyl can be further substituted with any moiety which allows the compounds of the invention to perform its intended function. For example, carbonyl moieties may be substituted with alkyls, alkenyls, alkynyls, aryls, alkoxy, aminos, etc. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom. The term also includes substituted moieties.

The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group. The term also includes substituted moieties.

The term "ester" includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above. The term also includes substituted moieties.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group. The term also includes substituted moieties.

The term "hydroxy" or "hydroxyl" includes groups with an –OH or –O$^-$.

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycyclic radical" refer to two or more cyclic rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, *e.g.*, the rings are "fused rings." Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkyl carbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amido, amino (including alkyl amino, dialkylamino,

arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

The term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Moreover, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)-, or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using

chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

The recitation of ranges of values in the present application are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range.

Any asymmetric carbon atom on the compounds of the present invention can be present in the (*R*)-, (*S*)- or (*R,S*)- configuration, preferably in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form. Therefore, the compounds of the present invention can be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, the imidazolyl moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Compounds of the present invention are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

The term "pharmaceutically acceptable salts" includes salts that retain the biological effectiveness and properties of the compounds of this invention and, which are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts

can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, etc. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*- toluenesulfonic acid, salicylic acid, etc. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, etc.; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, etc., specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Lists of additional suitable salts can be found, *e.g.*, in *Remington's Pharmaceutical Sciences,* 20th ed., Mack Publishing Company, Easton, Pa., (1985).

When a basic group is present in the compounds of the present invention, the compounds can be converted into acid addition salts thereof, in particular, acid addition salts with the imidazolyl moiety of the structure, preferably pharmaceutically acceptable salts thereof. These are formed, with inorganic acids or organic acids. Suitable inorganic acids include but are not limited to, hydrochloric acid, sulfuric acid, a phosphoric or hydrohalic acid. Suitable organic acids include but are not limited to, carboxylic acids, such as (C_1-C_4)alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, *e.g.*, acetic acid, such as saturated or unsaturated dicarboxylic acids, *e.g.*, oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, *e.g.*, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, *e.g.*, aspartic or glutamic acid, organic sulfonic acids,

such as (C_1-C_4)alkylsulfonic acids, *e.g.*, methanesulfonic acid; or arylsulfonic acids which are unsubstituted or substituted, *e.g.*, by halogen. Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

When an acidic group is present in the compounds of the present invention, the compounds can be converted into salts with pharmaceutically acceptable bases. Such salts include alkali metal salts, like sodium, lithium and potassium salts; alkaline earth metal salts, like calcium and magnesium salts; ammonium salts with organic bases, *e.g.*, trimethylamine salts, diethylamine salts, *tris*(hydroxymethyl)methylamine salts, dicyclohexylamine salts and *N*-methyl-*D*-glucamine salts; salts with amino acids like arginine, lysine, etc. Salts may be formed using conventional methods, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, *e.g.*, diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention can also form internal salts.

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention, i.e. compounds of formula (I) or (Ia), wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention comprises isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I) or (Ia), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) or (Ia) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

The present invention also provides prodrug moieties of the compounds of the present invention that convert *in vivo* to the compounds of the present invention. A prodrug moiety is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism, etc., into a compound of this invention following administration of the prodrug to a subject. The term "prodrug moiety" includes moieties which can be metabolized *in vivo* to a hydroxy group and moieties which may advantageously remain esterified *in vivo.* Preferably, the prodrugs moieties are metabolized *in vivo* by esterases or by other mechanisms to hydroxy groups or other advantageous groups. Examples of prodrugs and their uses are well known in the art (See, *e.g.*, Berge et al. (1977) "Pharmaceutical Salts" *J. Pharm. Sci.* 66:1-19). The prodrugs can be prepared *in*

situ during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form or hydroxy with a suitable esterifying agent. Hydroxy groups can be converted into esters *via* treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (*e.g.*, propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (*e.g.*, dimethylaminoethyl ester), acylamino lower alkyl esters (*e.g.*, acetyloxymethyl ester), acyloxy lower alkyl esters (*e.g.*, pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (*e.g.*, benzyl ester), substituted (*e.g.*, with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionoic acid esters and acyl esters.

The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds are inactive or have low activity compared to the corresponding active drug compound that contains one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Typically, the formation of active drug compound involves a metabolic process or reaction that is one of the follow types:

1. Oxidative reactions, such as oxidation of alcohol, carbonyl, and acid functions, hydroxylation of aliphatic carbons, hydroxylation of alicyclic carbon atoms, oxidation of aromatic carbon atoms, oxidation of carbon-carbon double bonds, oxidation of nitrogen-containing functional groups, oxidation of silicon, phosphorus, arsenic, and sulfur, oxidative N-delakylation, oxidative O- and S-dealkylation, oxidative deamination, as well as other oxidative reactions.

2. Reductive reactions, such as reduction of carbonyl groups, reduction of alcoholic groups and carbon-carbon double bonds, reduction of nitrogen-containing functions groups, and other reduction reactions.

3. Reactions without change in the state of oxidation, such as hydrolysis of esters and ethers, hydrolytic cleavage of carbon-nitrogen single bonds, hydrolytic cleavage of non-aromatic heterocycles, hydration and dehydration at multiple bonds, new atomic

linkages resulting from dehydration reactions, hydrolytic dehalogenation, removal of hydrogen halide molecule, and other such reactions.

Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. See, Cheng *et al.*, US20040077595, incorporated herein by reference. Such carrier prodrugs are often advantageous for orally administered drugs. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxy groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, *e.g.*, aliphatic alcohols. Wermuth, *The Practice of Medicinal Chemistry*, Ch. 31-32, Ed. Werriuth, Academic Press, San Diego, Calif., 2001.

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl and *O*-acyl derivatives of thiols, alcohols or phenols, wherein acyl has a meaning as defined herein. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester, etc. conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole, etc., have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

In view of the close relationship between the compounds, the compounds in the form of their salts and the prodrugs, any reference to the compounds of the present invention is to be understood as referring also to the corresponding prodrugs of the compounds of the present invention, as appropriate and expedient.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Compounds of the present invention are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following conditions without limitation:

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallization, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, etc.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are

inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190 °C, including, for example, from approximately -80 °C to approximately 150 °C, for example at from -80 to -60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

Generally, enantiomers of the compounds of the present invention can be prepared by methods known to those skilled in the art to resolve racemic mixtures, such as by formation and recrystallization of diastereomeric salts or by chiral chromatography or HPLC separation utilizing chiral stationery phases.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, thiol, carboxyl and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, thiol, carboxyl and hydroxy groups are those that can be converted under mild conditions into free amino thiol, carboxyl and hydroxy groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably, such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents, respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably at or near the boiling point of the solvents used, and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative Examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Abbreviations:

AIBN	azobisisobutyrylnitrile
App	apparent
APC	allophycocyanin
ATP	adenosine 5'-triphosphate
BINAP	racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOC	tertiary butyl carboxy
br	broad
bs	broad singlet
BSA	bovine serum albumin
d	doublet
DAST	(diethylamino)sulfur trifluoride
dd	doublet of doublets
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIEA	diethylisopropylamine
DIPEA	N,N-diisopropyl-ethylamine
DME	1,4-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorylazide
DTT	dithiothreitol
EDC/EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediamine tetraacetic acid
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FCC	flash column chromatography
h	hour(s)
HATU	*O*-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate
HBTU	1-[bis(dimethylamino)methylene]-1*H*-benzotriazoliumhexafluorophosphate(1-) 3-oxide
HOBt	1-hydroxy-7-azabenzotriazole

HPLC	high pressure liquid chromatography
IR	infrared spectroscopy
LCMS	liquid chromatography and mass spectrometry
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilylamine
LHMDS	lithium hexamethyldisilylamine
Me	methyl
MeOD	methanol-d4
MeOH	methanol
MS	mass spectrometry
MW	microwave
m	multiplet
min	minutes
mL	milliliter(s)
m/z	mass to charge ratio
NBS:	N-bromosuccinimide
NMR	nuclear magnetic resonance
ppm	parts per million
Pr	propyl
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
RP-HPLC	reverse phase high pressure liquid chromatography
rac	racemic
rt	room temperature
s	singlet
t	triplet
TBDMS:	*tert*-butyl-dimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tris·HCl	aminotris(hydroxymethyl)methane hydrochloride
TsOH	tosic acid: p-toluene sulfonic acid

Methods of the Invention

The invention pertains, at least in part, to methods for treating a subject for a disorder or disease, by administering to a subject a therapeutically effective amount of a compound of the invention, (*e.g.*, a compound of Formula I-VIor a compound otherwise described herein), such that said subject is treated for said disease or disorder.

The term "disorder" or "disease" includes any pathological condition, derangement, or abnormality of function of a part, organ, or system of an organism resulting from various causes, such as infection, genetic defect, or environmental stress, and characterized by an identifiable group of signs or symptoms; and any morbid physical or mental state. See *Dorland's Illustrated Medical Dictionary,* (W.B. Saunders Co. 27th ed. 1988).

In one embodiment, the disorder or disease is heart failure.

In another embodiment, the disorder or disease involves regulation of cell growth. The term "regulation of cell growth" includes mediation of cell size and cell division. Disorders involving the regulation of cell growth include cancers (*e.g.*, breast cancer, colorectal cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, epidermoid cancer, melanoma, ovarian cancer, pancreas cancer, neuroblastoma, head and/or neck cancer bladder cancer, renal cancer, brain cancer, myeloid cancer, or gastric cancer), tumors (*e.g.*, a breast tumor; an epidermoid tumor, such as an epidermoid head and/or neck tumor or a mouth tumor; a lung tumor, for example a small cell or non-small cell lung tumor; a gastrointestinal tumor, for example, a colorectal tumor; or a genitourinary tumor, for example, a prostate tumor or a tumor that is refractory to treatment with other chemotherapeutics due to multidrug resistance), small cell lung carcinoma, large cell lung carcinoma, melanoma, prostate carcinoma, neoplasias, hyperplasias, fibrosis (*e.g.*, pulmonary fibrosis or renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle cell proliferation in the blood vessels, such as stenosis or restenosis following angioplasty, tumors of blood and lymphatic system (*e.g.*, Hodgkin's disease, Non-Hodgkin's lymphoma, Burkitt's lymphoma, AIDS-related lymphomas, malignant immunoproliferative diseases, multiple myeloma and malignant plasma cell neoplasms, lymphoid leukemia, acute or chronic myeloid leukemia, acute or chronic lymphocytic leukemia, monocytic leukemia, other leukemias of specified cell type, leukemia of unspecified cell type, other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissues, for example diffuse large cell lymphoma, T-cell lymphoma or cutaneous T-cell lymphoma) or a proliferative disease that is refractory to the treatment with other chemotherapeutics.

Where a tumor, a tumor disease, a carcinoma or a cancer are mentioned, metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

Examples of hyperproliferative skin disorders include psoriasis, atopic dermatitis, eczematous dermatitises, seborrhoeic dermatitis, pemphigus, and contact dermatitis (*e.g.*, allergic contact dermatitis).

The invention also pertains to a method for treating autoimmune disorders or chronic inflammatory diseases. "Autoimmune disorders" include any of a group of disorders in which tissue injury is associated with humoral or cell-mediated responses to the body's own constituents. Such disorders may be systemic or organ-specific. Examples of autoimmune disorders or chronic inflammatory diseases include sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, obstructive airways disease, including conditions such as asthma, intrinsic asthma, extrinsic asthma, dust asthma, particularly chronic or inveterate asthma (*e.g.*, late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, infantile asthma, rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, nephrotic syndrome lupus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes mellitus and complications associated therewith, type II adult onset diabetes mellitus, uveitis, nephrotic syndrome, steroid dependent and steroid-resistant nephrosis, palmoplantar pustulosis, allergic encephalomyelitis, glomerulonephritis, psoriasis, psoriatic arthritis, atopic eczema (atopic dermatitis), allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, acne, alopecia areata, eosinophilic fasciitis, atherosclerosis, conjunctivitis, keratoconjunctivitis, keratitis, vernal conjunctivitis, uveitis associated with Behcet's disease, herpetic keratitis, conical cornea, dystorphia epithelialis corneae, keratoleukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, severe intraocular inflammation, inflammation of mucosa or blood vessels such as leukotriene B4-mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, cardiac hypertrophy, ischemic bowel disease, inflammatory bowel disease (*e.g.*, Crohn's disease or ulcerative colitis), necrotizing enterocolitis, renal diseases including interstitial nephritis, Goodpasture's syndrome hemolytic uremic syndrome and diabetic nephropathy, nervous diseases selected from multiple myositis, Meniere's disease and radiculopathy, collagen disease including scleroderma, chronic autoimmune liver diseases including autoimmune hepatitis, primary

biliary cirrhosis and sclerosing cholangitis), partial liver resection, acute liver necrosis (*e.g.*, necrosis caused by toxins, viral hepatitis, shock or anoxia), cirrhosis, fulminant hepatitis, pustular psoriasis, Behcet's disease, active chronic hepatitis, Evans syndrome, pollinosis, idiopathic hypoparathyroidism, autoimmune atrophic gastritis, lupoid hepatitis, tubulointerstitial nephritis, membranous nephritis, rheumatic fever, acute disseminated encephalomyelitis, Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune oophoritis, Celiac disease, hestational pemphigoid, Graves' disease, Guillain-Barré syndrome, Hashimoto's disease, idiopathic thrombocytopenic purpura, Kawasaki's Disease, mixed connective tissue disease, opsoclonus myoclonus syndrome, optic neuritis, Ord's thyroiditis, pemphigus, pernicious anaemia, polyarthritis in dogs, Reiter's syndrome, Sjögren's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, and Wegener's granulomatosis.

In yet another embodiment, the disorder or disease is mediated by T lymphocytes, B lymphocytes, mast cells, eosinophils or cardiomyocytes *e.g.*, acute or chronic rejection of organ or tissue allo- or xenografts, graft-versus-host disease, host-versus-graft disease, atheriosclerosis, cerebral infarction, vascular occlusion due to vascular injury such as angioplasty, restenosis, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS disease such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious disease such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury *e.g.*, myocardial infarction, stroke, gut ischemia, renal failure or hermorrhage shock, or traumatic shock.

The invention also pertains, at least in part, to methods of modulating (*e.g.*, inhibiting) PKD activity in a subject, by administering to a subject a therapeutically effective amount of a compound of the invention, (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein), such that PKD activity is modulated.

Another embodiment of the present invention includes methods for treating a PKD associated state in a subject, by administering to a subject a therapeutically effective amount of a compound of the invention, (*e.g.*, a compound of Formula I-VI or a otherwise described herein), such that said subject is treated.

In certain embodiments, the compounds of the present invention may be used as modulators (*e.g.*, PKD modulators or PKD inhibitors).

The term "PKD associated state" refers to a state, disease, or disorder which can be treated by the modulation, (*e.g.*, inhibition) of PKD. PKD is a family of serine/threonine

protein kinases (*e.g.*, PKD1, 2 and 3) that is now classified as a subfamily of the Ca^{2+}/calmodulin-dependent kinase (CaMK) super family. Reports have demonstrated the biological functions of PKD. See Wang QJ, *TRENDS Pharm. Sci.,* 27(6): 3170323 (2006). For example, it has been found that activation of PKD regulates fission of transport carriers from the Golgi to the plasma membrane. See Liljedahl, M. *et al.*, *Cell*, 104: 409-420 (2001). PKD has a major role in cell motility, invasion, and adhesion. PKD has also been demonstrated to have pro-proliferative effect in many cellular systems, as well as promotes antiapoptotic responses in tumor cells. See Prigozhina, NL *et al.*, *Curr. Biol.,*14: 88-98 (2004), Rozengurt E. *et al.*, *JBC,* 280(14): 13205-13208 (2005). PKD has also been found to regulate agonist-dependent cardiac hypertrophy through the nuclear export of class II histone deacetylase (HDAC5). See Vega, RB *et al.*, *Mol. Cell. Biol.,* 24: 8374-8385 (2004). PKD is also involved in oxidative stress response by activating the transcription factor Nf-kB to protect the cell from oxidative-stress-induced cell death. See Storz, P. and Toker, A., *EMBO J.*, 22: 109-120 (2003). Sjoblom, T. *et al.* linked PKD to breast and colorectal cancers. See Sjoblom, T. *et al.*, *Science*, 314:268-274 (2006). PKD has been found to regulate gene expression related to immune response and function of skin. See Matthews, SA *et al.*, *Mol. Cell. Biol.*, 26(4): 1569-1577 (2006), Irie, A. *et al.*, *Int. Immunology,*18(12): 1737-1747 (2006), Bollag, WB *et al.*, *Drug News Perspect,* 17(2): 117 (2004), etc. Therefore examples of PKD associated disorders include heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, and hyperproliferative skin disorders, etc.

In one embodiment, PKD associated states are characterized by an abnormal activity of PKD and/or abnormal expression of PKD.

The term "abnormal" includes an activity or feature which differs from a normal activity or feature.

The term "abnormal activity" includes an activity which differs from the activity of the wild-type or native gene or protein, or which differs from the activity of the gene or protein in a healthy subject. The abnormal activity can be stronger or weaker than the normal activity.

In one embodiment, the "abnormal activity" includes the abnormal (either over- or under-) production of mRNA transcribed from a gene. In another embodiment, the "abnormal activity" includes the abnormal (either over- or under-) production of polypeptide from a gene. In another embodiment, the abnormal activity refers to a level of a mRNA or polypeptide that is different from a normal level of said mRNA or polypeptide by about 15%, about 25%, about 35%, about 50%, about 65%, about 85%, about 100% or greater. Preferably, the abnormal level of the mRNA or polypeptide can be either higher or lower than

the normal level of said mRNA or polypeptide. Yet in another embodiment, the abnormal activity refers to functional activity of a protein that is different from a normal activity of the wild-type protein. Abnormal activity may be due to the mutations in the corresponding gene, and the mutations can be in the coding region of the gene or non-coding regions such as transcriptional promoter regions. The mutations can be substitutions, deletions, insertions.

The compounds of the present invention, as PKD modulating compounds, are useful for treatment of a disorder or disease mediated by PKD or responsive to inhibition of PKD. In particular, the compounds of the present invention are useful for treatment of a PKD associated state including heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, and hyperproliferative skin disorders, etc.

The term "PKD modulating compound" includes compounds, which modulate, *e.g.*, inhibit, promote or otherwise alter the activity of PKD. PKD modulating compounds include PKD agonists, inverse agonists, and antagonists. This term includes, but is not limited to, compounds of formulae I-VI.

The term "PKD inhibiting compound" includes compounds which reduce the activity of PKD, *e.g.*, the ability of PKD to phosphorylate substrate (e.g., HDAC), *in vivo* or *in vitro*. In one embodiment, the PKD inhibiting compounds are PKD antagonists or inverse agonists. In another embodiment, the PKD inhibiting compounds are HDAC phosphorylation inhibiting compounds.

The term "inhibition" or "inhibiting" includes the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process. In one embodiment, the condition or symptom or disorder or disease is mediated by PKD activity. In another embodiment, the condition or symptom or disorder or disease is associated with the abnormal activity of PKD, or the condition or symptom or disorder or disease is associated with the abnormal expression of PKD.

The term "subject" includes animals (*e.g.*, mammals) A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds, etc.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when

administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by PKD, or (ii) associated with PKD activity, or (iii) characterized by abnormal activity of PKD; or (2) reducing or inhibiting the activity of PKD; or (3) reducing or inhibiting the expression of PKD. In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of PKD; or at least partially reducing or inhibiting the expression of PKD.

The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular organic compound. For example, the choice of the organic compound can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the organic compound without undue experimentation.

The term "treating" or "treatment" of any disease or disorder includes curing as well as ameliorating at least one symptom of the state, disease, or disorder (*e.g.*, the PKD associated state). The term may also include alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient; or modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. The terms may also include preventing or delaying the onset or development or progression of the disease or disorder.

A further embodiment includes methods for treating a PKD disorder in a subject by administering to a subject an effective amount of a compound of the invention (*e.g.*, a compound of any one of Formulae I-VI or a compound otherwise described herein) in combination with a second agent, such that the subject is treated for said PKD disorder.

The term "in combination with" a second agent or treatment includes co-administration of the compound of the invention (*e.g.*, a compound of any one of Formulae I-VI or a compound otherwise described herein) with the second agent or treatment, administration of the compound of the invention first, followed by the second agent or treatment and administration of the second agent or treatment first, followed by the compound of the invention.

The term "second agent" includes any agent which is known in the art to treat, prevent, or reduce the symptoms of a disease or disorder described herein, *e.g.*, PKD

associated disorder, such as, for example, heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, and hyperproliferative skin disorders, etc. Furthermore, the second agent may be any agent of benefit to the patient when administered in combination with the administration of compound of the invention. Examples of second agents include chemotherapeutic agents, radiation therapy, and cardiovascular protective agents, etc. as described below.

The term "chemotherapeutic agent" includes chemical reagents which inhibit the growth of proliferating cells or tissues wherein the growth of such cells or tissues is undesirable or otherwise treat at least one resulting symptom of such a growth. Chemotherapeutic agents are well known in the art (see *e.g.*, Gilman A.G., *et al., The Pharmacological Basis of Therapeutics*, 8th Ed., Sec 12:1202-1263 (1990)), and are typically used to treat neoplastic diseases. Examples of chemotherapeutic agents include: bleomycin, docetaxel (Taxotere), doxorubicin, edatrexate, etoposide, finasteride (Proscar), flutamide (Eulexin), gemcitabine (Gemzar), goserelin acetate (Zoladex), granisetron (Kytril), irinotecan (Campto/Camptosar), ondansetron (Zofran), paclitaxel (Taxol), pegaspargase (Oncaspar), pilocarpine hydrochloride (Salagen), porfimer sodium (Photofrin), interleukin-2 (Proleukin), rituximab (Rituxan), topotecan (Hycamtin), trastuzumab (Herceptin), tretinoin (Retin-A), Triapine, vincristine, and vinorelbine tartrate (Navelbine).

Other examples of chemotherapeutic agents include alkylating drugs such as nitrogen mustards (*e.g.*, Mechlorethamine (HN_2), cyclophosphamide, Ifosfamide, Melphalan (L-sarcolysin), Chlorambucil, *etc.*); ethylenimines, methylmelamines (*e.g.*, Hexamethylmelamine, Thiotepa, *etc.*); alkyl sulfonates (*e.g.*, Busulfan, *etc.*), nitrosoureas (*e.g.*, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), Streptozocin (streptozotocin), *etc.*), triazenes (*e.g.*, Decarbazine (DTIC; dimethyltriazenoimi-dazolecarboxamide)), alkylators (*e.g.*, cis-diamminedichloroplatinum II (CDDP)), *etc.*

Other examples of chemotherapeutic agents include antimetabolites such as folic acid analogs (*e.g.*, Methotrexate (amethopterin)); pyrimidine analogs (*e.g.*, fluorouracil ('5-fluorouracil; 5-FU); floxuridine (fluorode-oxyuridine); Fudr; Cytarabine (cyosine arabinoside), *etc.*); purine analogs (*e.g.*, Mercaptopurine (6-mercaptopurine; 6-MP); Thioguanine (6-thioguanine; TG); and Pentostatin (2'–deoxycoformycin)), *etc.*

Other examples of chemotherapeutic agents also include vinca alkaloids (*e.g.*, Vinblastin (VLB) and Vincristine); topoisomerase inhibitors (*e.g.*, Etoposide, Teniposide, Camptothecin, Topotecan, 9-amino-campotothecin CPT-11, *etc.*); antibiotics (*e.g.*, Dactinomycin (actinomycin D), adriamycin, daunorubicin, doxorubicin, bleomycin, plicamycin

(mithramycin), mitomycin (mitomycin C), Taxol, Taxotere, *etc.*); enzymes (*e.g.*, L-Asparaginase); and biological response modifiers (*e.g.*, interferon-; interleukin 2, *etc.*). Other chemotherapeutic agents include cis-diaminedichloroplatinum II (CDDP); Carboplatin; Anthracendione (*e.g.*, Mitoxantrone); Hydroxyurea; Procarbazine (N-methylhydrazine); and adrenocortical suppressants (*e.g.*, Mitotane, aminoglutethimide, *etc.*).

Other chemotherapeutic agents include adrenocorticosteroids (*e.g.*, Prednisone); progestins (*e.g.*, Hydroxyprogesterone caproate, Medroxyprogesterone acetate, Megestrol acetate, *etc.*); estrogens (*e.g.*, diethylstilbestrol; ethenyl estradiol, *etc.*); antiestrogens (*e.g.* Tamoxifen, *etc.*); androgens (*e.g.*, testosterone propionate, Fluoxymesterone, *etc.*); antiandrogens (*e.g.*, Flutamide); and gonadotropin-releasing hormone analogs (*e.g.*, Leuprolide).

The term "radiation therapy" includes the application of a genetically and somatically safe level of x-rays, both localized and non-localized, to a subject to inhibit, reduce, or prevent symptoms or conditions associated with cancer or other undesirable cell growth. The term "x-rays" includes clinically acceptable radioactive elements and isotopes thereof, as well as the radioactive emissions therefrom. Examples of the types of emissions include alpha rays, beta rays including hard betas, high energy electrons, and gamma rays. Radiation therapy is well known in the art (see *e.g.*, Fishbach, F., *Laboratory Diagnostic Tests*, 3rd Ed., Ch. 10: 581-644 (1988)), and is typically used to treat neoplastic diseases.

The term "cardiovascular protective agent" includes HMG-Co-A reductase inhibitors, angiotensin II receptor antagonists, angiotensin converting enzyme (ACE) Inhibitors, calcium channel blockers (CCB), dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, renin inhibitors, diuretics, ApoA-I mimics, anti-diabetic agents, obesity-reducing agents, aldosterone receptor blockers, endothelin receptor blockers, and CETP inhibitors.

The term "HMG-Co-A reductase inhibitor" (also called beta-hydroxy-beta-methylglutaryl-co-enzyme-A reductase inhibitors) includes active agents that may be used to lower the lipid levels including cholesterol in blood. Examples include atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluindostatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or, pharmaceutically acceptable salts thereof.

The term "ACE-inhibitor" (also called angiotensin converting enzyme inhibitors) includes molecules that interrupt the enzymatic degradation of angiotensin I to angiotensin II. Such compounds may be used for the regulation of blood pressure and for the treatment of

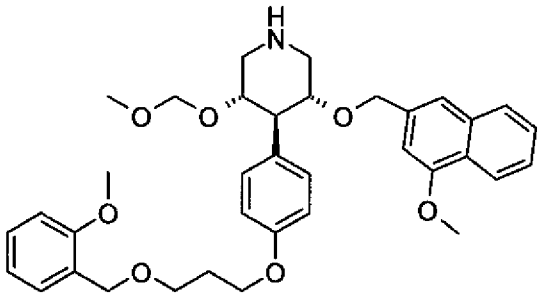
congestive heart failure. Examples include alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, pharmaceutically acceptables salt thereof.

The term "calcium channel blocker (CCB)" includes dihydropyridines (DHPs) and non-DHPs (*e.g.*, diltiazem-type and verapamil-type CCBs). Examples include amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, or, pharmaceutically acceptable salts thereof. CCBs may be used as anti-hypertensive, anti-angina pectoris, or anti-arrhythmic drugs.

The term "dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor" includes omapatrilate (cf. EP 629627), fasidotril or fasidotrilate, or pharmaceutically acceptable salts thereof.

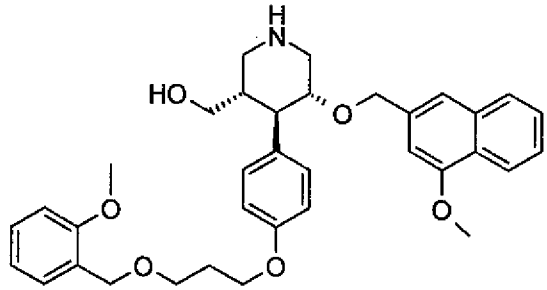
The term "endothelin antagonist" includes bosentan (cf. EP 526708 A), tezosentan (cf. WO 96/19459), or, pharmaceutically acceptable salts thereof.

The term "renin inhibitor" includes ditekiren (chemical name: [1*S*-[1*R**,2*R**,4*R**(1*R**,2*R**)]]-1-[(1,1-dimethylethoxy)carbonyl]-L-proly l-L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmrthyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-*N*-alfa-methyl-L-histidinamide); terlakiren (chemical name: [*R*-(*R**,*S**)]-N-(4-morpholinylcarbonyl)-L-phenylalanyl-N-[1-(cyclohexy lmethyl)-2-hydroxy-3-(1-methylethoxy)-3-oxopropyl]-S-methyl-L-cysteineamide); and zankiren (chemical name: [1*S*-[1*R**[*R**(*R**)],2*S**,3*R**]]-*N*-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-m ethylhexyl]-alfa-[[2-[[(4-methyl-1-piperazinyl)sulfonyl]methyl]-1-oxo-3-phenylpropyl]-amino]-4-thiazolepropanamide), or, hydrochloride salts thereof, or, SPP630, SPP635 and SPP800 as developed by Speedel, or RO 66-1132 and RO 66-1168 of Formula (A) and (B):



(A)

and



(B)

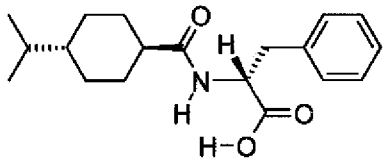
,

or, pharmaceutically acceptable salts thereof.

The term "diuretic" includes thiazide derivatives (*e.g.*, chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon).

The term "ApoA-I mimic" includes D4F peptides (*e.g.*, formula D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F)

The term "anti-diabetic agent" includes insulin secretion enhancers that promote the secretion of insulin from pancreatic β-cells. Examples include biguanide derivatives (*e.g.*, metformin), sulfonylureas (SU) (*e.g.*, tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-*N*-[(1-pyrolidinylamino)carbonyl]-benzensulfonamide (glycopyramide), glibenclamide (glyburide), gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, and tolylcyclamide), or pharmaceutically acceptable salts thereof. Further examples include phenylalanine derivatives (*e.g.*, nateglinide [*N*-(*trans*-4-isopropylcyclohexylcarbonyl)-*D*-phenylalanine] (cf. EP 196222 and EP 526171) of the formula:



;

repaglinide [(*S*)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl}benzoic acid] (cf. EP 589874, EP 147850 A2, in particular Example 11 on page 61, and EP 207331 A1); calcium (2*S*)-2-benzyl-3-(*cis*-hexahydro-2-isoindolinlycarbonyl)-propionate dihydrate (*e.g.*, mitiglinide (cf. EP 507534)); and glimepiride (cf. EP 31058). Further examples include DPP-IV inhibitors, GLP-1 and GLP-1 agonists.

DPP-IV is responsible for inactivating GLP-1. More particularly, DPP-IV generates a GLP-1 receptor antagonist and thereby shortens the physiological response to GLP-1. GLP-

1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal.

The DPP-IV inhibitor can be peptidic or, preferably, non-peptidic. DPP-IV inhibitors are in each case generically and specifically disclosed *e.g.* in WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309. Preferred are those compounds that are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively.

GLP-1 is an insulinotropic protein which is described, *e.g.*, by W.E. Schmidt et al. in *Diabetologia*, 28, 1985, 704-707 and in US 5,705,483.

The term "GLP-1 agonists" includes variants and analogs of GLP-1(7-36)NH_2 which are disclosed in particular in US 5,120,712, US 5,118666, US 5,512,549, WO 91/11457 and by C. Orskov et al in J. Biol. Chem. 264 (1989) 12826. Further examples include GLP-1(7-37), in which compound the carboxy-terminal amide functionality of Arg^{36} is displaced with Gly at the 37th position of the GLP-1(7-36)NH_2 molecule and variants and analogs thereof including GLN^{9}-GLP-1(7-37), D-GLN^{9}-GLP-1(7-37), acetyl LYS^{9}-GLP-1(7-37), LYS^{18}-GLP-1(7-37) and, in particular, GLP-1(7-37)OH, VAL^{8}-GLP-1(7-37), GLY^{8}-GLP-1(7-37), THR^{8}-GLP-1(7-37), MET^{8}-GLP-1(7-37) and 4-imidazopropionyl-GLP-1. Special preference is also given to the GLP agonist analog exendin-4, described by Greig *et al.* in Diabetologia 1999, 42, 45-50.

Also included in the definition "anti-diabetic agent" are insulin sensitivity enhancers which restore impaired insulin receptor function to reduce insulin resistance and consequently enhance the insulin sensitivity. Examples include hypoglycemic thiazolidinedione derivatives (*e.g.*, glitazone, (*S*)-((3,4-dihydro-2-(phenyl-methyl)-2*H*-1-benzopyran-6-yl)methyl-thiazolidine-2,4-dione (englitazone), 5-{[4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-methyl}-thiazolidine-2,4-dione (darglitazone), 5-{[4-(1-methyl-cyclohexyl)methoxy)-phenyl]methyl}-thiazolidine-2,4-dione (ciglitazone), 5-{[4-(2-(1-indolyl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (DRF2189), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy)]benzyl}-thiazolidine-2,4-dione (BM-13.1246), 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione (AY-31637), bis{4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl}methane (YM268), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-thiazolidine-2,4-dione (AD-5075), 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-benzyl]-thiazolidine-2,4-dione (DN-108) 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl)thiazolidine-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenyl-sulfonyl)thiazolidine-2,4-dione, 5-{[4-(2-(methyl-2-pyridinyl-amino)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (rosiglitazone), 5-{[4-(2-(5-

ethyl-2-pyridyl)ethoxy)phenyl]-methyl}thiazolidine-2,4-dione (pioglitazone), 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-methyl}-thiazolidine-2,4-dione (troglitazone), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]-thiazolidine-2,4-dione (MCC555), 5-{[2-(2-naphthyl)-benzoxazol-5-yl]-methyl}thiazolidine-2,4-dione (T-174) and 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-benzyl)benzamide (KRP297)).

Further anti-diabetic agents include, insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), antidiabetic non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT); compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK); pyruvate dehydrogenase kinase (PDHK) inhibitors; inhibitors of gastric emptying; insulin; inhibitors of GSK-3; retinoid X receptor (RXR) agonists; agonists of Beta-3 AR; agonists of uncoupling proteins (UCPs); non-glitazone type PPARα agonists; dual PPARα/ PPARγ agonists; antidiabetic vanadium containing compounds; incretin hormones, like glucagon-like peptide-1 (GLP-1) and GLP-1 agonists; beta-cell imidazoline receptor antagonists; miglitol; α_2-adrenergic antagonists; and pharmaceutically acceptable salts thereof.

The term "obesity-reducing agent" includes lipase inhibitors (*e.g.*, orlistat) and appetite suppressants (*e.g.*, sibutramine and phentermine).

The term "aldosterone receptor blocker" includes spironolactone and eplerenone.

The term "endothelin receptor blocker" includes bosentan.

The term "CETP inbihitor" refers to a compound that inhibits the cholesteryl ester transfer protein (CETP) mediated transport of various cholesteryl esters and triglycerides from HDL to LDL and VLDL. Such CETP inhibition activity is readily determined by those skilled in the art according to standard assays (*e.g.*, U.S. Pat. No. 6,140,343). Examples include compounds disclosed in U.S. Pat. No. 6,140,343 and U. S. Pat. No. 6,197,786 (*e.g.*, [2R,4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl- amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (torcetrapib); compounds disclosed in U.S. Pat. No. 6,723,752 (*e.g.*, (2R)-3-{[3-(4-Chloro-3-ethyl-phenoxy)-phenyl]-[[3-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methyl]-amino}-1,1,1-trifluoro-2-propanol); compounds disclosed in U.S. patent application Ser. No. 10/807,838; polypeptide derivatives disclosed in U.S. Pat. No. 5,512,548; rosenonolactone derivatives and phosphate-containing analogs of

cholesteryl ester disclosed in *J. Antibiot.*, 49(8): 815- 816 (1996), and *Bioorg. Med. Chem. Lett.;* 6:1951-1954 (1996), respectively. Furthermore, the CETP inhibitors also include those disclosed in WO2000/017165, WO2005/095409 and WO2005/097806.

Pharmaceutical Compositions of the Invention

The invention also pertains to pharmaceutical compositions comprising a compound of the invention, (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein), and, optionally, one or more pharmaceutically acceptable carriers.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredients for a subject of about 50-70 kg, preferably about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, preferably between about 1-100 mg/kg.

The activities of a compound according to the present invention can be assessed by both *in vitro* and *in vivo* methods, such as the DSS rat model as described in Journal of Hypertension (2005) 23, 87, the mouse pressure overload model Circulation (1999) 84, 735.

The term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, wetting agents, emulsifiers, buffers, disintegration agents, lubricants, coatings, sweetening agents, flavoring agents, dyes, such like materials and combinations thereof, as would be known to one of ordinary skill in the art

(see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329, incorporated herein by reference). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic aid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc.

The pharmaceutical compositions of the invention can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form including capsules, tablets, pills, granules, powders or suppositories, or in a liquid form including solutions, suspensions or emulsions. The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers, etc.

In certain embodiments, the pharmaceutical compositions are tablets and gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, preferably about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for

delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.*, for the treatment of skin cancer, *e.g.*, for prophylactic use in sun creams, lotions, sprays, etc. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, *e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice,* 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e. g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

A further embodiment includes pharmaceutical compositions comprising an effective amount of a compound of the present invention, (*e.g.*, a compound of Formula I-VI or a

compound otherwise described herein), in combination with a second agent and a pharmaceutical carrier.

In yet another embodiment, the invention pertains to compounds of the present invention, (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein), for use as a medicament.

Further embodiments of the invention include uses of compounds of the present invention, (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein), for the preparation of a pharmaceutical composition for the treatment of a disorder or disease in a subject mediated by PKD.

Still further embodiments of the invention include uses of pharmaceutical compositions of the present invention, (*e.g.*, a compound of Formula I-VI or a compound otherwise described herein), for the preparation of a medicament for the treatment of a disorder or disease in a subjectmediated by PKD.

The disorder or disease may be characterized by an abnormal activity of PKD or abnormal expression of PKD.

In one embodiment the disorder or disease includes but is not limited to heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, or hyperproliferative skin disorders.

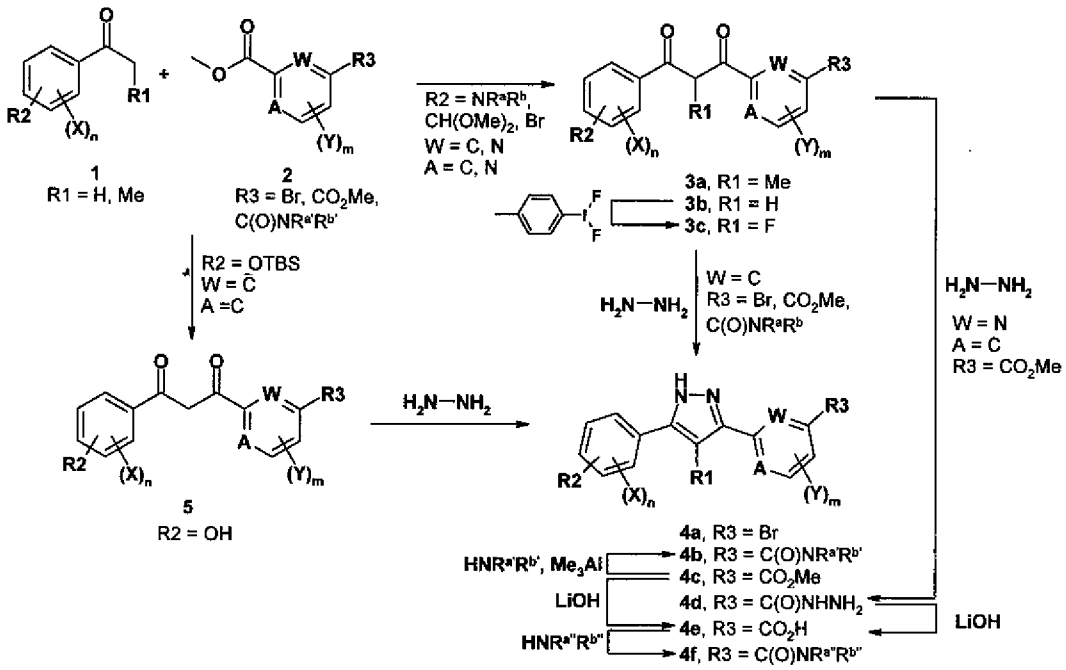
Advantageously, the present invention also provides kits for use by a consumer for treating disease. The kits comprise a) a pharmaceutical composition comprising the compound of Formulas I-VI, a pharmaceutically acceptable carrier, vehicle or diluents; and, optionally, b) instructions describing a method of using the pharmaceutical composition for treatment of a PKD associated disorder.

A "kit" as used in the instant application includes a container for containing the separate unit dosage forms such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

Methods for Synthesizing Compounds of the Invention

The compounds of the invention can be synthesized using the methods described in the following schemes, examples, and by using techniques recognized by those skilled in the art. All compounds described herein are included in the invention as compounds.

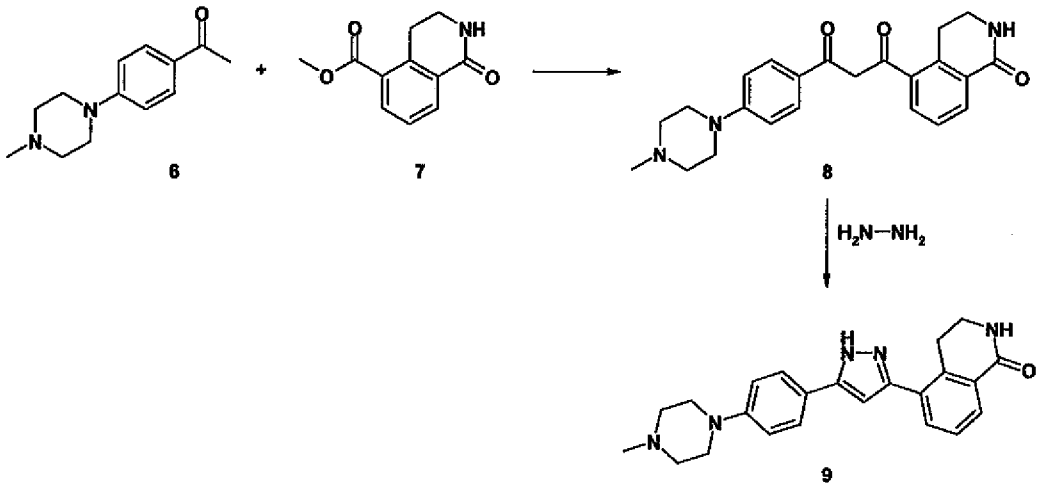
As shown in scheme 1, Reaction of an aryl ketone **1** and a benzoate **2** under basic conditions provides a 1,3-diketone **3**. When R2 = OTBS, this reaction also results in *in situ* removal of the TBS group, providing the phenol substituted compound **5**, (R2 = OH). The diketo-compound **3b**, where the 2-position of the diketone is unsubstituted, is converted to the 2-fluoro-1,3-diketone **3c** by treatment with an electrophilic fluorinating agent (for example, difluoroiodosotoluene). The diketones **3** and **5** can be converted to pyrazoles **4** by cyclocondensation with hydrazine. While generally the identity of R3 is unchanged in this transformation, as shown for a representative example of compound **3**, in which W = N, A = C and R3 = CO_2Me, the benzoate ester can also converted to a benzoic acid hydrazide **4d**.



Scheme 1

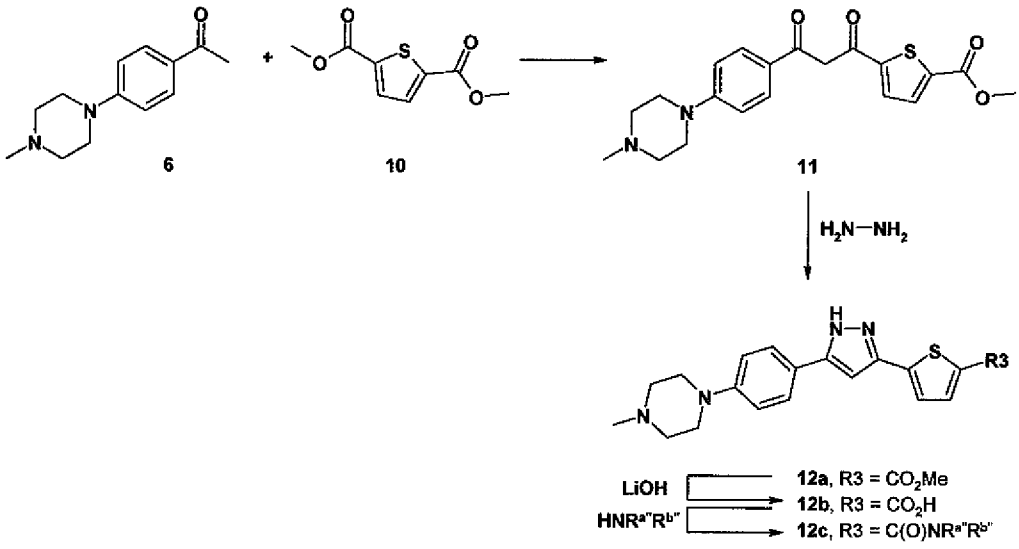
Manipulation of substituent R3 in compound **4** can be accomplished utilizing transformations well known to those skilled in the art. Thus, benzoate **4c** can converted directly to a benzamide **4b** by reaction with a primary or secondary amine, $HNR^{a'}R^{b'}$. Alternatively, either benzoate **4c** or hydrazide **4d** can be hydrolyzed to benzoic acid **4e**, followed by coupling

with a primary or secondary amine $HNR^{a''}R^{b''}$ in the presence of amide bond forming reagents, such as HATU, to provide benzamides **4f**. Substituents present in the X, Y, R^a, R^b, $R^{a'}$, $R^{b'}$, $R^{a''}$, $R^{b''}$ moieties of compounds **4a-f** can be further manipulated by methods known in the art or as described below.



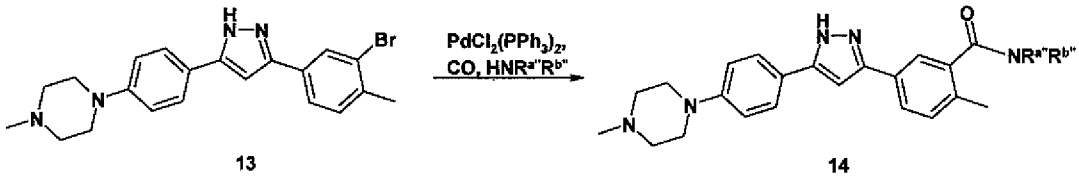
Scheme 2

The methods illustrated in scheme 1 can also be utilized with other variations of benzoic acid ester **2**, such as the benzamide derivative **7** (scheme 2), in which the substitution of the amide forms a cycle with the aromatic ring, or with other heteroaromatics, such as the representative example of thiophene **10** (scheme 3). Reaction with aryl ketones such as **6** (as a representative example of ketone **1**, scheme 1) in the presence of a suitable base can therefore provide pyrazole compounds such as dihydro-isoquinolinone **9**, and thiophene **12a**. Compound **12a** can be further derivatized to thiophene carboxylate **12b** and thiophene carboxamide **12c** by utilizing well-known transformations, as discussed above for compounds **4** (scheme 1).

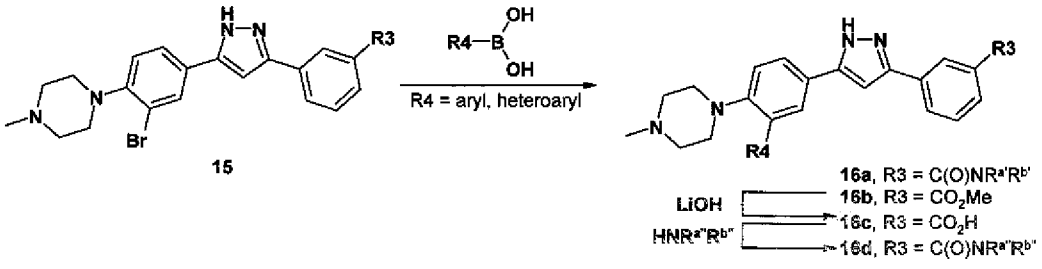


Scheme 3

Compounds **4** (scheme 1), in which R2 or R3 is Br can be further derivatized using methods known to those skilled in the art. As a representative example, aryl bromide **13** (scheme 4) can be converted into carboxamide **14** by carbonylative amidation with a suitable palladium catalyst. In another representative example, the aryl bromide of compound **15** (scheme 5) can be converted to an aromatic substituent R4 by Suzuki coupling with an aryl boronic acid and a suitable palladium catalyst to provide compounds such as **16a** or **16b**. As described above benzoate **16b** can be to carboxylate **16c**, and carboxamide **16d** using methods well known in the art. Substituents present in the R3 and R4 moieties of compounds **16a-d** can be further manipulated by methods known in the art or as described below.

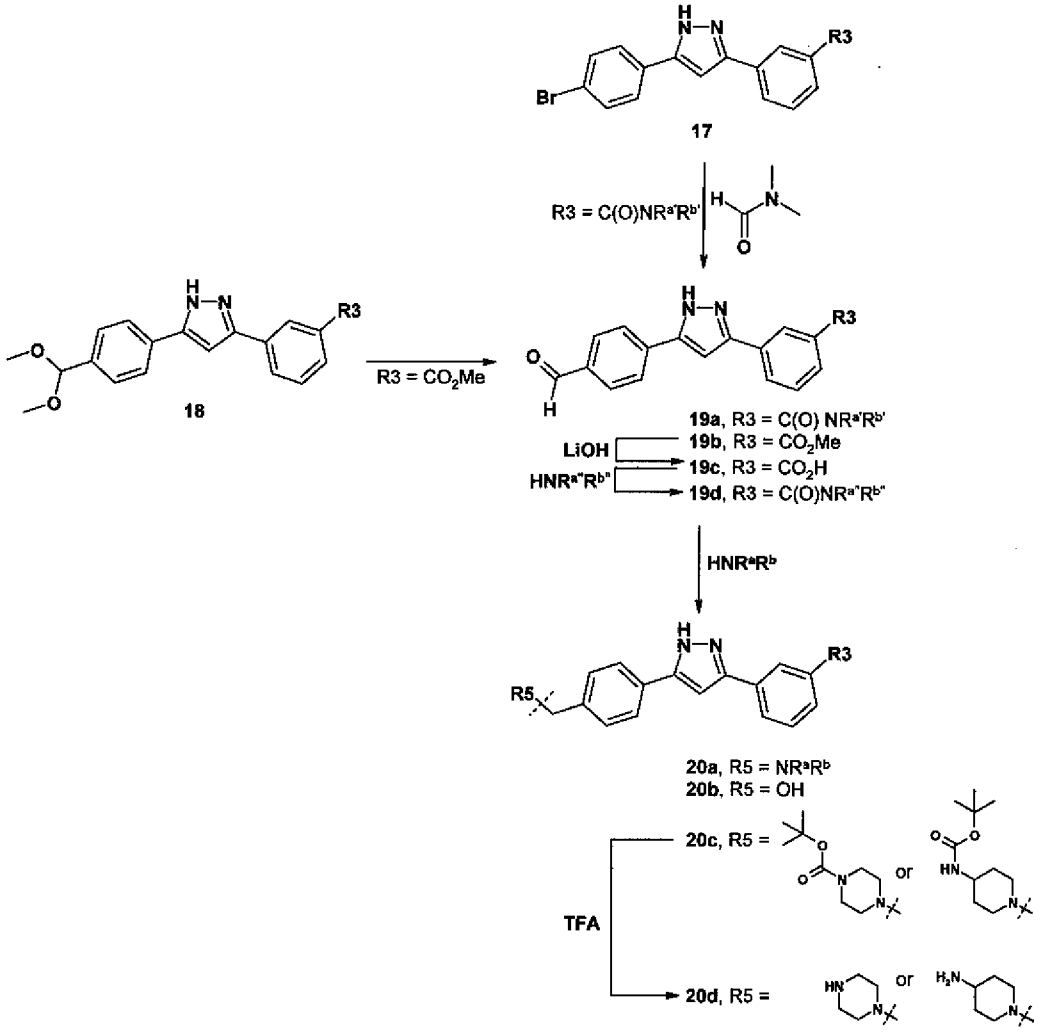


Scheme 4



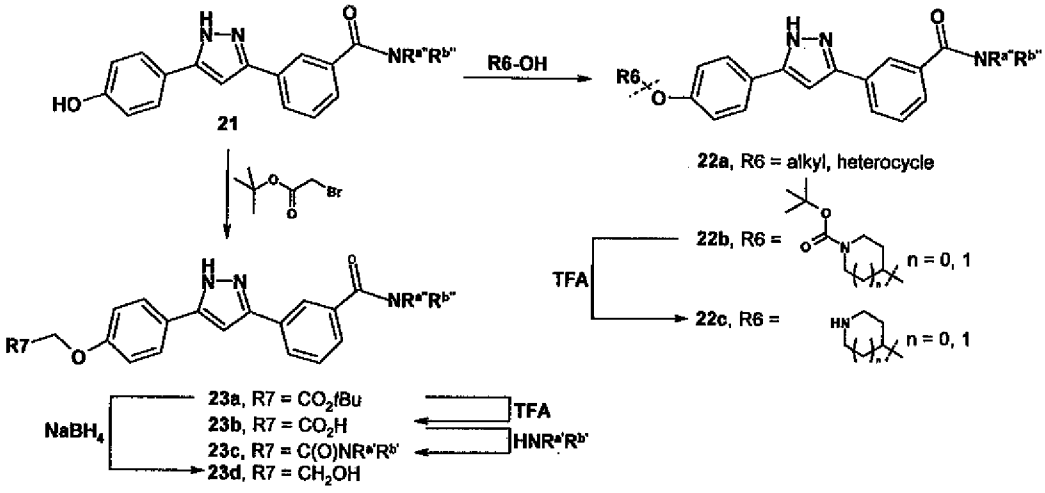
Scheme 5

As illustrated in scheme 6, the aryl bromide **17**, which is a representative example of compound **4b** (Scheme 1) with R2 = Br, can be converted to benzaldehyde **19a** by metal-halogen exchange and trapping of the resulting aryl metalate with dimethylformamide. Alternatively, the benzaldehyde **19b** can be synthesized from the acetal **18**, which is a representative example of compound **4c** (scheme 1), by treatment with water and an acid, such as trifluoroacetic acid (TFA). Utilizing well known methods discussed above, The benzoate of **19b** can be further manipulated to the benzoic acid of **19c** and the benzamide of **19d**. Reductive amination onto the aldehyde of compounds **19a-d** utilizing a primary or secondary amine (HNR^aR^b) and a suitable hydride source (for example, sodium tris-acetoxyborohydride) provides benzylic amines **20a**, along with benzylic alcohol **20b**, resulting from the direct reduction of the aldehyde. Substituents present in the R^a and R^b moieties of compound **20b** can be manipulated further by methods known in the art, such as by deprotection of heteroatom moieties. As representative examples, compounds **20c**, in which the R^a and R^b moeties of compound **20a** together form a Boc-protected piperazine or Boc-protected aminopiperidine, can be deprotected using TFA to provide compounds **20d**.



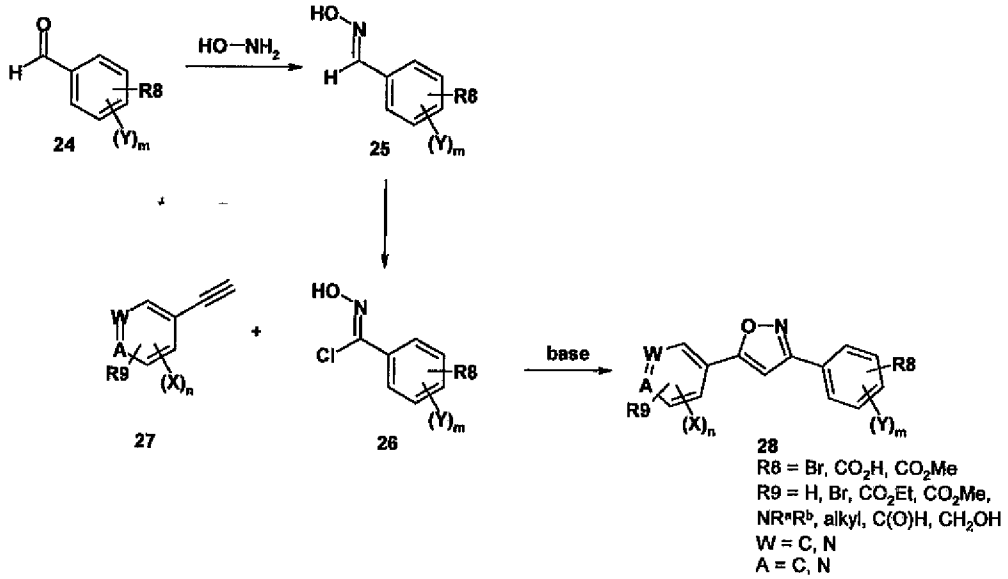
Scheme 6

As described in scheme 7, the phenol **21**, which is a representative example of compound **4f** (scheme 1) with R2 = OH, can be further reacted with suitable alcohols under Mitsinobu conditions to provide phenyl ethers **22a**, or by alkylation with suitable bromides, such as *tert*-butyl bromoacetate, to provide phenyl ether **23a**. Substituents on the R6 and R7 moieties of compounds **22a** and **23a** can be further manipulated by methods known in the art. For example, compounds **22b**, in which R6 is a Boc-protected 5 or 6 membered ring heterocycle, can be treated with TFA to provide deprotected compounds **22c**. The acetate of compound **23a** can be reduced by treatment with hydride donors such as sodium borohydride to afford the alcohol **23d**, or it can be deprotected to the carboxylic acid **23b**, which can be further converted to the amide **23c** by treatment with a primary or secondary amine $HNR^{a'}R^{b'}$ in the presence of amide bond forming reagents, such as HOAt and EDCI, or HATU.



Scheme 7

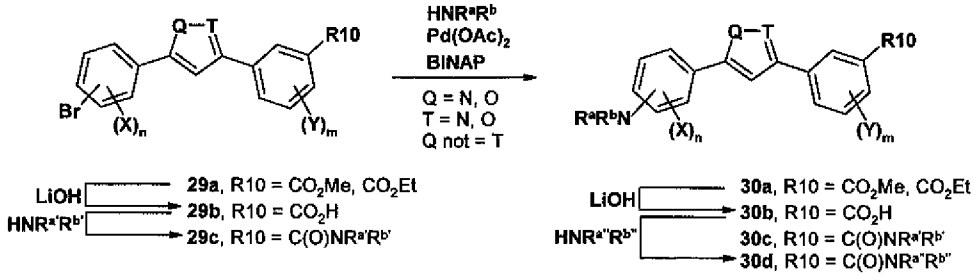
As shown in schame 8, condensation of an aldehyde **24** with hydroxylamine followed by treatment with an electrophilic chlorinating agent, such as N-chlorosuccinimide provides chlorohydroxyimines **26**. Bis-aryl-isoxazole compounds **28** can be synthesized by dipolar cycloaddition of **26** with alkynes **27** in the presence of a suitable base, such as triethylamine. Substituents in the R8, R9, X, Y, R^a, and R^b moieties of compound **28** can be further manipulated as known to those skilled in the art or as described below.



Scheme 8

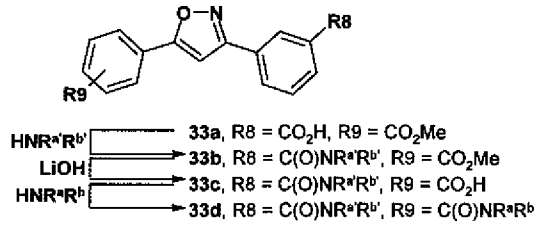
Compounds **28** (Scheme 8), in which R8 = Br or R9 = Br can be further derivatized using methods known to those skilled in the art. As a representative example, aryl bromides **29** (Scheme 9), can be converted to anilines **30** under Buchwald amination conditions employing a primary or secondary amine and a suitable palladium catalyst. Manipulation of

R10 in either compounds **29** or compounds **30** can be accomplished using transformations well known to those skilled in the art. Thus, the benzoic acid esters **29a** or **30a** can be hydrolyzed to benzoic acids **29b** or **30b**, followed by coupling with a primary or secondary amine $HNR^{a'}R^{b'}$ or $HR^{a''}R^{b''}$, to provide benzamides **29c** or **30d**.



Scheme 9

The substitutents R8 and R9 of compound **33a**, which can be synthesized according to the methods illustrated in scheme 1, can be differentially modified using methods known in the art. For example, as shown in scheme 10, the benzoic acid substituent R8 of compound **33a** can be coupled with a primary or secondary amine $HNR^{a'}R^{b'}$ in the presence of a suitable amide bond-forming reagent, such as HATU to provide **33b**. Hydrolysis of the R9 ester of **33b** to the carboxylic acid **33c** followed by a similar amide bond coupling with a different primary or secondary amine $HNR^{a''}R^{b''}$ can provide the bis-carboxamide **33d**.

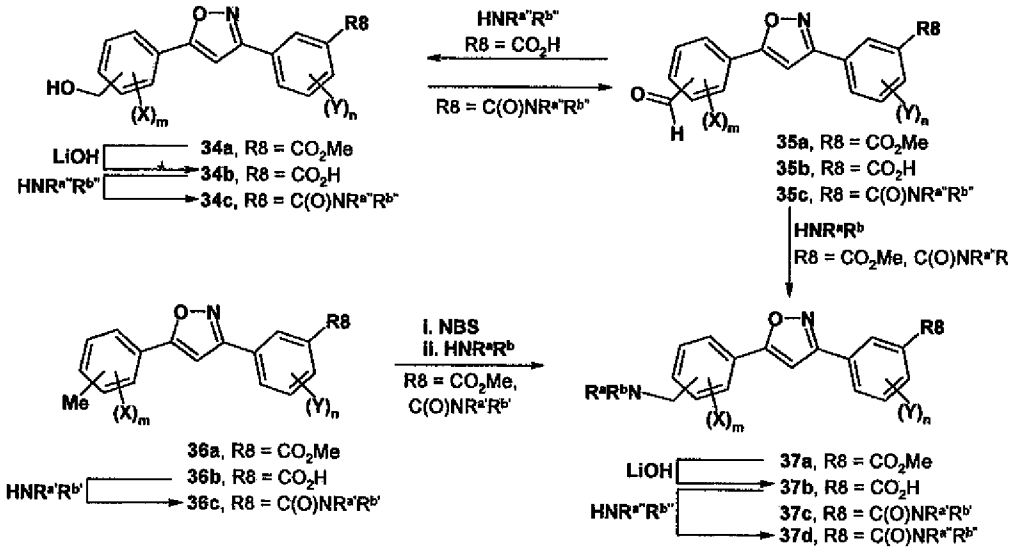


Scheme 10

As shown in scheme 11, compound **34a**, which can be synthesized according to the methods described in scheme 8, can be further modified to generate additional targets by modifications of the group R8 and the benzylic alcohol moiety shown. For example, hydrolysis of the R8 benzoic acid ester and coupling of the resulting carboxylic acid **34b** with a primary or secondary amine $HNR^{a''}R^{b''}$ in the presence of an amide bond-forming reagent, such as HATU, can provide benzamide **34c**. Oxidation of the benzylic alcohol of **34c** to the benzaldehyde **35c** can be accomplished under Swern conditions or with other oxidizing reagents well known in the art, such as SO_3-pyridine complex in DMSO. Treatment of aldehyde **35c** under reductive amination conditions in the presence of a primary or

secondary amine HNR^aR^b and a suitable hydride donor (such as sodium tris-acetoxy-borohydride or sodium borohydride) can provide benzylic amines **37d**. Similarly, ester **35a**, which can be synthesized using the methods described in scheme 8, can be treated under reductive amination conditions to provide benzylic amine **37a**, in which R8 = CO_2Me. Alternatively, compound **37a** can be synthesized from compound **36a**, which is available through the methods described in scheme 8, by benzylic halogenation with electrophilic brominating agents, such as N-bromo-succinimide, followed by nucleophilic substitution with primary or secondary amines, HNR^aR^b. The R8 moiety of **37a** can be converted to carboxylic acid **37b** and subsequently to carboxamide **37d** using methods described above. Alternatively, coupling of a primary or secondary amine $HNR^{a'}R^{b'}$ with carboxylic acid **36b** (synthesized by the methods described in scheme 8) can provide carboxamide **36c**, which can be converted to benzylic amine **37c** using the benzylic bromination and nucleophilic substitution described above.

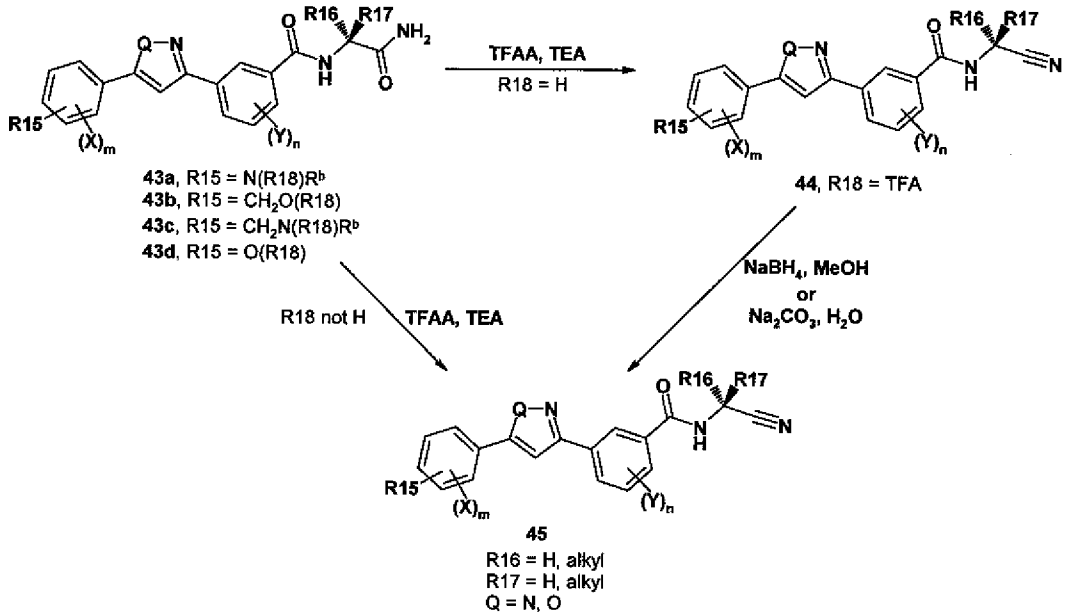
Benzaldehyde **35b** (scheme 11), which can be synthesized according to the methods described in scheme 8, can undergo a Cannizaro disproportionation upon amidation with a primary or secondary amine $HNR^{a''}R^{b''}$ in the presence of an amide bond-forming reagent to provide benzylic alcohol **34c**.



Scheme 11

In scheme 12, a method of synthesis of nitrile amides **45** is described. The dipeptides **43a-d**, which can be further modified by treatment with TFAA and TEA to afford dehydration of the primary amide to the cyano group, which occurs with retention of stereochemistry and enantiopurity of the

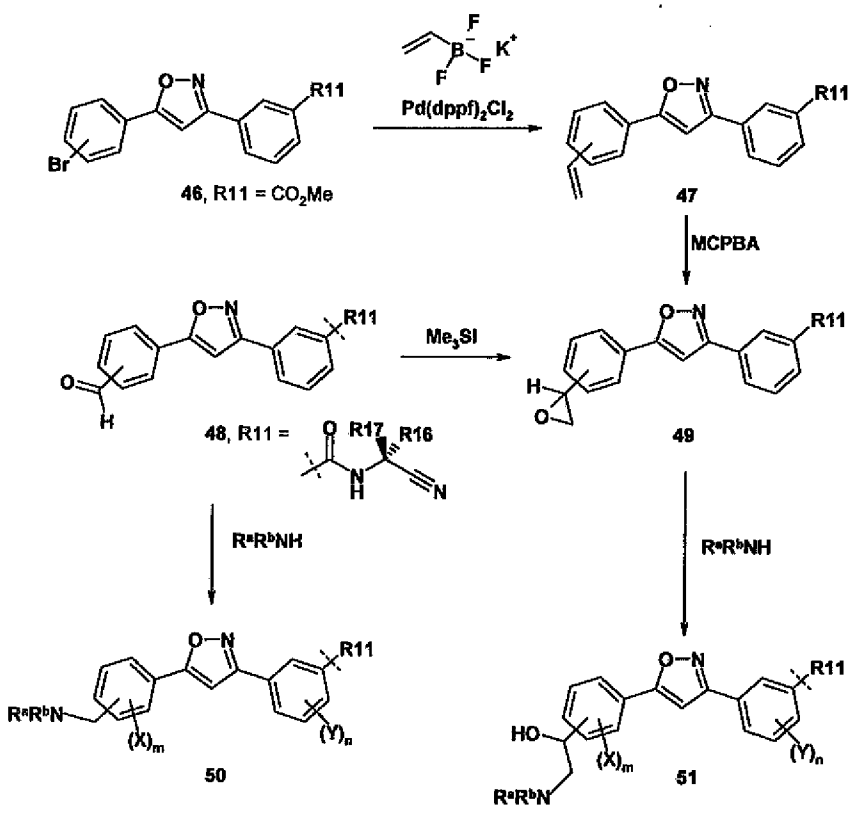
substituents R16 and R17. If an unprotected heteroatom substituent is present in the R15 moiety of compounds **43a-d** (for example R18 = H), this method can result in *in situ* protection of the heteroatom with a TFA moiety (R18 = TFA) in compound **44**, which can be subsequently removed under mild nucleophilic conditions to provide compound **45** with R18 = H. In cases of compounds **43a-d** in which all heteroatom substituents in R15 are protected (for example, R18 is not H), the method can provide nitrile amide **45** directly with no further manipulations.



Scheme 12

Compound **48** (Scheme 13), which can be synthesized according to the methods described in scheme 12 and scheme 11, can be further modified to provide additional compounds of the invention. Reductive amination of the aldehyde of **48** in the presence of a primary or secondary amine HNR^aR^b and a suitable hydride donor, such as sodium borohydride or sodium tris-acetoxy borohydride can provide benzylic amines **50**. Alternatively, treatment of compounds **48** with trimethylsulfonium iodide in the presence of a suitable base, such as sodium hydride, can afford the epoxides **49**, which can be subsequently reacted with primary or secondary amines HNR^aR^b to provide amino alcohols **51**.

Similarly, aryl bromides, such as **46**, which can be synthesized according to the methods described in scheme 8, can be vinylated with vinyl trifluoroborates in the presence of a suitable palladium catalyst to give alkenes, such as **47**. Epoxidation of the olefin with MCPBA can provide epoxide 49, in which R11 = CO_2Me. This can be subsequently converted to amino alcohol 51 by reacting with a primary or secondary amine HNR^aR^b.



Scheme 13

Exemplification of the Invention

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centrigrade. If not mentioned otherwise, all evaporative concentrations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis or spectroscopic characteristics, *e.g.*, MS, IR, or NMR. Abbreviations used are those conventional in the art.

Flash column purification is preferably carried out on silica gel using an appropriate eluent of isocratic or gradient composition.

RP-HPLC purification is performed on a Waters X-bridge C8, C18, RP-18, or Phenyl column (30 x 50 mm, 5 µm) and is performed with an appropriate gradient eluent, which is

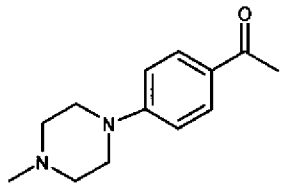
preferably composed of between 5% and 100% acetonitrile in water modified with 15 mM ammonia (pH = 11) or 0.1% v/v trifluoroacetic acid (pH = 1). Alternatively, purification is carried out on a Waters Sunfire C8 or C18 column (30 x 50 mm, 5 μm) and is performed with an appropriate gradient eluent, which is preferably composed of between 5% and 100% acetonitrile in water modified with 0.1% v/v trifluoroacetic acid (pH = 1).

Preparative TLC purification is preferably carried out on silica gel coated glass plates using an appropriate eluent of isocratic or gradient composition.

HPLC analysis is performed on a Waters Atlantis dC18 column (4.6 x 150 mm, 3 μm), with gradient elution (0% to 95% acetonitrile in water modified with 0.1% v/v trifluoroacetic acid over 20 min and a flow rate of 1.4 mL/min), unless otherwise described.

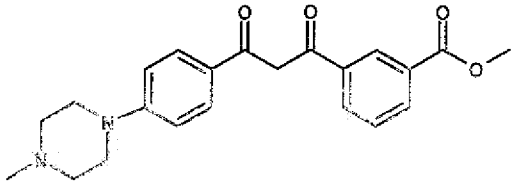
Example 1. 3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.

1-A 1-[4-(4-methylpiperazin-1-yl)-phenyl]-ethanone.



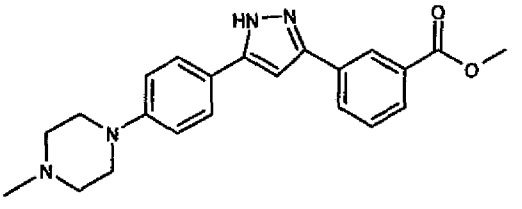
To a 100 mL DMSO solution of 4-Fluoroacetophenone (24 mL, 0.2 mol) at room temperature, is added N-methyl piperazine (22.2 mL, 0.2 mol). The mixture is heated in a 100 °C oil bath and stirred for 12-18 h, until LC-MS indicates that conversion is complete. The mixture is cooled to ambient temperature and saturated aqueous sodium carbonate solution (100 mL) is added. The aqueous phase is extracted with ethyl acetate (200 mL x 3) and the combined organic layers are dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude product is precipitated from a mixture of dichloromethane and ethanol to give compound **1-A** a pale yellow solid. MS(ESI) m/z = 219 (M+1).

1-B. 3-{3-[4-(4-Methyl-piperazin-1-yl)-phenyl]-3-oxo-propionyl}-benzoic acid methyl ester.



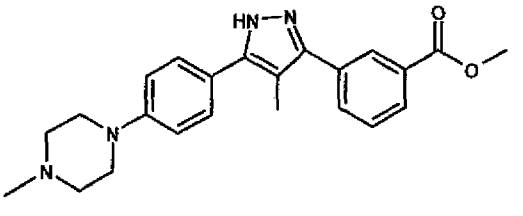
To a mixture of dimethylisophthalate (3.9 g, 20 mmol) and sodium hydride (576 mg, 24 mmol, 95%) in anhydrous tetrahydrofuran (40 mL) at 0°C, is slowly added a solution of 1-[4-(4-methylpiperazin-1-yl)-phenyl]-ethanone **1-A** (4.4g, 20 mmol) in tetrahydrofuran (10 mL). The mixture is heated in a 50 °C oil bath and stirred for 5 hours, until LC-MS indicates that conversion is complete. The mixture is cooled to room temperature, and saturated ammonium chloride solution (20 mL) is added. The aqueous phase is extracted with dichloromethane (150 mL x 2). The combined organic layers are dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is purified by flash column chromatography with 0 – 5% MeOH/DCM to afford product as a yellow solid. MS(ESI) m/z = 381.2 (M+1)

1-C. 3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.



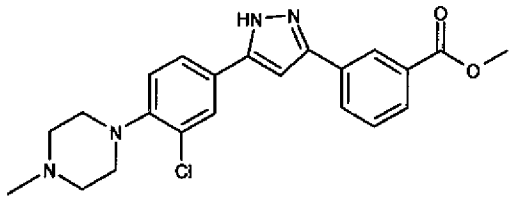
To a solution of diketone **1-B** (5.48g, 14mmol) in anhydrous ethanol (10 mL), are added hydrazine (1.13 mL, 36 mmol) and diisopropylethylamine (3.8 mL, 22 mmol). The reaction vessel is sealed and the mixture is heated in a 120 °C oil bath and stirred for 12-18h. The mixture is cooled to ambient temperature, during which a white precipitate is formed. The reaction is filtered and the residue is washed with ether three times. The collected solid is dried in vacuum oven to provide the product as a white solid. MS(ESI) m/z = 377.2 (M+1). HPLC R_t = 10.66 min.

Example 2. 3-{4-Methyl-5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.



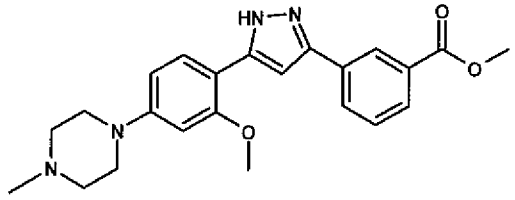
The title compound is prepared by methods similar to those utilized for the preparation of compound 1-C. MS(ESI) m/z = 391.2132 (M+1). HPLC R_t = 10.59 min.

Example 3. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.



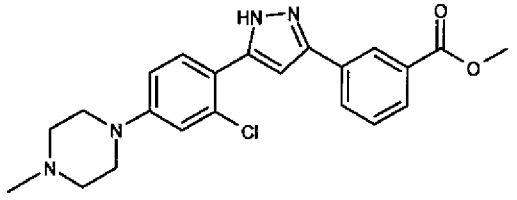
The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) m/z = 411.1598 (M+1). HPLC R_t = 11.35 min.

Example 4. 3-{5-[2-Methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.



The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) m/z = 407.2076 (M+1). HPLC R_t = 10.75 min.

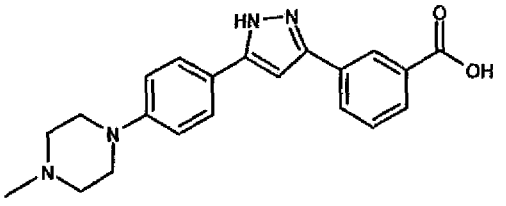
Example 5. 3-{5-[2-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.



The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) m/z = 411.1604 (M+1). HPLC R_t = 11.14 min.

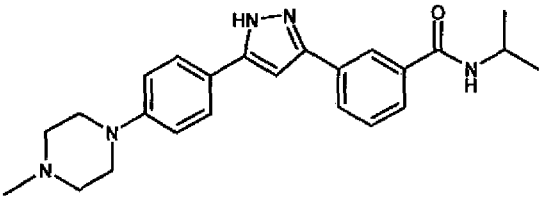
Example 6. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.

6-A. 3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid.



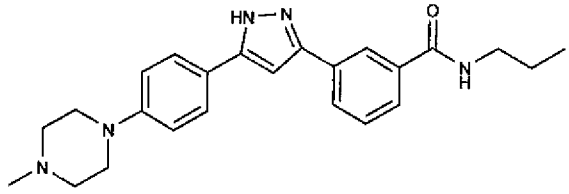
To a mixture of compound **1-C** (4.95 g, 13 mmol) in tetrahydrofuran (20 mL) and water (10 mL) is added lithium hydroxide monohydrate (1.2 g, 29 mmol). The reaction is stirred at ambient temperature, until LC-MS indicates that conversion is complete. The solvents are evaporated at reduced pressure to afford product as a white solid, contaminated with residual lithium hydroxide. MS(ESI) m/z = 363.2 (M+1)

6-B. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



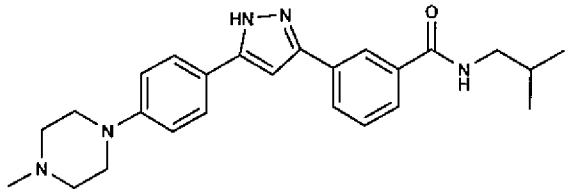
To a solution of compound **6-A** (179 mg, 0.49mmol) in dimethylformamide (2 mL) is added diisopropylethylamine (102 uL, 0.59mmol), isopropyl amine (50 uL, 0.59mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (223 mg, 0.59mmol). The mixture is stirred at ambient temperature until LC-MS indicates that conversion is complete. Water (10 mL) is added and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The combined organic layers are dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude product is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) m/z = 404.2458 (M+1). HPLC R_t = 9.65 min.

Example 7. 3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-propyl-benzamide.



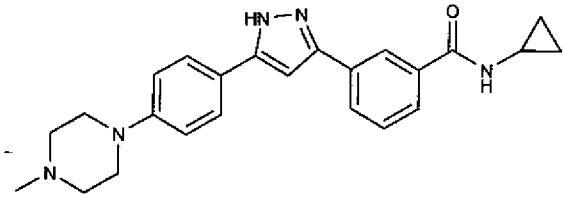
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 404.2447 (M+1). HPLC R_t = 9.79 min.

Example 8. N-Isobutyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



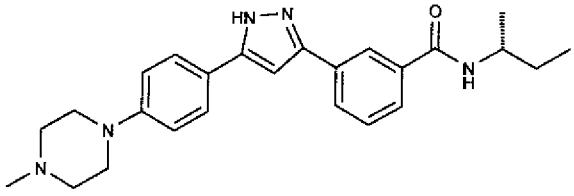
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 418.2602 (M+1). HPLC R_t = 10.40 min.

Example 9. N-Cyclopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



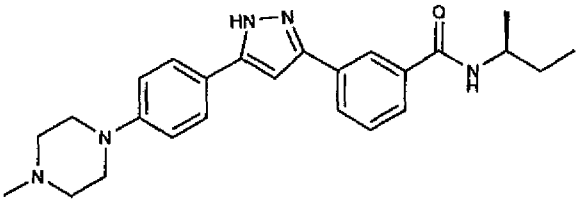
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 402.2289 (M+1). HPLC R_t = 9.29 min.

Example 10. N-((R)-sec-Butyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



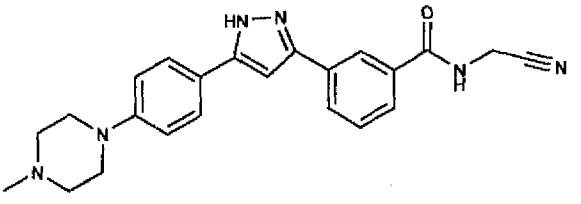
The title compound is prepared by methods similar to those utilized for the preparation of compound 6-B. MS(ESI) *m/z* = 418.2614 (M+1). HPLC R_t = 10.27 min.

Example 11. N-((S)-sec-Butyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



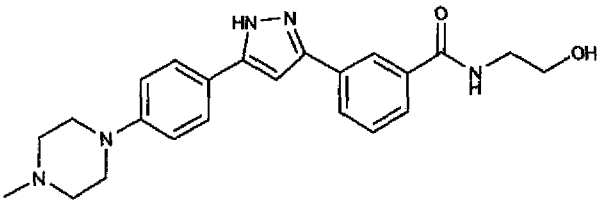
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 418.2607 (M+1). HPLC R_t = 10.25 min.

Example 12. N-Cyanomethyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



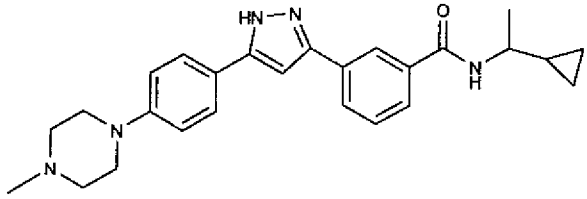
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 401.2098 (M+1). HPLC R_t = 10.48 min.

Example 13. N-(2-Hydroxy-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



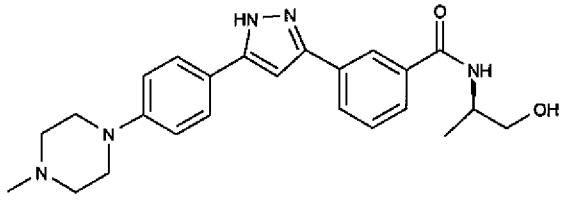
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 406.2232 (M+1). HPLC R_t = 8.10 min.

Example 14. N-(1-Cyclopropyl-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



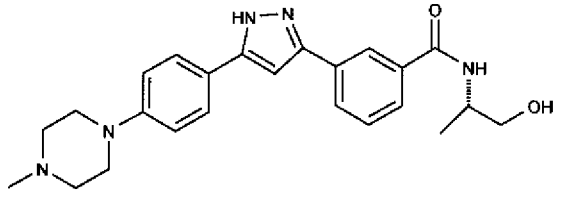
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 430.2604 (M+1). HPLC R_t = 10.52 min.

Example 15. N-((R)-2-Hydroxy-1-methyl-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



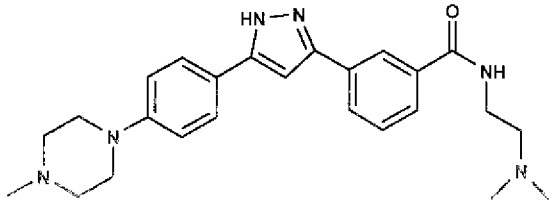
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 420.2408 (M+1). HPLC R_t = 8.44 min.

Example 16. N-((S)-2-Hydroxy-1-methyl-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



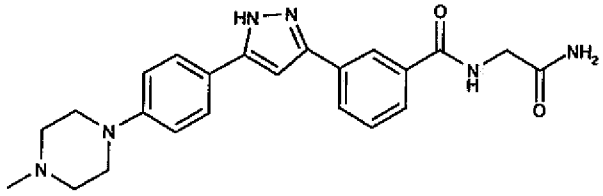
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 420.2401 (M+1). HPLC R_t = 8.43 min.

Example 17. N-(2-Dimethylamino-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



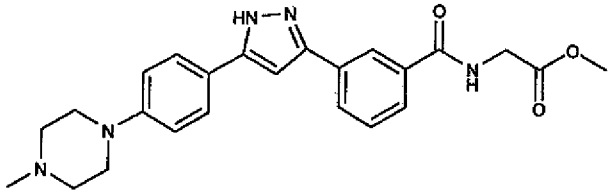
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 433.2729 (M+1). HPLC R_t = 7.79 min.

Example 18. N-Carbamoylmethyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



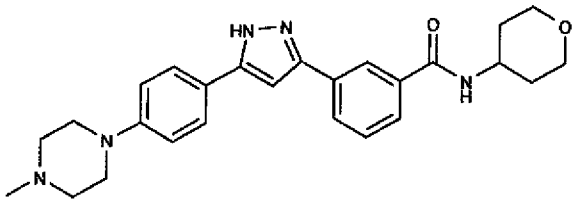
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 419.2176 (M+1). HPLC R_t = 7.90 min.

Example 19. (3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoylamino)-acetic acid methyl ester.



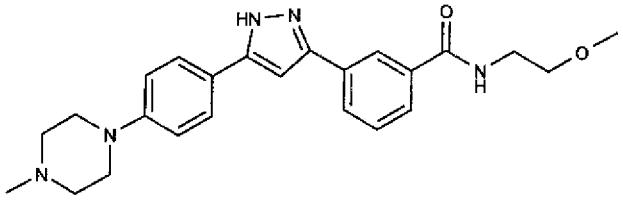
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 434.2190 (M+1). HPLC R_t = 8.99 min.

Example 20. 3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-(tetrahydro-pyran-4-yl)-benzamide.



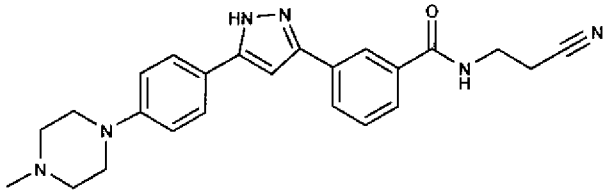
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 446.2551 (M+1). HPLC R_t = 9.17 min.

Example 21. N-(2-Methoxy-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



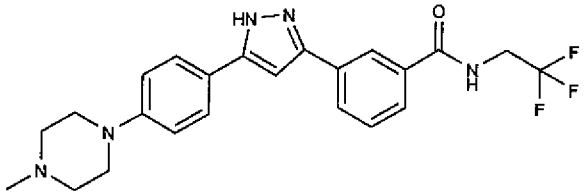
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 420.2397 (M+1). HPLC R_t = 8.97 min.

Example 22. N-(2-Cyano-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



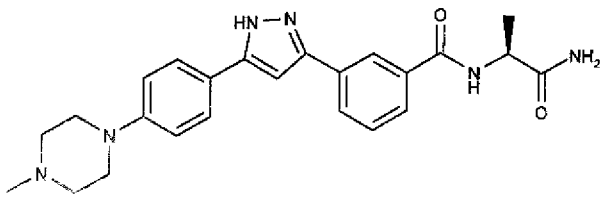
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 415.2247 (M+1). HPLC R_t = 8.91 min.

Example 23. 3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-(2,2,2-trifluoro-ethyl)-benzamide.



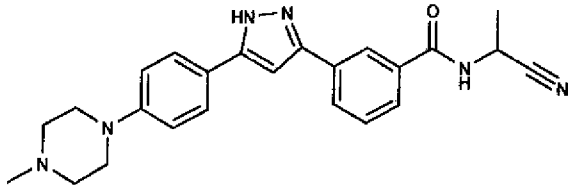
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 444.2010 (M+1). HPLC R_t = 10.22 min.

Example 24. N-((S)-1-Carbamoyl-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



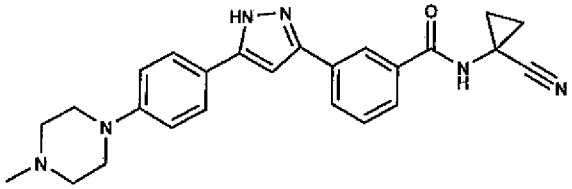
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 433.2340 (M+1). HPLC R_t = 8.21 min.

Example 25. N-(Cyano-methyl-methyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



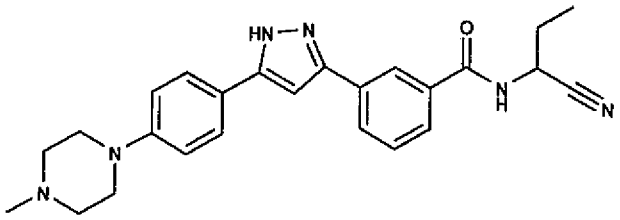
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 415.2236 (M+1). HPLC R_t = 9.20 min.

Example 26. N-(1-Cyano-cyclopropyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



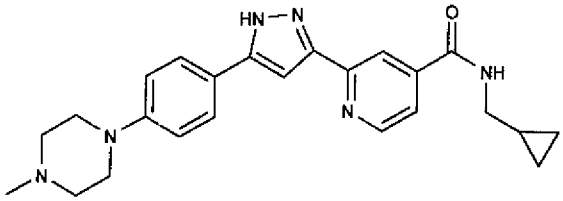
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 427.2253 (M+1). HPLC R_t = 9.20 min.

Example 27. N-(1-Cyano-propyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



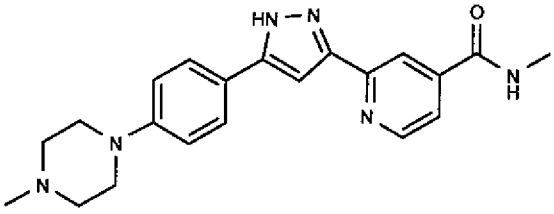
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 429.2395 (M+1). HPLC R_t = 9.92 min.

Example 28. N-Cyclopropylmethyl-2-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-isonicotinamide.



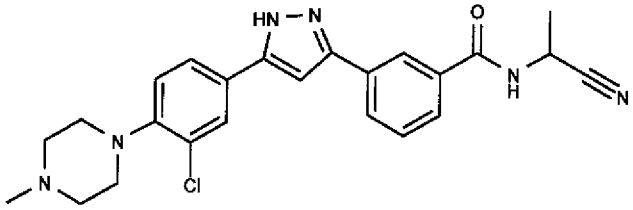
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 417.2412 (M+1). HPLC R_t = 8.77 min.

Example 29. N-Methyl-2-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-isonicotinamide.



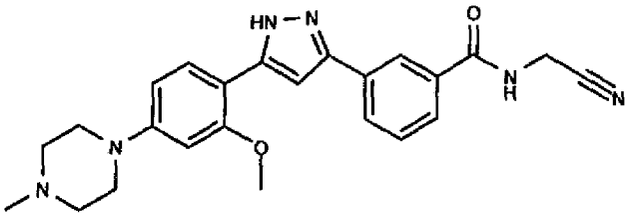
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 377.2084 (M+1). HPLC R_t = 7.40 min.

Example 30. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-(cyano-methyl-methyl)-benzamide.



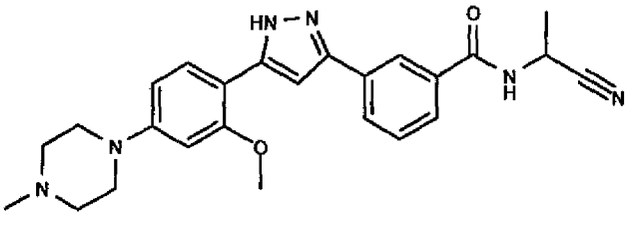
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 449.1862 (M+1). HPLC R_t = 10.22 min.

Example 31. N-Cyanomethyl-3-{5-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



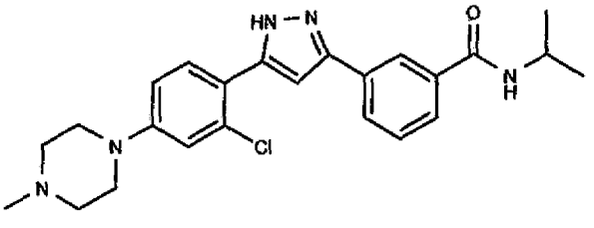
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 431.2214 (M+1). HPLC R_t = 9.14 min.

Example 32. N-(Cyano-methyl-methyl)-3-{5-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



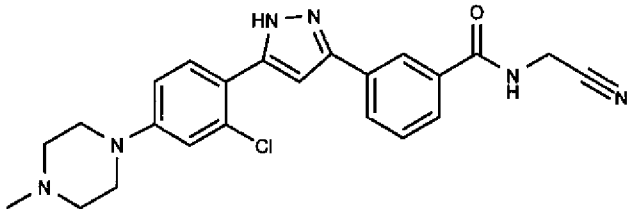
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 445.2348 (M+1). HPLC R_t = 9.62 min.

Example 33. 3-{5-[2-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



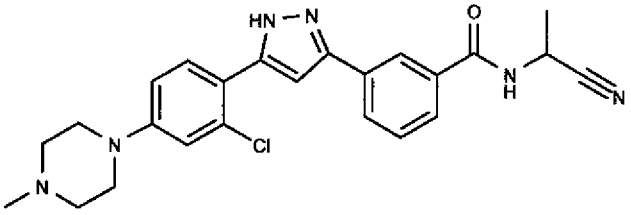
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 438.2058 (M+1). HPLC R_t = 10.27 min.

Example 34. 3-{5-[2-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-cyanomethyl-benzamide.



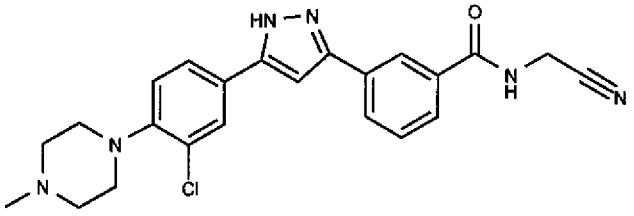
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 435.1695 (M+1). HPLC R_t = 10.28 min.

Example 35. 3-{5-[2-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-(cyano-methyl-methyl)-benzamide.



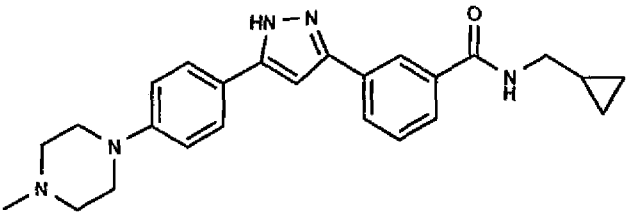
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 449.1853 (M+1). HPLC R_t = 10.02 min.

Example 36. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-cyanomethyl-benzamide.



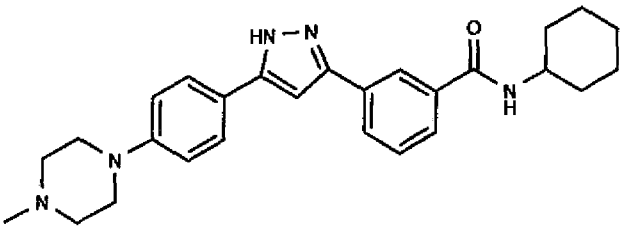
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 435.1684 (M+1). HPLC R_t = 9.76 min.

Example 37. N-Cyclopropyimethyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



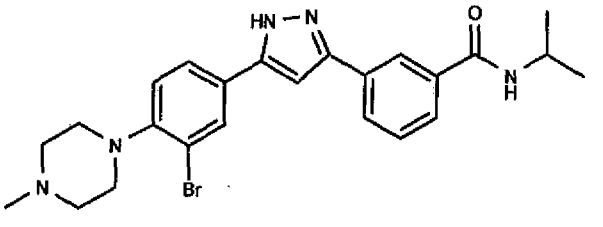
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 416.2441. HPLC R_t = 10.03 min.

Example 38. N-Cyclohexyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



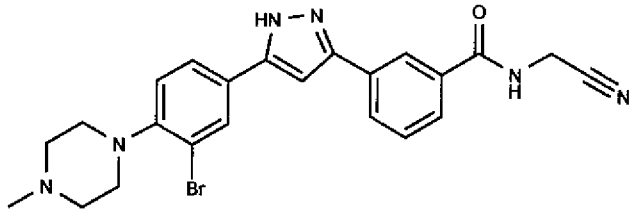
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 444.2756. HPLC R_t = 11.14 min.

Example 39. 3-{5-[3-Bromo-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



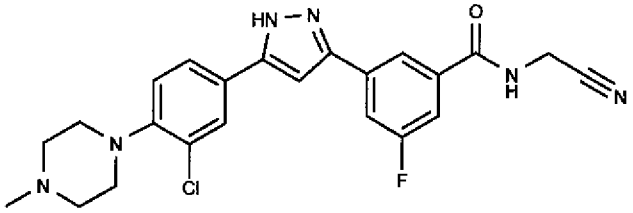
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 482.1566 (M+1). HPLC R_t = 10.59 min.

Example 40. 3-{5-[3-Bromo-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-cyanomethyl-benzamide.



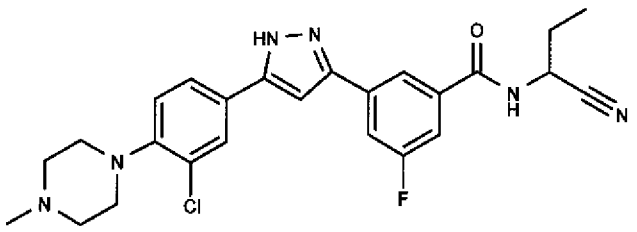
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 479.1201 (M+1). HPLC R_t = 9.92 min.

Example 41. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-cyanomethyl-5-fluoro-benzamide.



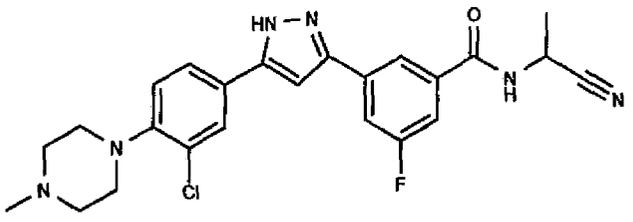
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 453.16 (M+1). HPLC R_t = 10.63 min.

Example 42. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-(1-cyano-propyl)-5-fluoro-benzamide.



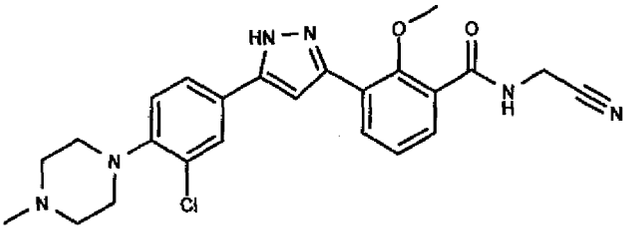
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 481.1895 (M+1). HPLC R_t = 11.79 min.

Example 43. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-(cyano-methyl-methyl)-5-fluoro-benzamide.



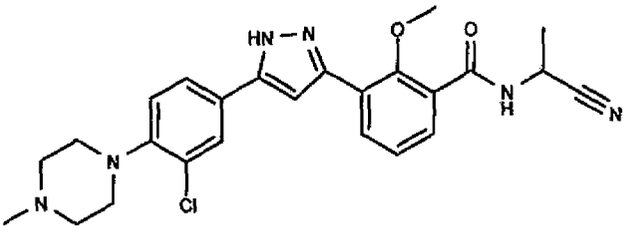
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 467.1758 (M+1). HPLC R_t = 11.31 min.

Example 44. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-cyanomethyl-2-methoxy-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 465.1793 (M+1). HPLC R_t = 10.3 min.

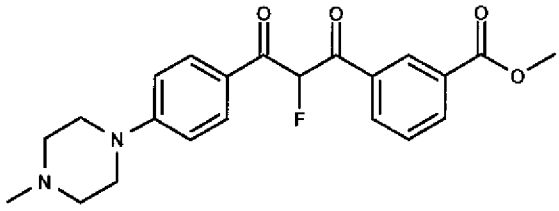
Example 45. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-(cyano-methyl-methyl)-2-methoxy-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 479.1965 (M+1). HPLC R_t = 10.59 min.

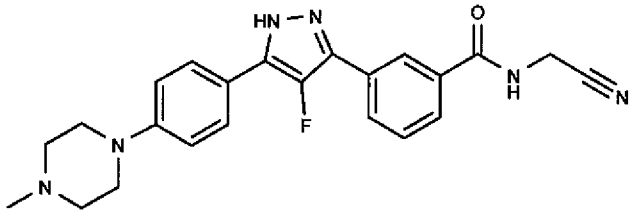
Example 46. N-Cyanomethyl-3-{4-fluoro-5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.

46-A. 3-{2-Fluoro-3-[4-(4-methyl-piperazin-1-yl)-phenyl]-3-oxo-propionyl}-benzoic acid methyl ester.



A chloroform (3 ml) solution of compound **1-B** (380 mg, 1.0 mmol) and 4-iodotoluene difloride (333 mg, 1.30 mmol) is stirred at r.t. overnight. The dark-brown mixture is then poured into water (50 ml) and extracted with EtOAc (50 ml x 2) and DCM (50 ml x 2). The combined organic layers are dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue is purified by flash column chromatography with 0 - 5% MeOH/DCM to afford product as a yellow oil. MS(ESI) *m/z* = 399.2 (M+1).

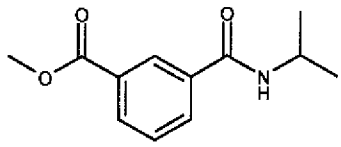
46-B. N-Cyanomethyl-3-{4-fluoro-5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 419.1987 (M+1). HPLC R_t = 9.35 min.

Example 47. 3-{5-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.

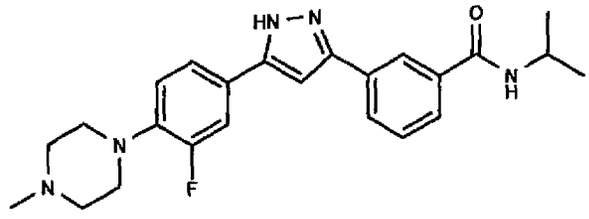
47-A. N-Isopropyl-isophthalamic acid methyl ester.



To a solution of mono-methyl isophthalate (91.53 g, 8.5 mmol) in dimethylformamide is added DIPEA (1.77 ml, 10.2 mmol), isopropyl amine (1.41 ml, 10.2 mmol) and HATU (6.46 g, 17 mmol). The reaction mixture is stirred at ambient temperature for 4 hours, until conversion is judged to be complete. Water (100 mL) is added, and the aqueous phase is

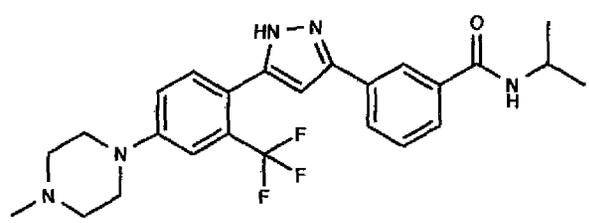
extracted with ethyl acetate (400 ml). The organic layer is washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 to 33% EtOAc in hexanes to afford the product as a white solid. MS(ESI) *m/z* = 222.3 (M+1).

47-B. 3-{5-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



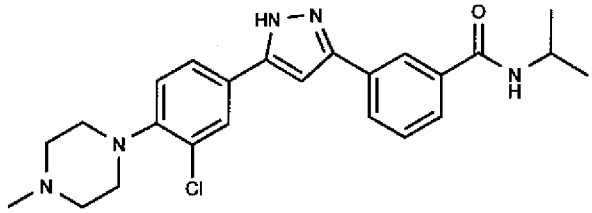
To a solution of 1-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-ethanone (236 mg, 1.0 mmol) in tetrahydrofuran (3 ml) cooled in a bath of dry ice in acetone, a 1 M solution of LiHMDS in THF (2 ml) is added dropwise. The reaction mixture is stirred for 30 min and then compound **47-A** (221 mg, 1.0 mmol) is added. The reaction mixture is slowly warmed to ambient temperature and stirred for an additional 1 hour. Hydrazine (0.06 ml, 2.0 mmol) and a 12% (w/w) solution of p-TsOH in acetic acid (0.3 mL) are added to the reaction mixture and the mixture is heated at reflux for 12 hours. The reaction is quenched with water (30 mL). The aqueous layer is extracted with EtOAc (100 ml x 2). The combined organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is purified by reverse phase HPLC to afford the product as a white solid. MS(ESI) *m/z* = 422.2343 (M+1). HPLC R_t = 9.98 min.

Example 48. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-2-trifluoromethyl-phenyl]-1H-pyrazol-3-yl}-benzamide.



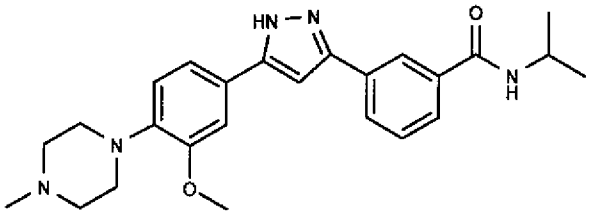
The title compound is prepared by methods similar to those utilized for the preparation of compound **47-B**. MS(ESI) *m/z* = 472.2325 (M+1). HPLC R_t = 10.51 min.

Example 49. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



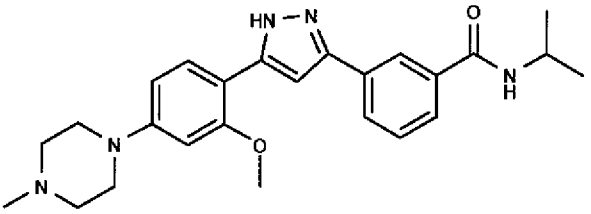
The title compound is prepared by methods similar to those utilized for the preparation of compound **47-B**. MS(ESI) *m/z* = 438.3000 (M+1). HPLC R_t = 10.43 min.

Example 50. N-Isopropyl-3-{5-[3-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



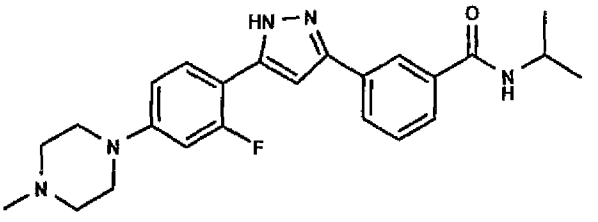
The title compound is prepared by methods similar to those utilized for the preparation of compound **47-B**. MS(ESI) *m/z* = 434.2560 (M+1). HPLC R_t = 10.35 min.

Example 51. N-Isopropyl-3-{5-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



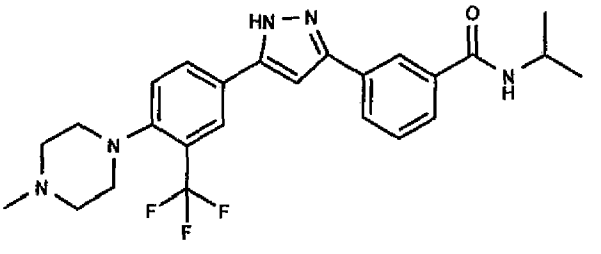
The title compound is prepared by methods similar to those utilized for the preparation of compound **47-B**. MS(ESI) *m/z* = 434.2550 (M+1). HPLC R_t = 9.86 min.

Example 52. 3-{5-[2-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



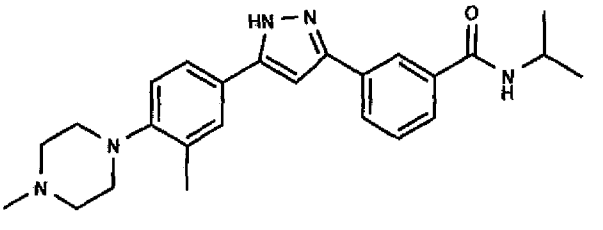
The title compound is prepared by methods similar to those utilized for the preparation of compound **47-B**. MS(ESI) *m/z* = 422.2356 (M+1). HPLC R_t = 9.93 min.

Example 53. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-3-trifluoromethyl-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **47-B**. MS(ESI) *m/z* = 472.2320 (M+1). HPLC R_t = 11.15 min.

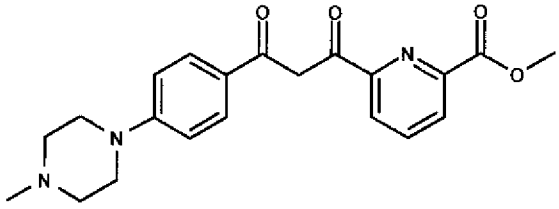
Example 54. N-Isopropyl-3-{5-[3-methyl-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **47-B**. MS(ESI) *m/z* = 418.2603 (M+1). HPLC R_t = 10.26 min.

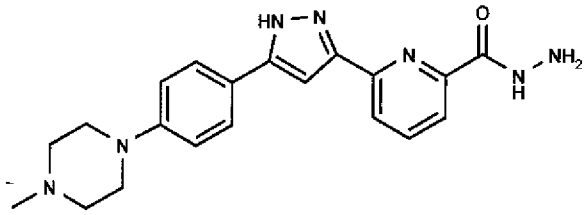
Example 55. 6-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-pyridine-2-carboxylic acid hydrazide.

B55-A. 6-{3-[4-(4-Methyl-piperazin-1-yl)-phenyl]-3-oxo-propionyl}-pyridine-2-carboxylic acid methyl ester.



To a solution of compound **1-A** (1.09 g, 5.0 mmol) in tetrahydrofuran (15 mL) cooled in an ice water bath, is added a 25% (w/w) solution of sodium methoxide in methanol (1.5 mL) and 2, 6- dimethyl pyridine dicarboxylate (1.07 g, 5.5 mmol). The reaction mixture is warmed to ambient temperature and stirred for 12 hours before saturated aqueous ammonium chloride solution (10 mL) is added to quench the reaction. Water (100 mL) is added to dilute the mixture and the aqueous layer is extracted with ethyl acetate (400 ml). The combined organic layers are washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford product as a a yellow solid. MS(ESI) *m/z* = 418.2603 (M+1).

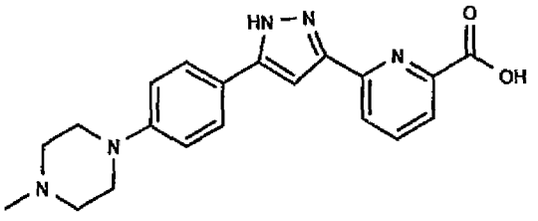
55-B. 6-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-pyridine-2-carboxylic acid hydrazide.



Compound **55-A** (1.58 g, 4.15 mmol), hydrazine (265 mg, 8.30 mmol) and DIPEA (0.72 ml, 4.15 mmol) are dissolved in anhydrous ethanol (35 ml). The reaction mixture heated at reflux for 12 h. The reaction is cooled to ambient temperature and then concentrated under reduced pressure. The resulting precipitate is collected by filtration and washed with 5 ml cold ethanol to provide product as a white solid. MS(ESI) *m/z* = 378.1941 (M+1). HPLC R_t = 7.54 min.

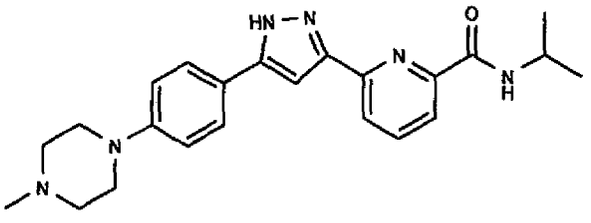
Example 56. 6-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-pyridine-2-carboxylic acid isopropylamide

56-A. 6-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-pyridine-2-carboxylic acid.



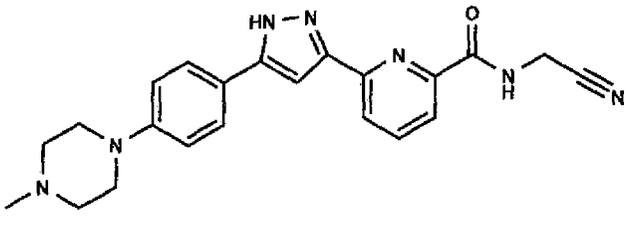
To a solution of compound **55-B** (1.11 g, 2.95 mmol) in tetrahydrofuran (20 ml) and water (10 ml) is added lithium hydroxide (406 mg, 16.9 mmol). The reaction mixture is stirred at ambient temperature for 72 h and is then neutralized with 1 N aqueous hydrochloric acid (17 mL). The organic solvent is removed under reduced pressure. The resulting precipitate is collected by filtration and washed with diethyl ether (15 mL) to afford product as a yellow solid contaminated with residual lithium chloride. MS(ESI) *m/z* = 376.2 (M-1).

56-B. 6-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-pyridine-2-carboxylic acid isopropylamide.



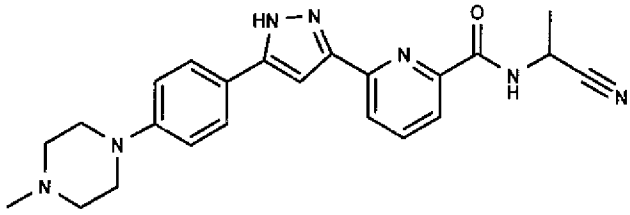
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 378.1941 (M+1). HPLC R_t = 9.85 min.

Example 57. 6-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-pyridine-2-carboxylic acid cyanomethyl-amide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **56-B**. MS(ESI) *m/z* = 402.2039 (M+1). HPLC R_t = 9.34 min.

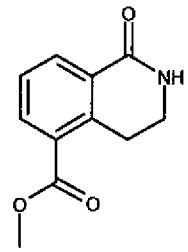
Example 58. 6-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-pyridine-2-carboxylic acid (cyano-methyl-methyl)-amide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **56-B**. MS(ESI) *m/z* = 416.2201 (M+1). HPLC R_t = 9.69 min.

Example 59. 5-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-3,4-dihydro-2H-isoquinolin-1-one.

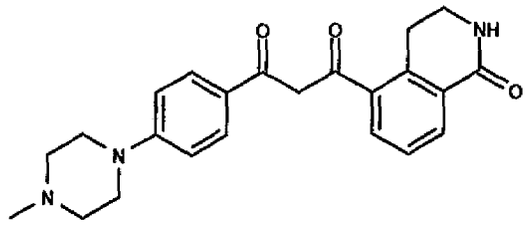
59-A. 1-Oxo-1,2,3,4-tetrahydro-isoquinoline-5-carboxylic acid methyl ester.



Indanone (200 mg, 1.05 mmol) and trichloroacetic acid (0.92 mL, 9.1 mmol) are combined in a round bottom flask. The reaction is heated in a 65-70°C oil bath and stirred until the mixture becomes homogenous. Sodium azide (137 mg, 2.1 mml) is added to the reaction by portions over 4 hrs. The reaction mixture is heated for additional 16 hours in a 60°C oil bath and then the reaction mixture is poured into ice water (20 mL) and stirred for 1 hr. The aqueous phase is extracted with dichloromethane (3 x 30 mL). The combined organic layers are washed with water and saturated aqueous sodium carbonate. The organic extracts are dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 50% ethyl acetate in heptane to afford product as a white solid.

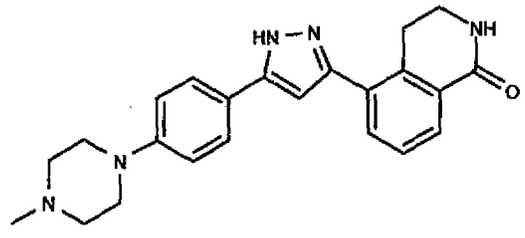
MS(ESI) *m/z* = 206.3 (M+1).

59-B. 1-[4-(4-Methyl-piperazin-1-yl)-phenyl]-3-(1-oxo-1,2,3,4-tetrahydro-isoquinolin-5-yl)-propane-1,3-dione.



To a solution of compound **59-A** (71.2 mg, 0.35 mmol) in anhydrous THF (2 mL) cooled in a bath of dry ice in acetone, is added a 1M solution of LHMDS in THF (0.7 mL, 0.7 mmol). A solution of compound **1-A** (91 mg, 0.42 mmol) in tetrahydrofuran (1 mL) is added dropwise. The mixture is warmed to ambient temperature, then heated in an 80°C oil bath and stirred for 2 hours, until conversion is judged to be complete. The mixture is cooled to ambient temperature and saturated aqueous ammonium chloride (5 mL) is added to quench the reaction. The aqueous phase is extracted with EtOAc (30 mL x 2). The combined organic layers are dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is purified by flash column chromatography with 0 – 10% methanol in dichloromethane to afford product as a yellow solid. MS(ESI) *m/z* = 392.2 (M+1).

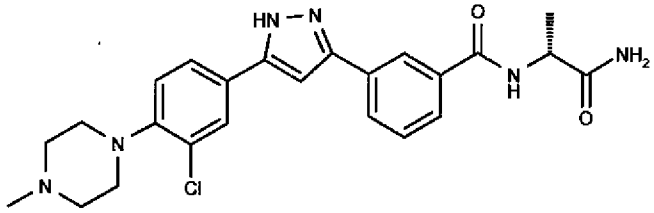
59-C. 5-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-3,4-dihydro-2H-isoquinolin-1-one.



To a solution of compound **59-B** (16 mg, 0.041 mmol) in anhydrous ethanol (1 mL) are added hydrazine (3.2 uL, 0.102 mmol) and diisopropylethylamine (11 uL, 0.062 mmol). The reaction vessel is sealed and the mixture is stirred and heated in a 120 °C oil bath for 18 h. The mixture is cooled to ambient temperature and concentrated under reduced pressure The residue is purified by preparative TLC with 25% methanol in dichloromethane to afford product as a white solid. MS(ESI) *m/z* = 388.2140 (M+1). HPLC R_t = 8.14 min.

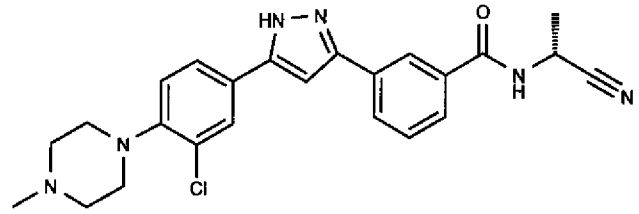
Example 60. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-((R)-cyano-methyl-methyl)-benzamide.

60-A. N-((R)-1-Carbamoyl-ethyl)-3-{5-[3-chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 467.5 (M+1).

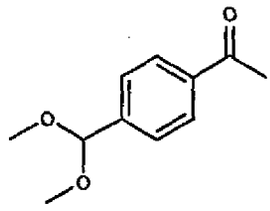
60-B. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-((R)-cyano-methyl-methyl)-benzamide.



A solution of compound **60-A** (1.30 g, 2.79 mmol) in anhydrous tetrahydrofuran (30 ml) is cooled in an ice water bath. Triethylamine (0.78 ml, 5.58 mmol) is added dropwise to the reaction, followed by dropwise addition of trifluoroacetic acid anhydride (0.39 ml, 2.79 mmol). After the mixture is stirred for 1 hour, additional trifluoroacetic anhydride (0.39 mL, 2.79 mmol) is added dropwise. The reaction mixture is warmed slowly to ambient temperature and stirred overnight. When conversion is complete, saturated aqueous sodium carbonate solution (10 mL) is added to quench the reaction. The mixture is partitioned between ethyl acetate (500 mL) and water (200 mL). The organic layer is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by RP-HPLC to afford product as a white solid. MS(ESI) *m/z* = 449.1840 (M+1). HPLC R_t = 10.17 min.

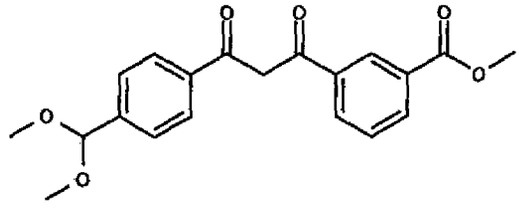
Example 61. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-benzamide.

61-A. 1-(4-Dimethoxymethyl-phenyl)-ethanone.



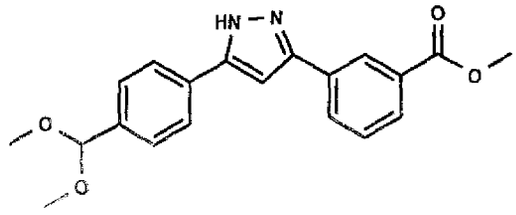
To a solution of 4-formylacetophenone (5.0 g, 34 mmol) in anhydrous methanol (50 mL), is added ruthenium chloride (350 mg, 1.7 mmol). The mixture is heated at reflux for 5 hours then cooled to ambient temperature. The reaction is concentrated under reduced pressure. The residue is adsorbed onto silica gel and purified by flash column chromatography with 10-50% ethyl acetate in heptane to afford product as a colorless oil.

61-B. 3-[3-(4-Dimethoxymethyl-phenyl)-3-oxo-propionyl]-benzoic acid methyl ester.



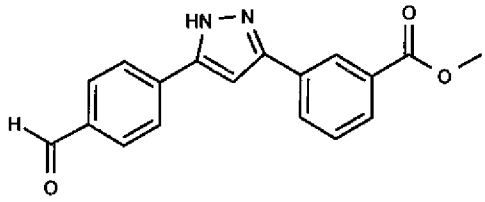
To a mixture of dimethylisophthalate (603 mg, 3.11 mmol) and sodium hydride (75 mg, 3.11 mmol, 95%) in anhydrous THF (4.5 mL) cooled in an ice water bath, is slowly added a solution of compound **61-A** (500 mg, 2.59 mmol) in tetrahydrofuran (2 mL). The mixture is heated in a 50 °C oil bath and stirred for 5 hours. The mixture is cooled to ambient temperature and saturated aqueous ammonium chloride solution (5 mL) is added to quench the reaction. The aqueous phase is extracted with dichloromethane (2 x 50 mL) and the combined organic layers are dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is purified by flash column chromatography with 0 – 5% methanol in dichloromethane to afford product as a pale yellow solid. MS(ESI) *m/z* = 357.21 (M+1).

61-C. 3-[5-(4-Dimethoxymethyl-phenyl)-1H-pyrazol-3-yl]-benzoic acid methyl ester.



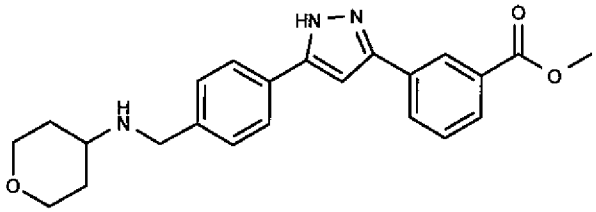
The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) *m/z* = 416.2201 (M+1).

61-D. 3-[5-(4-Formyl-phenyl)-1H-pyrazol-3-yl]-benzoic acid methyl ester.



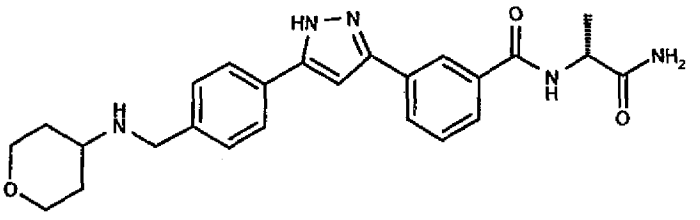
To a mixture of compound **61-C** (1.77 g, 5.03 mmol) in dichloromethane (30 mL) and water (15 mL) cooled in an ice water bath, is added trifluoroacetic acid (1.12 mL, 15.1 mmol) dropwise. The mixture is warmed to ambient temperature and stirred for 2 hours. Saturated aqueous sodium bicarbonate solution (15 mL) is added to quench the reaction. The aqueous phase is extracted with ethyl acetate. The combined organic layers are dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is purified by flash column chromatography with 6% methanol in dichloromethane to afford product as a pale yellow solid. MS(ESI) *m/z* = 307.24 (M+1).

61-E. 3-(5-{4-[(Tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-benzoic acid methyl ester.



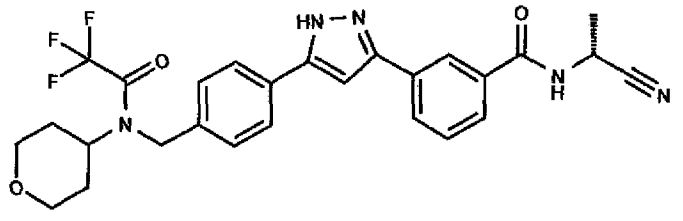
A mixture of compound **61-D** (338 mg, 1.1 mmol) and 4-aminomethyltetrahydropyran (210 uL, 1.66 mmol) in dichloromethane (11 mL) is cooled in an ice water bath. Sodium triacetoxyborohydride (696 mg, 3.3 mmol) is added and the resulting suspension is warmed to ambient temperature and stirred for 3 days. Saturated aqueous sodium bicarbonate solution (10 mL) is added and the aqueous phase is extracted with ethyl acetate (3 x 20 mL). The combined organic layers are dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 – 10% methanol in dichloromethane to give the product as a white solid. MS(ESI) *m/z* = 392.30 (M+1).

61-F. N-((R)-1-Carbamoyl-ethyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-benzamide.



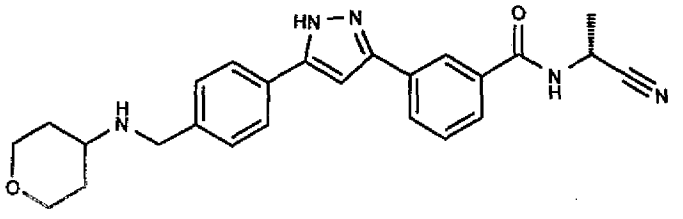
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 488.33 (M+1).

61-G. N-((R)-Cyano-methyl-methyl)-3-[5-(4-{[(tetrahydro-pyran-4-yl)-(2,2,2-trifluoro-acetyl)-amino]-methyl}-phenyl)-1H-pyrazol-3-yl]-benzamide.



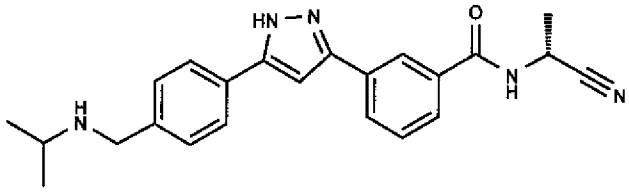
A solution of compound **61-F** (208 mg, 0.47 mmol) in anhydrous THF (4 mL) is cooled in an ice water bath. Triethyl amine (198 uL, 1.41 mmol) is added dropwise, followed by trifluoroacetic acid anhydride (129 uL, 0.93 mmol). The reaction is monitored and when conveniaon is judged to be complete, saturated aqueous sodium bicarbonate solution (10 mL) is added to the mixture to quench the reaction. The aqueous phase is extracted with ethyl acetate (20 mL x 3). The combined organic layers are dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 – 5% methanol in dichloromethane to afford product as a colorless oil. MS(ESI) *m/z* = 526.32 (M+1).

61-H N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-benzamide.



A solution of compound **61-G** (238 mg, 0.45 mmol) in anhydrous methanol (5 mL) is cooled in an ice water bath. Sodium borohydride (34 mg, 0.90 mmol) is added and the mixture is stirred for two hours until conversion is judged to be complete. Saturated sodium bicarbonate solution is added to quench the reaction. The aqueous phase is extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered, concentrated under reduced pressure. The residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 430.2255 (M+1). HPLC R_t = 9.05 min.

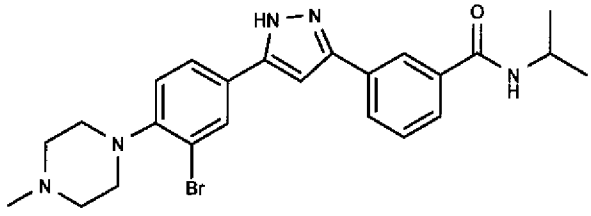
Example 62. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(isopropylamino-methyl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **61-H**. MS(ESI) *m/z* = 388.2148 (M+1). HPLC R_t = 9.35 min, ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm: 13.41 (1H), 9.25 (1H), 8.34 (1H), 8.04 (1H), 7.82 (1H), 7.78 (2H), 7.58 (1H), 7.43 (2H), 7.22 (1H), 5.03 (1H), 3.74 (2H), 2.75 (1H), 1.58 (3H), 1.03 (6H) ppm.

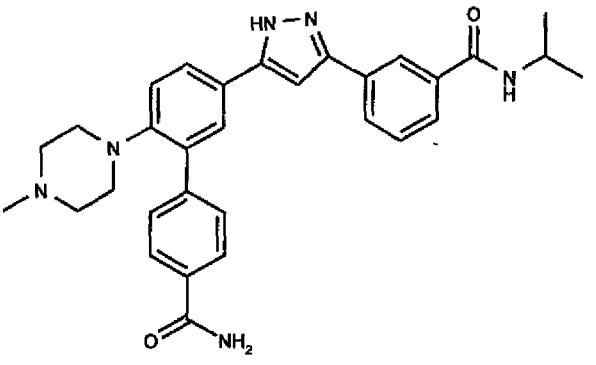
Example 63. 5'-[5-(3-Isopropylcarbamoyl-phenyl)-2H-pyrazol-3-yl]-2'-(4-methyl-piperazin-1-yl)-biphenyl-4-carboxylic acid amide.

63-A. 3-{5-[3-Bromo-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



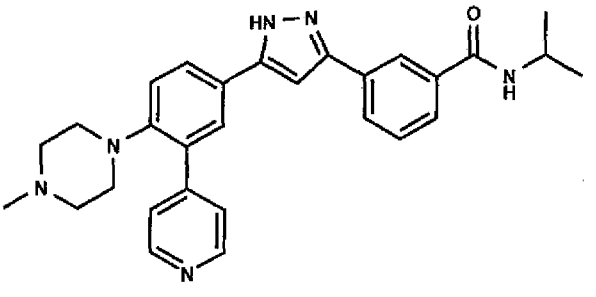
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 482.1566 (M+1).

63-B. 5'-[5-(3-Isopropylcarbamoyl-phenyl)-2H-pyrazol-3-yl]-2'-(4-methyl-piperazin-1-yl)-biphenyl-4-carboxylic acid amide



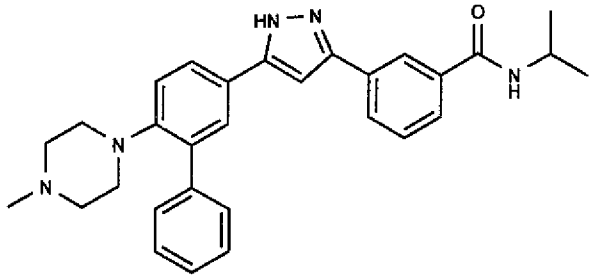
To a solution of compound **63-A** (87 mg, 0.18 mmol) and 4-carbamoylphenylboronic acid (45 mg, 0.27 mmol) in toluene (1.8 mL) and ethanol (0.2 mL) are added 2M aqueous potassium carbonate solution (0.18 ml) and $Pd(dppf)_2Cl_2$ (15 mg, 0.018 mmol). The reaction mixture is stirred at ambient temperature for 10 min and then heated in a 110 °C oil bath for 24 hours. After cooling to ambient temperature, the reaction mixture is partitioned between EtOAc (100 ml) and water (50 ml). The organic layer is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by reverse phase HPLC to afford the desired product as a white solid. MS(ESI) *m/z* = 523.2825 (M+1). HPLC R_t = 10.08 min.

Example 64. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-3-pyridin-4-yl-phenyl]-1H-pyrazol-3-yl}-benzamide.



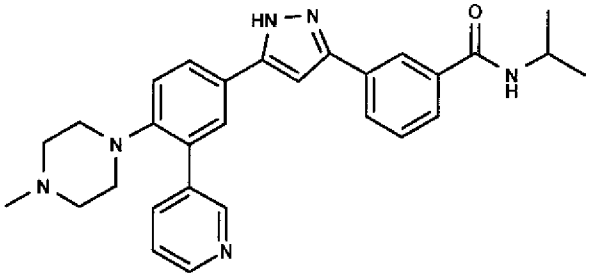
The title compound is prepared by methods similar to those utilized for the preparation of compound **63-B**. MS(ESI) *m/z* = 481.2701 (M+1). HPLC R_t = 11.58 min.

Example 65. N-Isopropyl-3-{5-[6-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **63-B**. MS(ESI) *m/z* = 480.2762 (M+1). HPLC R_t = 8.73 min.

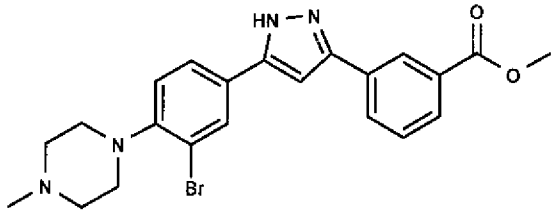
Example 66. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-3-pyridin-3-yl-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **63-B**. MS(ESI) *m/z* = 481.2729 (M+1). HPLC R_t = 8.76 min.

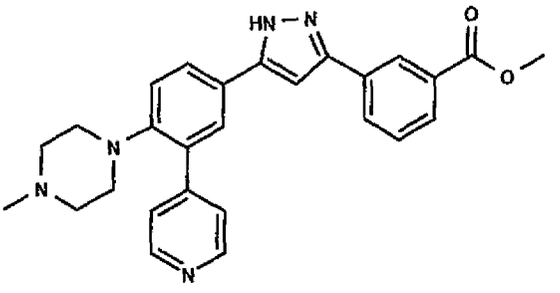
Example 67. N-((R)-1-Carbamoyl-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-3-pyridin-4-yl-phenyl]-1H-pyrazol-3-yl}-benzamide.

67-A. 3-{5-[3-Bromo-4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.



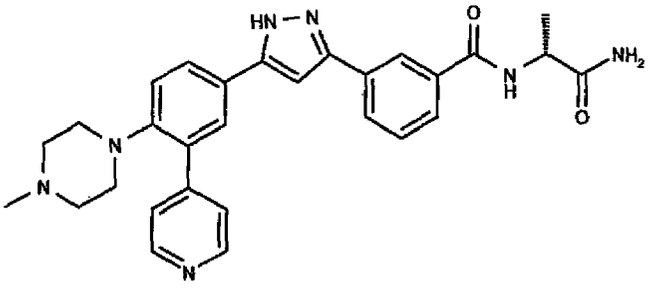
The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) *m/z* = 455.3, 457.3 (M+1).

67-B. 3-{5-[4-(4-Methyl-piperazin-1-yl)-3-pyridin-4-yl-phenyl]-1H-pyrazol-3-yl}-benzoic acid methyl ester.



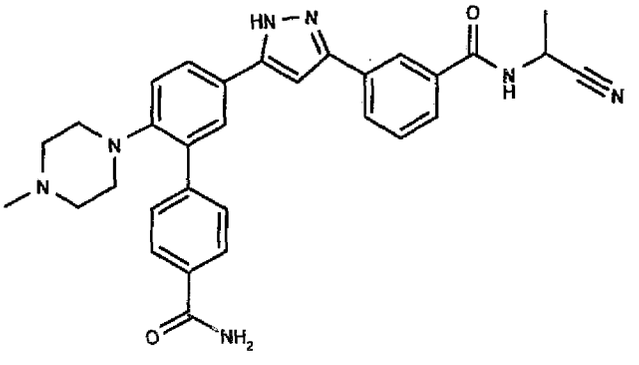
The title compound is prepared by methods similar to those utilized for the preparation of compound **63-B**. MS(ESI) *m/z* = 454.4 (M+1).

67-C. N-((R)-1-Carbamoyl-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-3-pyridin-4-yl-phenyl]-1H-pyrazol-3-yl}-benzamide.



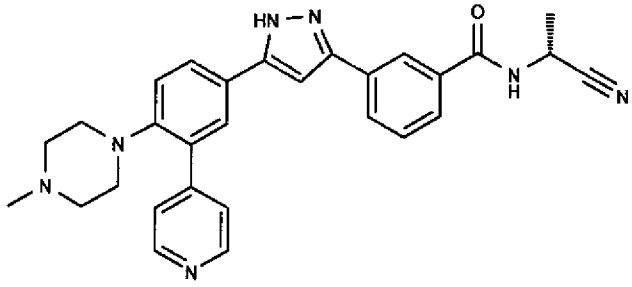
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-B**. MS(ESI) *m/z* = 510.2628 (M+1). HPLC R_t = 7.72 min.

Example 68. 5'-(5-{3-[(Cyano-methyl-methyl)-carbamoyl]-phenyl}-2H-pyrazol-3-yl)-2'-(4-methyl-piperazin-1-yl)-biphenyl-4-carboxylic acid amide.



The title compound is prepared by methods similar to those utilized for the preparation of compound 67-C. MS(ESI) *m/z* = 534.2609 (M+1). HPLC R_t = 10.57 min.

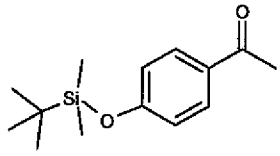
Example 69. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-3-pyridin-4-yl-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **60-B**. MS(ESI) *m/z* = 492.2527 (M+1). HPLC R_t = 8.70 min, ^{1}H NMR (400 MHz, 1:4 d_4-Methanol : d_2-dichloromethane) δ ppm: 13.28 (1H), 9.16 (1H), 2.27 (2H), 8.28 (1H), 7.97 (1H), 7.74 (2H), 7.69 (1H), 7.65 (2H), 7.49 (1H), 7.18 (1H), 7.14 (1H), 4.96 (1H), 2.74 (4H), 2.21 (4H), 2.09 (3H), 1.50 (3H) ppm.

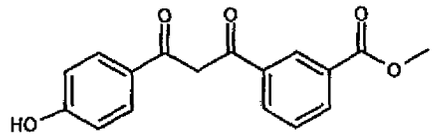
Example 70. 3-[5-(4-Hydroxy-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.

70-A. 1-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-ethanone.



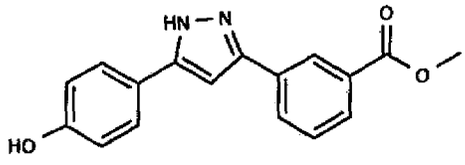
To a solution of 4-hydroxyphenyl methyl ketone (10 g, 73.4 mmol) in dichloromethane (100 mL) is added imidazole (6.5 g, 95.4 mmol) followed by TBDMSCl (12.2 g, 80.7 mmol). The mixture is stirred at ambient temperature overnight. The reaction is washed with water and brine. The organic phase is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by flash column chromatography with 10 to 15% ethyl acetate in heptane to afford product as a white solid.

70-B. 3-[3-(4-Hydroxy-phenyl)-3-oxo-propionyl]-benzoic acid methyl ester.



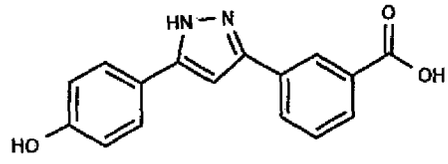
A solution of compound **70-A** (8 g, 32 mmol) and dimethylisophthalate (6.2 g, 32 mmol) and in anhydrous tetrahydrofuran (69 mL) is cooled in an ice water bath. Sodium hydride (1.47 g, 38.4 mmol, 60% w/w) is added portionwise. The mixture is warmed to ambient temperature and stirred overnight. Additional sodium hydride (0.8 g, 20.9 mmol, 60% w/w) is added and the mixture is heated in a 70°C oil bath until conversion is judged to be complete. The mixture is cooled to ambient temperature, and saturated ammonium chloride solution (20 mL) is added. The aqueous phase is extracted with ethyl acetate (150 mL x 2). The combined organic layers are washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 10 to 20% ethyl acetate in heptane to afford product as a yellow solid. MS(ESI) m/z = 299.3 (M+1)

70-C. 3-[5-(4-Hydroxy-phenyl)-1H-pyrazol-3-yl]-benzoic acid methyl ester.



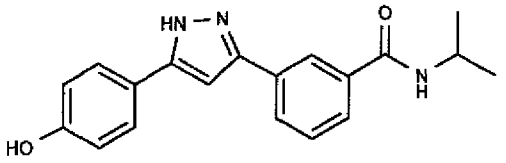
The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) m/z = 295.3 (M+1).

70-D. 3-[5-(4-Hydroxy-phenyl)-1H-pyrazol-3-yl]-benzoic acid.



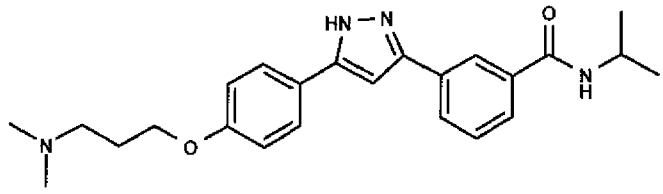
The title compound is prepared by methods similar to those utilized for the preparation of compound **6-A**. MS(ESI) m/z = 281.3 (M+1).

70-E. 3-[5-(4-Hydroxy-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.



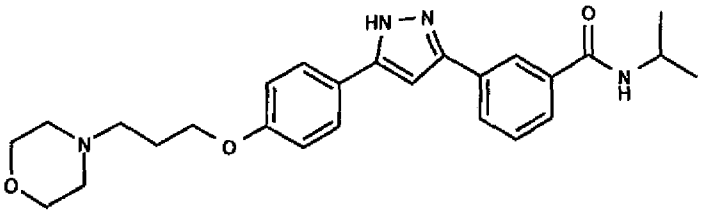
To a solution of **70-D** (1.1 g, 3.9 mmol) in dimethylformamide (3 mL) and dichloromethane (25 mL) are added HOAt (0.53 g, 3.9 mmol), isopropyl amine (0.33 mL, 3.9 mmol), and EDCI (0.82 g, 4.3 mmol). Additional DMF is added to until the reaction mixture becomes homogenous. The reaction is stirred at room temperature until conversion is judged to be complete. The mixture is diluted with ethyl acetate and washed with brine three times. The organic phase is further washed with saturated sodium bicarbonate, water, and brine. The organic phase is dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue is triturated with ethyl acetate and filtered to provide product as a white powder. MS(ESI) m/z = 322.1555 (M+1). HPLC R_t = 11.26 min.

Example 71. 3-{5-[4-(3-Dimethylamino-propoxy)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



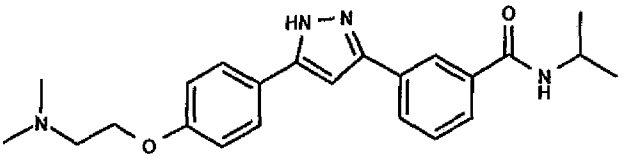
A solution of compound **70-E** (40 mg, 0.12 mmol), N,N-Dimethylpropanolamine (14 uL, 0.12 mmol), and triphenylphosphine (33 mg, 0.12 mmol) in THF (1.5 ml) is cooled in an ice water bath. DIAD (23 uL, 0.12 mmol) is added and the reaction mixture is warmed to ambient temperature and stirred overnight. The reaction mixture is diluted with EtOAc and washed with water and brine. The organic layer is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resudue is purified by reverse phase HPLC to afford product as a white solid. MS(ESI) *m/z* = 407.2432 (M+1). HPLC R_t = 10.52 min.

Example 72. N-Isopropyl-3-{5-[4-(3-morpholin-4-yl-propoxy)-phenyl]-1H-pyrazol-3-yl} benzamide.



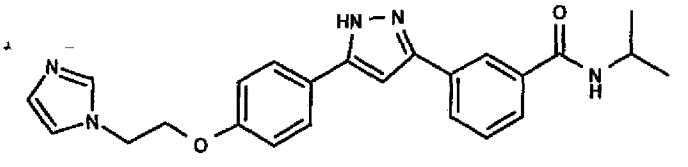
The title compound is prepared by methods similar to those utilized for the preparation of the compound of Example 71. MS(ESI) *m/z* = 435.2033 (M+1). HPLC R_t = 10.53 min.

Example 73. 3-{5-[4-(2-Dimethylamino-ethoxy)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



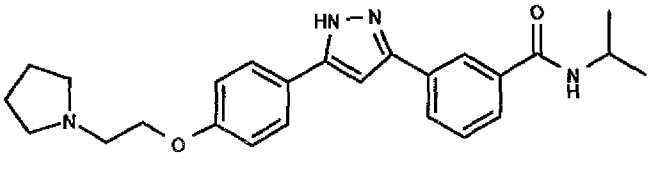
The title compound is prepared by methods similar to those utilized for the preparation of the compound of Example 71. MS(ESI) *m/z* = 393.2285(M+1). HPLC R_t = 10.21 min.

Example 74. 3-{5-[4-(2-Imidazol-1-yl-ethoxy)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



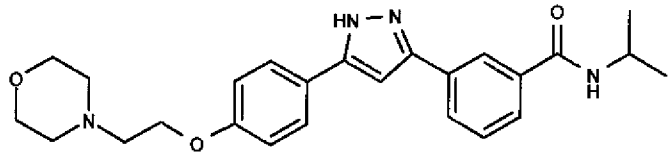
The title compound is prepared by methods similar to those utilized for the preparation of the compound of Example 71. MS(ESI) *m/z* = 416.2078 (M+1). HPLC R_t = 10.44 min.

Example 75. N-Isopropyl-3-{5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of the compound of Example 71. MS(ESI) *m/z* = 419.2463 (M+1). HPLC R_t = 10.55 min.

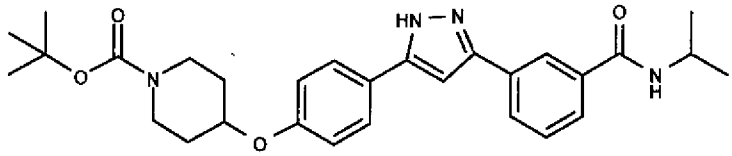
Example 76. N-Isopropyl-3-{5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of the compound of Example 71. MS(ESI) *m/z* = 435.2387 (M+1). HPLC R_t = 10.28 min.

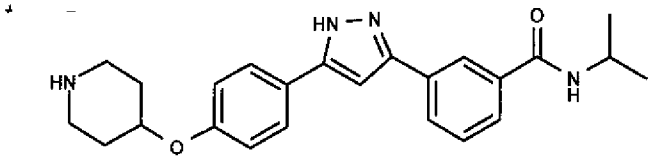
Example 77. N-Isopropyl-3-{5-[4-(piperidin-4-yloxy)-phenyl]-1H-pyrazol-3-yl}-benzamide.

77-A. 4-{4-[5-(3-Isopropylcarbamoyl-phenyl)-2H-pyrazol-3-yl]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester.



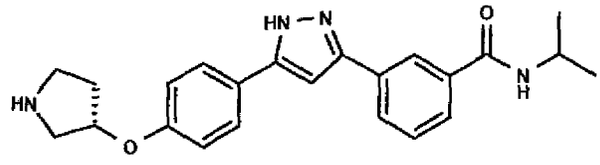
The title compound is prepared by methods similar to those utilized for the preparation of the compound of Example 71. MS(ESI) *m/z* = 505.2811 (M+1).

77-B. N-Isopropyl-3-{5-[4-(piperidin-4-yloxy)-phenyl]-1H-pyrazol-3-yl}-benzamide.



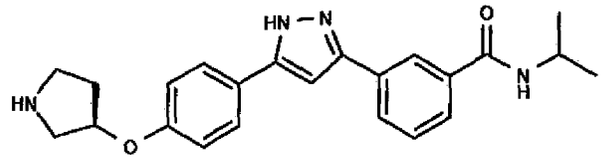
Trifluoroacetic acid is added to a solution of **77-A** in dichloromethane. The reaction is stirred at ambient temperature until conversion is judged to be complete. The reaction mixture is washed with saturated aqueous sodium bicarbonate solution followed by water. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product as a white solid. MS(ESI) *m/z* = 405.2286 (M+1). HPLC R_t = 10.36 min.

Example 78. N-Isopropyl-3-{5-[4-((S)-pyrrolidin-3-yloxy)-phenyl]-1H-pyrazol-3-yl}benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **77-B**. MS(ESI) *m/z* = 391.2140 (M+1). HPLC R_t = 10.16 min.

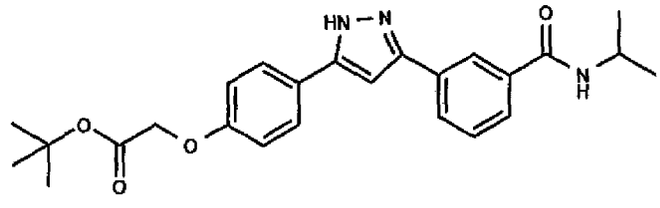
Example 79. N-Isopropyl-3-{5-[4-((R)-pyrrolidin-3-yloxy)-phenyl]-1H-pyrazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **77-B**. MS(ESI) *m/z* = 391.2130 (M+1). HPLC R_t = 10.20 min.

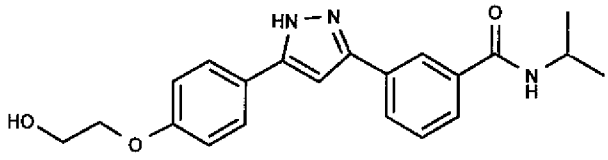
Example 80. 3-{5-[4-(2-Hydroxy-ethoxy)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.

80-A. {4-[5-(3-Isopropylcarbamoyl-phenyl)-2H-pyrazol-3-yl]-phenoxy}-acetic acid tert-butyl ester.



A solution of compound **70-E** (30 mg, 0.09 mmol) and potassium carbonate (37 mg, 0.27 mmol) in DMF (1.5 ml) is cooled in an ice water bath. *Tert*-butyl bromoacetate (12 uL, 0.09 mmol) is added and the reaction mixture is warmed to ambient temperature and stirred for 18 hours. The reaction mixture is diluted with ethyl acetate and washed with water and brine. The organic layer is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography to afford product as a white solid. MS(ESI) *m/z* = 436.2233 (M+1).

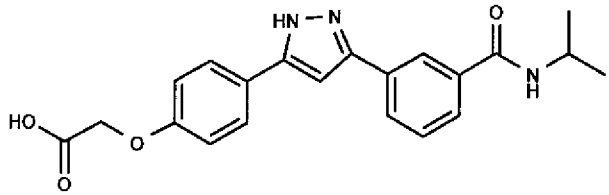
80-B. 3-{5-[4-(2-Hydroxy-ethoxy)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



A solution of compound **80-A** (35 mg, 0.08 mmol) in ethanol (2 ml) is cooled in an ice water bath. Sodium borohydride (18.2 mg, 0.48 mmol) is added and the reaction mixture is warmed to ambient temperature and stirred for 18 hours. Saturated aqueous ammonium chloride solution is added and the ethanol is evaporated under reduced pressure. The mixture is diluted with water and filtered to afford the desired product as a white solid. MS(ESI) *m/z* = 366.1813 (M+1). HPLC R_t = 11.25 min.

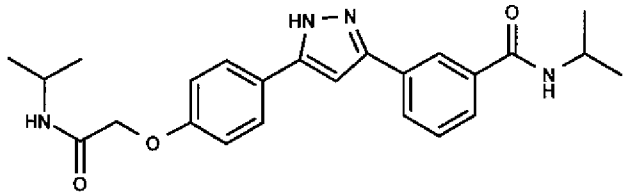
Example 81. N-Isopropyl-3-{5-[4-(isopropylcarbamoyl-methoxy)-phenyl]-1H-pyrazol-3-yl}-benzamide.

81-A. {4-[5-(3-Isopropylcarbamoyl-phenyl)-2H-pyrazol-3-yl]-phenoxy}-acetic acid.



Trifluoroacetic acid is added portionwise to a solution of compound **80-A** in DCM until conversion is judged to be complete. Reaction mixture is washed with water. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product as a white solid. MS(ESI) *m/z* = 380.1613 (M+1).

81-B. N-Isopropyl-3-{5-[4-(isopropylcarbamoyl-methoxy)-phenyl]-1H-pyrazol-3-yl}-benzamide.

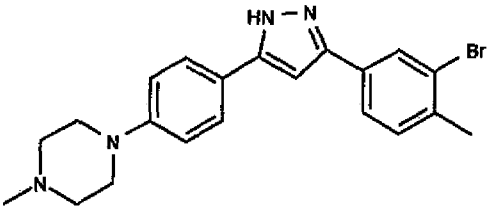


To a solution of compound **81-A** (55 mg, 0.15 mmol) in dimethylformamide (0.5 mL) and DCM (5 mL) are added HOAt (20 mg, 0.15 mmol), isopropyl amine (24 uL, 0.30 mmol) and EDCI (32 mg, 0.16 mmol). The mixture is stirred at room temperature for 16 hours. The

mixture is concentrated at reduced pressure and The residue is purified by reverse phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 421.2243 (M+1). HPLC R_t = 12.32 min.

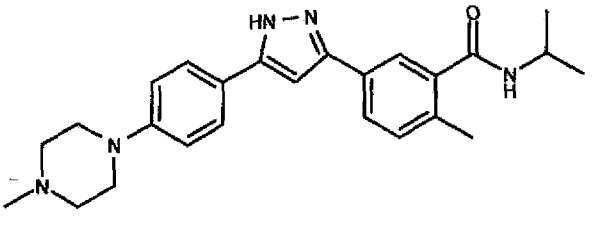
Example 82. N-Isopropyl-2-methyl-5-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide.

82-A. 1-{4-[5-(3-Bromo-4-methyl-phenyl)-2H-pyrazol-3-yl]-phenyl}-4-methyl-piperazine.



The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) m/z = 411.3, 413.3 (M+1).

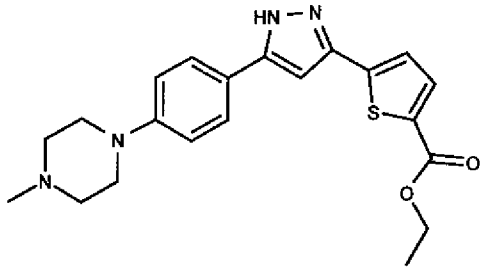
82-B. N-Isopropyl-2-methyl-5-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-benzamide trifluoroacetate.



Compound **82-A** (411 mg, 1.0 mmol), $Pd(Cl)_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), and isopropylamine (0.44 mL, 5.0 mmol) are taken into in DMF (10 ml) in a heavy-walled reaction vessel. The reaction is sparged with carbon monoxide gas from a needle for 10 minuteds. The vessel is sealed and the mixture is heated in a 100°C oil bath and stirred for 2 hours. The mixture is cooled to ambient temperature and filtered through a paper filter. The filtrate is purified by reverse phase HPLC to afford product as a white solid trifluoroacetate salt. MS(ESI) *m/z* = 418.2614 (M+1). HPLC R_t = 10.16 min.

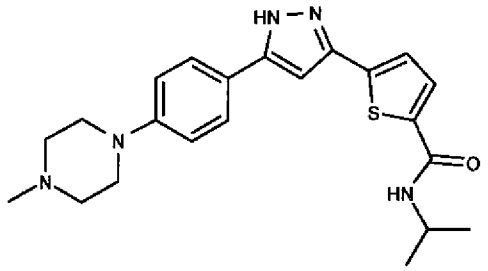
Example 83. 5-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-thiophene-2-carboxylic acid isopropylamide.

83-A. 5-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-thiophene-2-carboxylic acid ethyl ester.



The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) m/z = 397.3 (M+1).

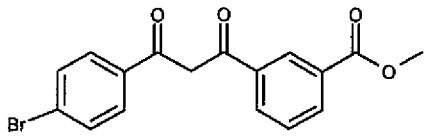
83-B. 5-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-1H-pyrazol-3-yl}-thiophene-2-carboxylic acid isopropylamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **1-C**. MS(ESI) *m/z* = 410.2014 (M+1). HPLC R_t = 10.26 min.

Example 84. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrazol-3-yl}-benzamide.

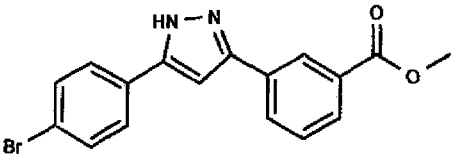
84-A. 3-[3-(4-Bromo-phenyl)-3-oxo-propionyl]-benzoic acid methyl ester.



A mixture of isophthalic acid dimethyl ester (5.84 g, 30.1 mmol), 4-bromoacetophenone (5 g, 25.1 mmol) in THF (70 mL) is cooled in an ice water bath. Sodium hydride (1.20 g, 30.1

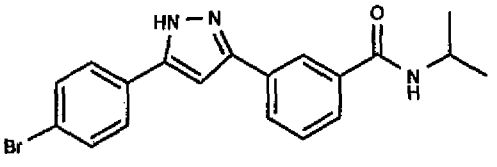
mmol) is added portionwise. The mixture is allowed to warm to ambient temperature and is stirred overnight. The pH of the mixture is then adjusted to 2-3 with the addition of saturated aqueous ammonium chloride solution and then 1 N aqueous hydrochloric acid. Solvents are removed under reduced pressure, and the residue is washed with ether and then heptane to afford product. MS (ESI) *m/z* = 383.8, 385.8 (M+1).

84-B. 3-[5-(4-Bromo-phenyl)-1H-pyrazol-3-yl]-benzoic acid methyl ester.



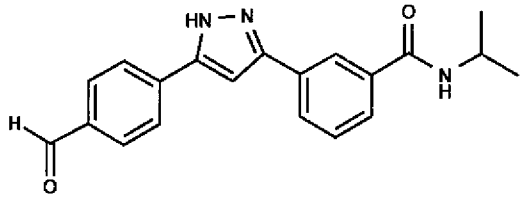
To a suspension of compound **84-A** (1.00 g, 2.77 mmol) and DIPEA (0.48 mL, 2.77 mmol) in EtOH (7.5 mL) and THF (7.5 mL) in a heavy-walled reaction vessel is added hydrazine (0.13 mL, 4.16 mmol). The reaction vessel is sealed and the reaction is heated in a 85 °C oil bath for 2.5 h. The solvent is removed under reduced pressure and the residue is diluted with dichloromethane, ethyl acetate, and diethyl ether. The mixture is filtered and the filtrate is washed with saturated aqueous $NaHCO_3$ and brine. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. Following concentration the residue is purified via flash chromatography with EtOAc in heptane to give product. MS (ESI) *m/z* = 356.8, 358.8 (M+1).

84-C. 3-[5-(4-Bromo-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.



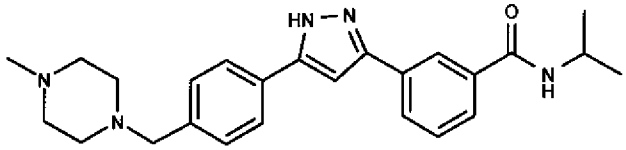
To a flask containing toluene (8 mL) is added $AlMe_3$ (3.40 mL, 6.72 mmol) followed by isopropylamine (0.57 mL, 6.72 mmol). After 15 min a solution of compound **84-B** (0.40 g, 1.12 mmol) in DCM (8 mL) is added and the contents of the flask are heated in an oil bath at 110 °C. After 2 h the reaction mixture is allowed to cool to ambient temperature and 1M aqueous HCl is added. The resulting mixture is then adjusted to pH > 7 with 1M aqueous NaOH and extracted three times with EtOAc. The combined organic layers are dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product. MS (ESI) *m/z* = 383.8, 385.8 (M+1).

84-D. 3-[5-(4-Formyl-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.



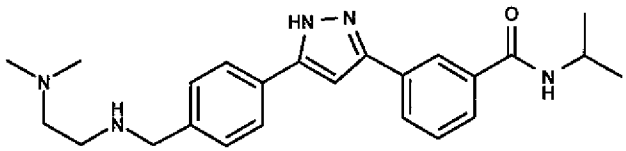
A solution of compound **84-C** (0.050 g, 0.130 mmol) in THF (2 mL) is cooled in a bath of dry ice in acetone. To this solution is added a 1.6M solution of nBuLi in heptane (0.28 mL). After 15 min dimethylformamide (0.02 mL, 0.314 mmol) is added. After 1 h, 1N aqueous HCl is added and the contents of the flask are allowed to warm to ambient temperature. At that point 1M aqueous NaOH is added until pH > 7 and the mixture is extracted with EtOAc (3 x). The combined organic layers are washed with brine and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford product. MS (ESI) *m/z* = 334 (M+1).

84-E. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



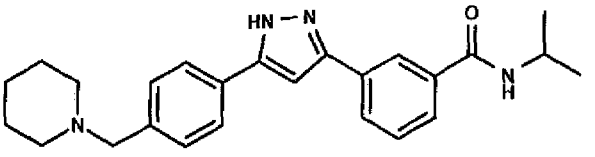
To a suspension of compound **84-D** (0.029 g, 0.087 mmol), N-methylpiperizine (0.012 mL, 0.105 mmol) and dichloroethane (3 mL) is added sodium triacetoxyborohydride (0.055 g, 0.261 mmol). After 16 h the mixture is concentrated to dryness under reduced pressure and the residue is purified by reverse phase HPLC to give the product as a white solid. MS(ESI) *m/z* = 418.2611 (M+1). HPLC R_t = 8.80 min.

Example 85. 3-(5-{4-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-N-isopropyl-benzamide.



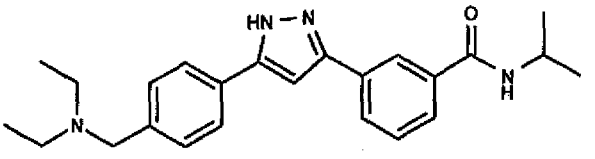
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 406.2612 (M+1). HPLC R_t = 8.69 min.

Example 86. N-Isopropyl-3-[5-(4-piperidin-1-ylmethyl-phenyl)-1H-pyrazol-3-yl]-benzamide.



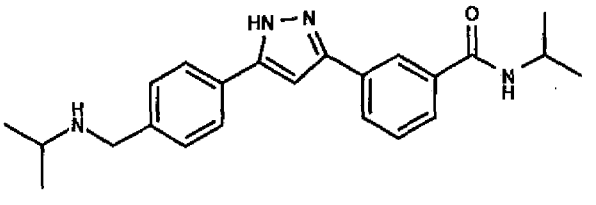
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 403.2512 (M+1). HPLC R_t = 10.14 min.

Example 87. 3-[5-(4-Diethylaminomethyl-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.



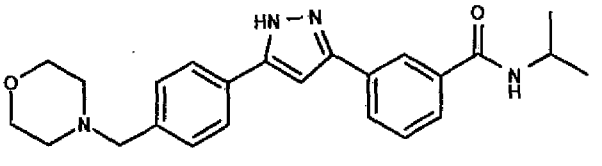
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 391.2500 (M+1). HPLC R_t = 10.04 min.

Example 88. N-Isopropyl-3-{5-[4-(isopropylamino-methyl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



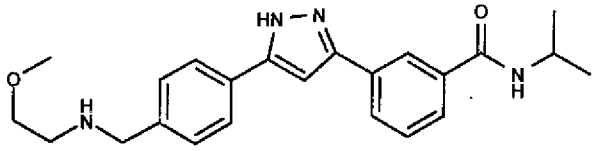
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 377.2341 (M+1). HPLC R_t = 9.93 min.

Example 89. N-Isopropyl-3-[5-(4-morpholin-4-ylmethyl-phenyl)-1H-pyrazol-3-yl]-benzamide.



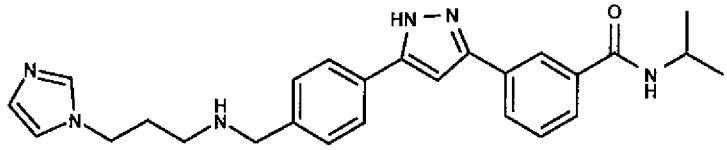
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 405.2305 (M+1). HPLC R_t = 9.70 min.

Example 90. N-Isopropyl-3-{5-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-benzamide.



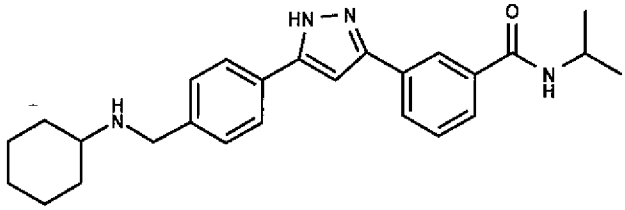
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 393.2286 (M+1). HPLC R_t = 9.93 min.

Example 91. 3-(5-{4-[(3-Imidazol-1-yl-propylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-N-isopropyl-benzamide.



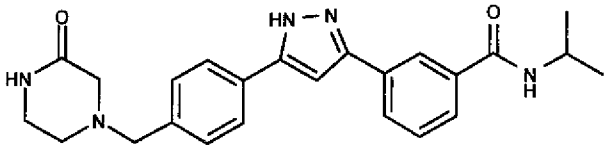
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 443.2551 (M+1). HPLC R_t = 9.14 min.

Example 92. 3-[5-(4-Cyclohexylaminomethyl-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.



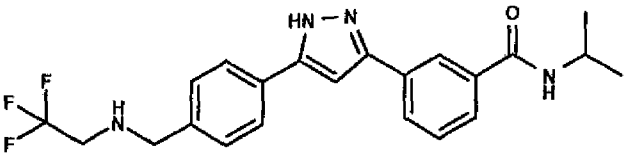
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 417.2661 (M+1). HPLC R_t = 11.03 min.

Example 93. N-Isopropyl-3-{5-[4-(3-oxo-piperazin-1-ylmethyl)-phenyl]-1H-pyrazol-3-yl}-benzamide.



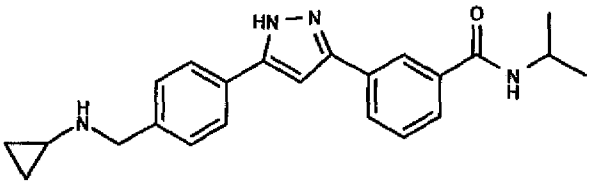
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 416.2243 (M+1). HPLC R_t = 9.45 min.

Example 94. N-Isopropyl-3-(5-{4-[(2,2,2-trifluoro-ethylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-benzamide.



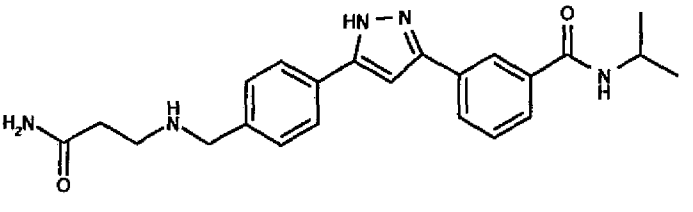
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 417.1911 (M+1). HPLC R_t = 10.26 min.

Example 95. 3-[5-(4-Cyclopropylaminomethyl-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.



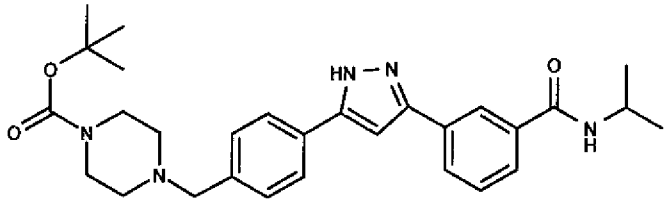
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 357.2192 (M+1). HPLC R_t = 10.08 min.

Example 96. 3-(5-{4-[(2-Carbamoyl-ethylamino)-methyl]-phenyl}-1H-pyrazol-3-yl)-N-isopropyl-benzamide.



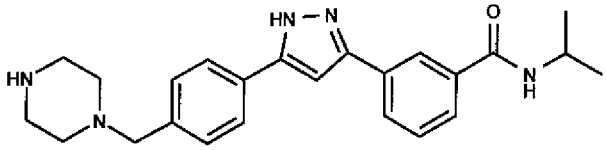
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 406.2235 (M+1). HPLC R_t = 9.45 min.

Example 97. 4-{4-[5-(3-isopropylcarbamoyl-phenyl)-2H-pyrazol-3-yl]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester.



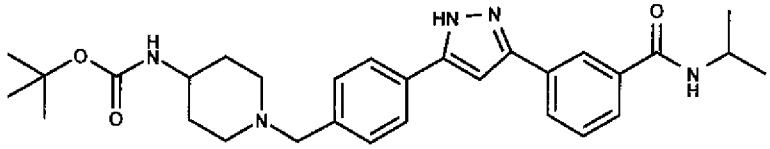
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 504.2953 (M+1). HPLC R_t = 11.17 min.

Example 98. N-Isopropyl-3-[5-(4-piperazin-1-ylmethyl-phenyl)-1H-pyrazol-3-yl]-benzamide.



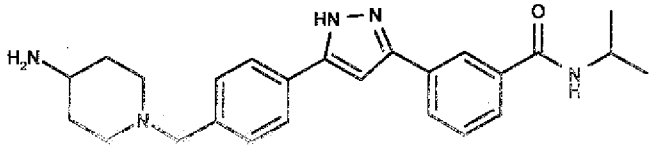
To a solution of the compound of Example 97 (0.098 g, 0.195 mmol) in DCM (8 mL) is added 4N HCl in dioxane (8 mL). A precipitate is formed and iPrOH (8 mL) is added. The mixture is stirred for 2 h before the solvent is removed in vacuo to give N-Isopropyl-3-[5-(4-piperazin-1-ylmethyl-phenyl)-1H-pyrazol-3-yl]-benzamide. MS(ESI) *m/z* = 404.2448 (M+1). HPLC R_t = 8.68 min.

Example 99. (1-{4-[5-(3-Isopropylcarbamoyl-phenyl)-2H-pyrazol-3-yl]-benzyl}-piperidin-4-yl)-carbamic acid tert-butyl ester.



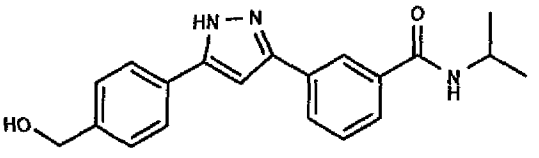
The title compound is prepared by methods similar to those utilized for the preparation of compound **84-E**. MS(ESI) *m/z* = 518.3126 (M+1). HPLC R_t = 11.11 min.

Example 100. 3-{5-[4-(4-Amino-piperidin-1-ylmethyl)-phenyl]-1H-pyrazol-3-yl}-N-isopropyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound of Example 98. MS(ESI) *m/z* = 418.2602 (M+1). HPLC R_t = 9.05 min.

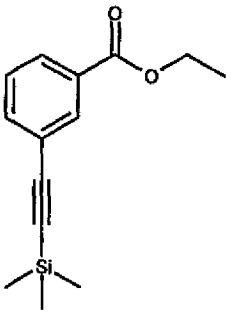
Example 101. 3-[5-(4-Hydroxymethyl-phenyl)-1H-pyrazol-3-yl]-N-isopropyl-benzamide.



To a suspension of compound **84-D** (0.15 g, 0.45 mmol), ammonium acetate (52 mg, 0.675 mmol) and dichloroethane (3 mL) is added sodium triacetoxyborohydride (0.285 g, 1.35 mmol). After 16 h the mixture is concentrated to dryness under reduced pressure and the residue is purified by reverse phase HPLC to give product. MS(ESI) *m/z* = 336.1705 (M+1). HPLC R_t = 10.74 min.

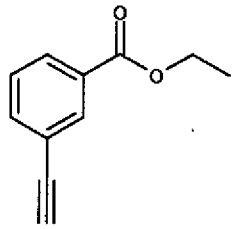
Example 102. 3-{3-[4-(4-Methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzoic acid ethyl ester.

102-A. 1-(3-Ethoxycarbonylphenyl)-2-(trimethylsilyl)acetylene.



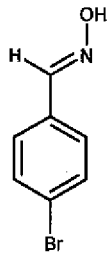
3-Ethyl-bromobenzoate (0.8 mL, 5 mmol), dichlorobis(triphenylphosphine)palladium (II) (210 mg, 0.3 mmol), cooper (I) iodide (58 mg, 0.3 mmol), trimethylsilylacetylene (0.7 mL, 5 mmol) and triethyl amine (8 mL, 60 mmol) are dissolved in 2.5 mL DMF in a heavy walled reaction vessel. The reaction is purged with nitrogen three times, then it is sealed and heated in a 120 °C oil bath for 30 min. The mixture is cooled to ambient temperature and poured into 150 mL 0.1 N aqueous HCl. The aqueous phase is extracted with ether (100 mL x 3). The organic layers are combined and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 to 5% ethyl acetate in hexanes to afford product as an oil.

102-B. 3-Ethynyl-benzoic acid ethyl ester.



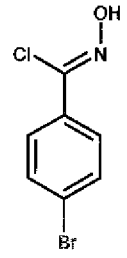
To a solution of **102-A** (4.8 g) in ethanol (100 mL) is added potassium carbonate (12 g, 87 mmol). The mixture is stirred at room temperature for 18 hours. The mixture is filtered, and the filtrate is diluted with water and extracted with dichloromethane (100 mL x 3). The organic layers are combined and dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product as a white solid.

102-C. 4-Bromo-benzaldoxime.



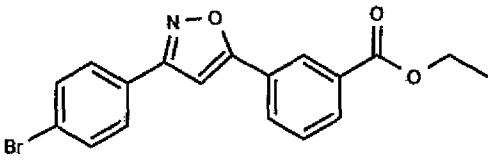
A mixed solution of **102-B.** (7.0 g, 37.8 mmol) and hydroxylamine hydroxylchloride (2.89 g, 41.6 mmol) in water (280 mL) and ethanol (140 mL) is cooled in an ice water bath. 50% (w/w) aqueous NaOH (7.56 mL) is added dropwise. And the mixture is stirred for 3 hours before it is neutralized to pH = 6 with 6 N aqueous HCl. The solution is transferred to a separation funnel and extracted with dichloromethane (200 mL x 3). The organic layers are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product as a white solid. MS(ESI) *m/z* = 200, 202 (M+1).

102-D. 4-Bromo-α-chloro-benzaldoxime



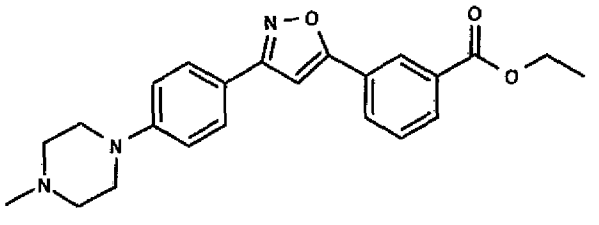
A solution of 4-bromo-benzaldoxime (7.01 g, 35 mmol) in DMF (140 mL) cooled in an ice water bath. N-chlorosuccinimide (4.68g, 35 mmol) is slowly added portionwise. The mixture is then warmed in a 50°C oil bath and stirred for 1 hour. The mixture is poured over about 100 g ice and ethyl acetate is added to dissolve precipitated solids. The aqueous phase is extracted with ethyl acetate (100 mL x 3). The organic layers are combined and washed with water followed by brine, then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is purified by flash column chromatography with 0 to 10% ethyl acetate in hexanes to afford product as a white solid.

102-E. 3-[3-(4-Bromo-phenyl)-isoxazol-5-yl]-benzoic acid ethyl ester.



To a solution of compound **102-B** (3.62 g, 21 mmol) in chloroform (43 mL) cooled in a ice water bath, is slowly added compound **102-D** (5.85 g, 25 mmol). Pyridine (1.02 mL, 13 mmol) is added dropwise to the solution followed by triethyl amine (4.42 mL, 315 mmol). The mixture is warmed to ambient temperature and stirred for 3 days. Saturated aqueous sodium carbonate solution (30 mL) is added to the mixture and the aqueous phase is extracted with DCM (100 mL x 3). The organic layers are combined and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 to 50% ethyl acetate in hexanes to afford product as a pale yellow solid. MS(ESI) *m/z* =372, 374 (M+1).

102-F. 3-{3-[4-(4-Methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzoic acid ethyl ester.

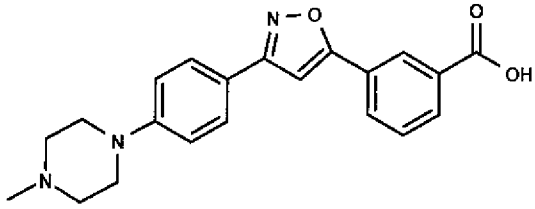


Aryl bromide **102-E** (240 mg, 0.65 mmol), palladium (II) acetate (3 mg, 0.013 mmol), cesium carbonate (300 mg, 0.91 mmol) and BINAP (17 mg, 0.026 mmol) are dissolved in anhydrous toluene (13 mL) in a heavy walled reaction vessel. The reaction is purged with nitrogen three times, followed by addition of N-methyl piperazine (93 uL, 0.84 mmol) to the mixture. The reaction is sealed and stirred in a 114°C oil bath for three days. When conversion is judged

to be complete, the mixture is cooled to ambient temperature, transferred to a test tube, and centrifuged for 5 min. The supernatant is purified by flash column chromatography with 0 to 10% MeOH in DCM to afford product as a yellow solid. MS(ESI) *m/z* = 392.1976 (M+1). HPLC Rt = 12.72 min.

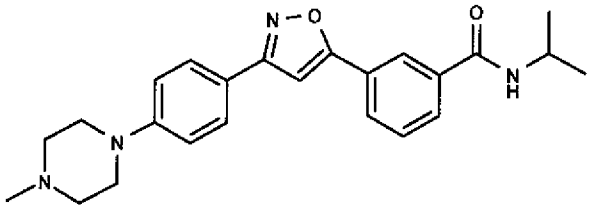
Example 103. N-Isopropyl-3-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzamide.

103-A. 3-{3-[4-(4-Methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzoic acid.



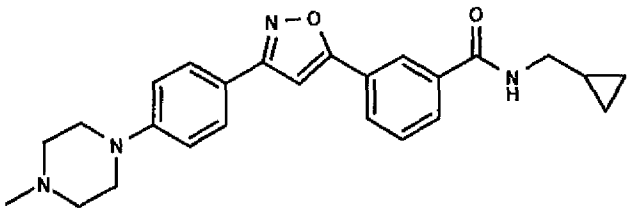
To a mixture of compound **102-F** (198 mg, 0.51 mmol) in THF (6 mL) and water (3 mL) is added lithium hydroxide monohydrate (43 mg, 1.01 mmol) in one portion. The mixture is stirred at room temperature until conversion is judged to be complete. The solvents are removed at reduced pressure to afford product as a white solid, contaminated with residual lithium hydroxide. MS(ESI) *m/z* = 364 (M+1).

103-B. N-Isopropyl-3-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzamide.



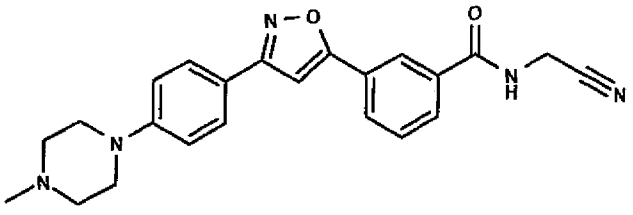
To a solution of ompound **103-A** (38.8 mg, 0.11 mmol) in DMF (0.6 mL) is added DIPEA (23 uL, 0.13mmol), isopropylamine (36.4 uL, 0.44 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (49.4 mg, 0.13 mmol). The mixture is stirred at ambient temperature until conversion is judged to be complete. Water (5 mL) is added and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 405.2271 (M+1). HPLC R_t = 10.89 min.

Example 104. N-Cyclopropylmethyl-3-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzamide.



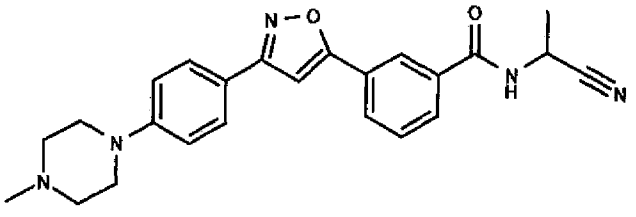
The title compound is prepared by methods similar to those utilized for the preparation of compound **103-B**. MS(ESI) *m/z* = 417.2296 (M+1). HPLC R_t = 11.19 min.

Example 105. N-Cyanomethyl-3-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzamide.



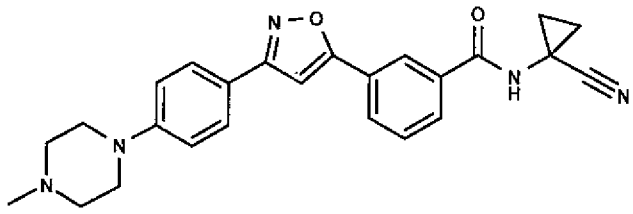
The title compound is prepared by methods similar to those utilized for the preparation of compound **103-B**. MS(ESI) *m/z* = 402.1928 (M+1). HPLC R_t = 9.94 min.

Example 106. N-(Cyano-methyl-methyl)-3-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **103-B**. MS(ESI) *m/z* = 416.2081 (M+1). HPLC R_t = 10.40 min.

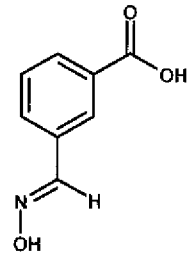
Example 107. N-(1-Cyano-cyclopropyl)-3-{3-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-5-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **103-B**. MS(ESI) *m/z* = 428.2081 (M+1). HPLC R_t = 10.31 min.

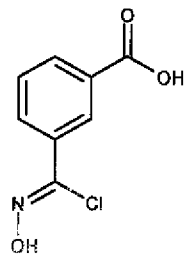
Example 108. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.

108-A. 3-(Hydroxyimino-methyl)-benzoic acid.



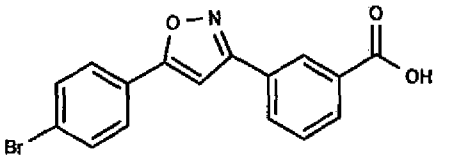
A mixture of methyl 3-formylbenzoate (5.0 g, 30 mmol) and hydroxylamine hydroxylchloride (2.3 g, 33 mmol) in water (280 mL) and ethanol (140 mL) is cooled in an ice water bath. 50% (w/w) aqueous NaOH solution (6 mL) is added dropwise and the mixture is stirred for 3 hours before it is neutralized to pH 2-3 with 6 N aqueous HCl. The mixture is transferred to a separation funnel and extracted with EtOAc (200 mL x3). The organic layers are combined and dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product as a white solid. MS(ESI) *m/z* = 166 (M+1).

108-B. 3-[chloro(hydroxyimino)methyl]-benzoic acid.



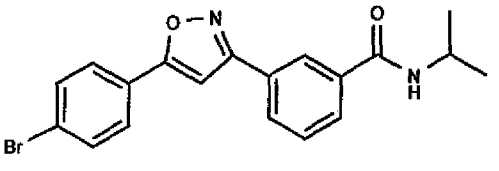
To a solution of compound **108-A** (495 mg, 3 mmol) in DMF (6 mL) cooled in an ice water bath, is slowly added N-chlorosuccinimide (441 mg, 3.3 mmol). The mixture is warmed in a 50°C oil bath and stirred for 1 hour. The mixture is then poured over about 30 g ice and ethyl acetate is added to dissolve precipitated solids. The aqueous phase is extracted with ethyl acetate (100 mL x 3). The organic layers are combined and washed with water follwed by brine, then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 to 100% ethyl acetate in hexanes to afford product as a white solid.

108-C. 3-[5-(4-Bromo-phenyl)-isoxazol-3-yl]-benzoic acid.



A solution of 4-bromo-ethynylbenzene (166 mg, 0.92 mmol) and compound **108-B** (550 mg, 2.8 mmol) in DCM (10 mL) is cooled in an ice water bath. DIPEA (0.64 mL, 3.68 mmol) is added and the mixture is warmed to ambient temperature and stirred for 3 hours. Saturated aqueous sodium carbonate solution (10 mL) is added and the aqueous phase is then acidified to pH = 3 with aqueous HCl solution. The aqueous phase is extracted with EtOAc (100 mL x 3). The organic layers are combined and dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product as a white solid. MS(ESI) *m/z* = 344, 346 (M+1).

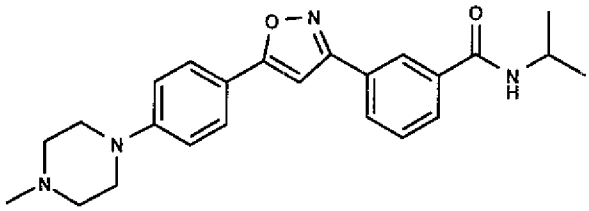
108-D. 3-[5-(4-Bromo-phenyl)-isoxazol-3-yl]-N-isopropyl-benzamide.



To a stirring solution of compound **108-C** (153.3 mg, 0.45 mmol) in DMF (2 mL) are added DIPEA (94 uL, 0.54 mmol), isopropyl amine (152 uL, 1.78mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (342 mg, 0.90 mmol). The mixture is stirred at ambient temperature until conversion is judged to be complete. Water (10 mL) is added and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced

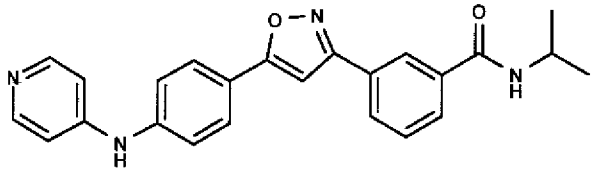
pressure. The residue is purified by flash column chromatography with 0 to 10% MeOH in DCM to give the product as a white powder. MS(ESI) *m/z* = 385, 387 (M+1).

108-E. N-Isopropyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



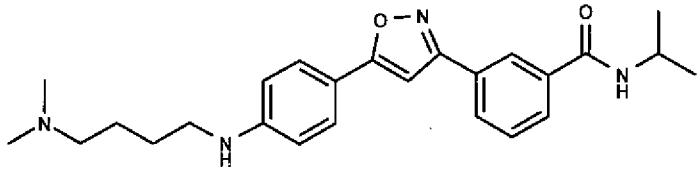
Compound **108-D** (84 mg, 0.22 mmol), palladium (II) acetate (2 mg, 0.009 mmol), cesium carbonate (100 mg, 0.31 mmol) and BINAP (12 mg, 0.018 mmol) are dissolved in anhydrous toluene (3 mL) in a heavy walled reaction vessel. The reaction is purged with nitrogen three times, then N-methyl piperazine (48 uL, 0.44 mmol) is added to the mixture. The vessel is sealed and heated in a 114°C oil bath for 18h. When conversion is judged to be complete, the mixture is cooled to ambient temperature, transferred to a test tube, and centrifuged for 5 min. The supernatant is purified by flash column chromatography with 0 to 10% MeOH in DCM to afford product as a yellow solid. MS(ESI) *m/z* = 405.2292 (M+1). HPLC R_t = 10.83 min.

Example 109. N-Isopropyl-3-{5-[4-(pyridin-4-ylamino)-phenyl]-isoxazol-3-yl}-benzamide.



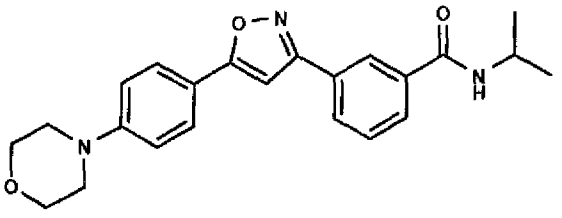
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 399.1819 (M+1). HPLC R_t = 11.06 min.

Example 110. 3-{5-[4-(4-Dimethylamino-butylamino)-phenyl]-isoxazol-3-yl}-N-isopropyl-benzamide.



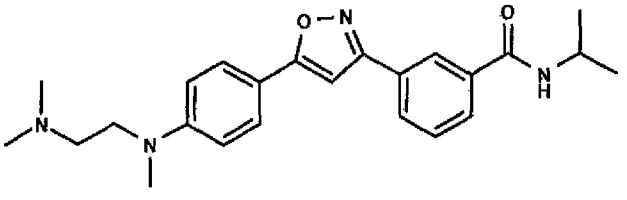
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 421.2596 (M+1). HPLC R_t = 11.11 min.

Example 111. N-Isopropyl-3-[5-(4-morpholin-4-yl-phenyl)-isoxazol-3-yl]-benzamide.



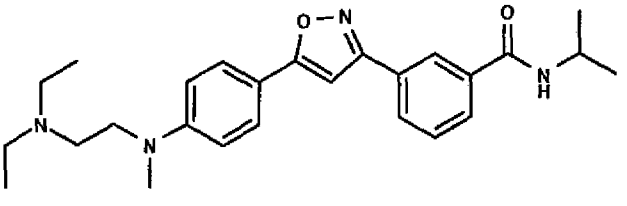
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 392.1968 (M+1). HPLC R_t = 14.44 min.

Example 112. 3-(5-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-isoxazol-3-yl)-N-isopropyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 407.2451 (M+1). HPLC R_t = 11.29 min.

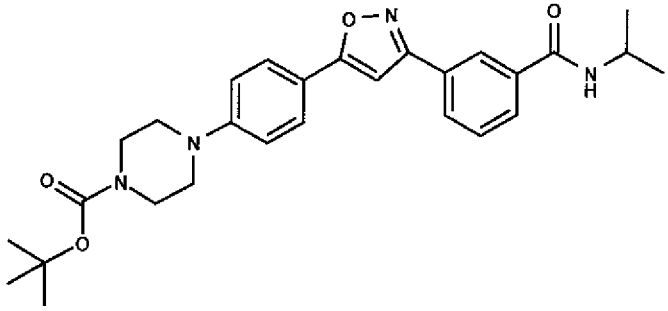
Example 113. 3-(5-{4-[(2-Diethylamino-ethyl)-methyl-amino]-phenyl}-isoxazol-3-yl)-N-isopropyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 435.2752 (M+1). HPLC R_t = 11.65 min.

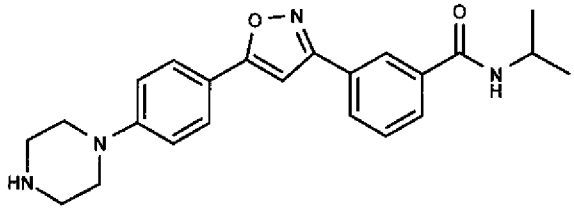
Example 114. N-Isopropyl-3-[5-(4-piperazin-1-yl-phenyl)-isoxazol-3-yl]-benzamide.

114-A. 4-{4-[3-(3-Isopropylcarbamoyl-phenyl)-isoxazol-5-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester.



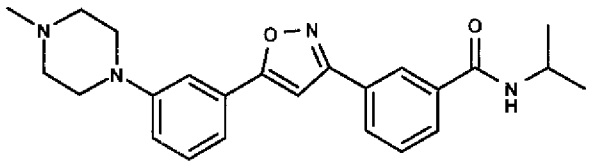
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 491.3 (M+1).

114-B. N-Isopropyl-3-[5-(4-piperazin-1-yl-phenyl)-isoxazol-3-yl]-benzamide.



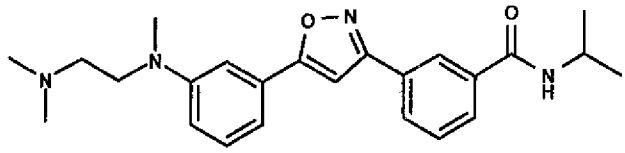
Trifluroracetic acid (130 uL, 1.72 mmol) is added to a solution of **114-A** in DCM, which is cooled in a ice water bath. The mixture is warmed to ambient temperature and stirred until conversion is judged to be complete. The reaction is quenched with saturated aqueous sodium bicarbonate solution. The aqueous phase is extracted with ethyl acetate three times. The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by preparative TLC with 30% methanol in dichloromethane to afford product as a white solid. MS(ESI) *m/z* = 391.2127 (M+1). HPLC R_t = 10.48 min.

Example 115. N-Isopropyl-3-{5-[3-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound 108-E. MS(ESI) *m/z* = 405.2291 (M+1). HPLC R_t = 11.01 min.

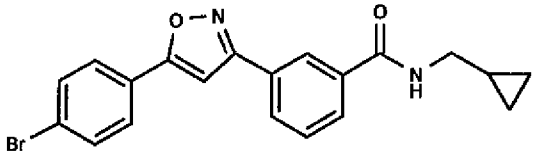
Example 116. 3-(5-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-isoxazol-3-yl)-N-isopropyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 407.2434 (M+1). HPLC R_t = 11.18 min.

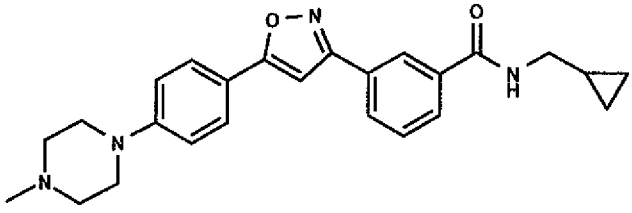
Example 117. N-Cyclopropylmethyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.

117-A. 3-[5-(4-Bromo-phenyl)-isoxazol-3-yl]-N-cyclopropylmethyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-D**. MS(ESI) *m/z* = 397, 399 (M+1).

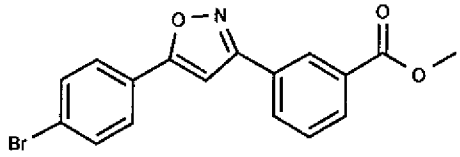
117-B. N-Cyclopropylmethyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 417.2281 (M+1). HPLC R_t = 11.16 min.

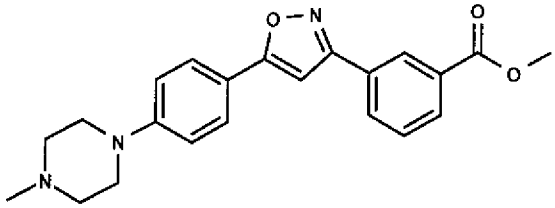
Example 118. N-Cyanomethyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.

118-A. 3-[5-(4-Bromo-phenyl)-isoxazol-3-yl]-benzoic acid methyl ester.



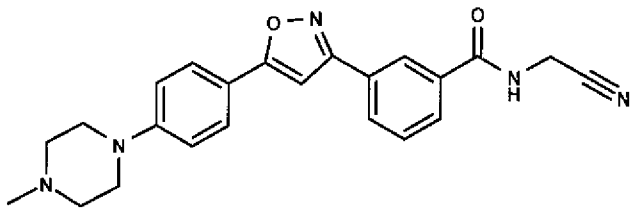
To a solution of compound **108-C** (300 mg, 0.87 mmol) in methanol (6 mL) is added trimethylsilylchloride (880 uL, 6.96 mmol) dropwise. The mixture is stirred at ambient temperature for 18 hours. The mixture is concentrated under reduced pressure and saturated aqueous sodium carbonate is added to the residue. The aqueous phase is extracted with ethyl acetate (50 mL x 3). The organic layers are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is washed with methanol and filtered to afford product as a white solid. MS(ESI) *m/z* = 358.0, 360.0 (M+1).

118-B. 3-{5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzoic acid methyl ester.



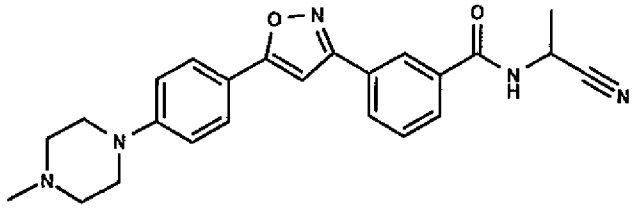
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-E**. MS(ESI) *m/z* = 378.3 (M+1).

118-C. N-Cyanomethyl-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



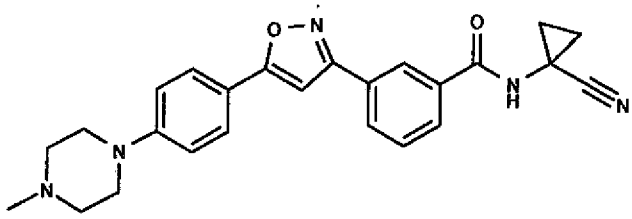
The title compound is prepared by methods similar to those utilized for the preparation of compound **103-B**. MS(ESI) *m/z* = 402.1915 (M+1). HPLC R_t = 10.14 min.

Example 119. N-(Cyano-methyl-methyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **118-C**. MS(ESI) *m/z* = 416.2095 (M+1). HPLC R_t = 10.41 min.

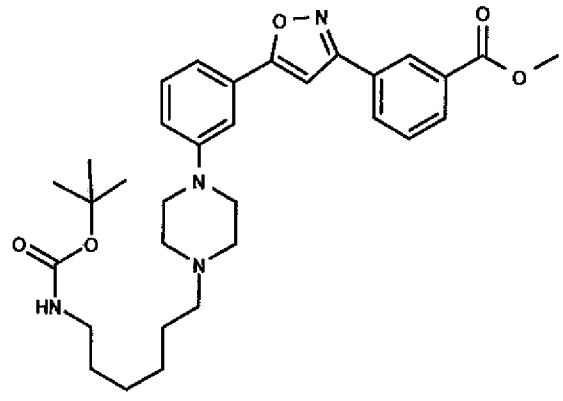
Example 120. N-(1-Cyano-cyclopropyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **118-C**. MS(ESI) *m/z* = 428.2084 (M+1). HPLC R_t = 10.36 min.

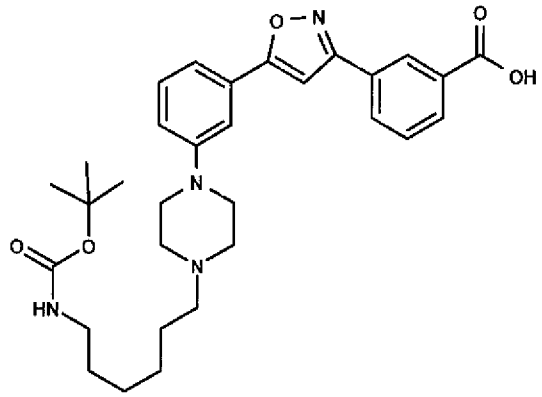
Example 121.

121-A. 3-(5-{3-[4-(6-tert-Butoxycarbonylamino-hexyl)-piperazin-1-yl]-phenyl}-isoxazol-3-yl)-benzoic acid methyl ester.



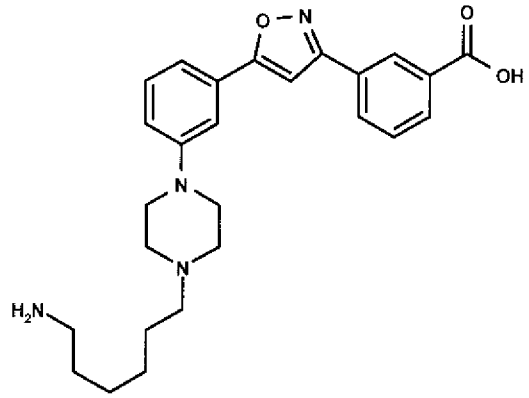
The title compound is prepared by methods similar to those utilized for the preparation of compound **118-B**. MS(ESI) *m/z* = 563.5 (M+1).

121-B 3-(5-{3-[4-(6-tert-Butoxycarbonylamino-hexyl)-piperazin-1-yl]-phenyl}-isoxazol-3-yl)-benzoic acid.



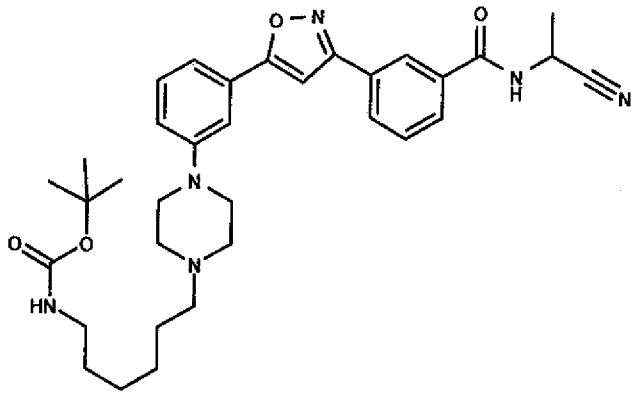
The title compound is prepared by methods similar to those utilized for the preparation of compound **103-A**. MS(ESI) *m/z* = 549.5 (M+1).

121-C. 3-(5-{3-[4-(6-Amino-hexyl)-piperazin-1-yl]-phenyl}-isoxazol-3-yl)-benzoic acid.



The title compound is prepared by methods similar to those utilized for the preparation of compound **114-B**. MS(ESI) *m/z* = 449.4 (M+1).

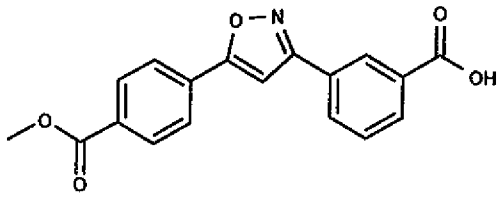
Example 122. (6-{4-[3-(3-{3-[(Cyano-methyl-methyl)-carbamoyl]-phenyl}-isoxazol-5-yl)-phenyl]-piperazin-1-yl}-hexyl)-carbamic acid tert-butyl ester.



To a solution of **121-B** (20 mg, 0.036 mmol) in DMF (2 mL) are added HOBt (149 mg, 1.09 mmol), DIPEA (383 uL, 2.19 mmol) and EDC-HCl (216 mg, 1.1 mmol). The mixture is stirred for 1 min before 2-aminopropanenitrile hydrochloride (117 mg, 1.1 mmol) is added. The mixture is stirred for 18 hours. The mixture is purifed by RP-HPLC to afford the desired product. MS(ESI) *m/z* = 601.3481 (M+1). HPLC R_t = 10.16 min (Inertsil C18 4.6 x 150 mm HPLC column, 10% to 95% acetonitrile in 0.1% (v/v) aqueous trifluoroacetic acid solution elution gradient over 15 minutes, 1.2 mL/min. flow rate).

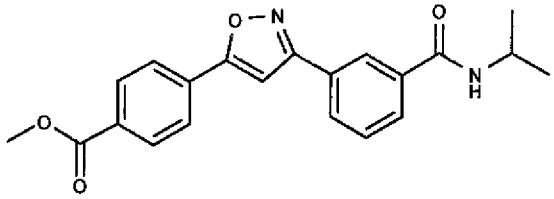
Example 123. 4-[3-(3-Isopropylcarbamoyl-phenyl)-isoxazol-5-yl]-(2-diethylamino-ethyl)-benzamide.

123-A. 4-[3-(3-Carboxy-phenyl)-isoxazol-5-yl]-benzoic acid methyl ester.



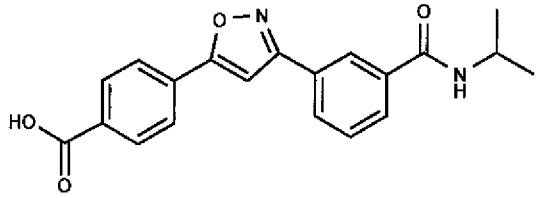
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-C**. MS(ESI) *m/z* = 324.2 (M+1).

123-B. 4-[3-(3-Isopropylcarbamoyl-phenyl)-isoxazol-5-yl]-benzoic acid methyl ester.



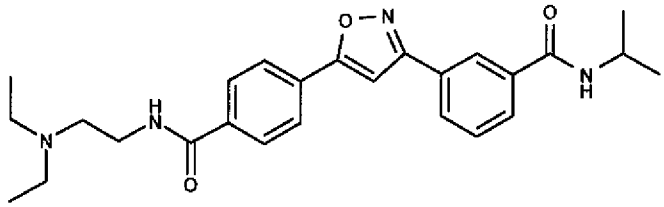
The title compound is prepared by methods similar to those utilized for the preparation of compound **180-D**. MS(ESI) *m/z* = 365.2 (M+1).

123-C. 4-[3-(3-Isopropylcarbamoyl-phenyl)-isoxazol-5-yl]-benzoic acid.



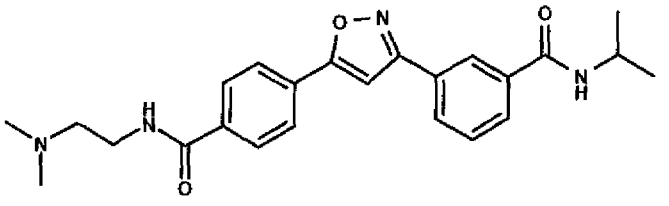
To a mixture of **123-B** (519 mg, 1.43 mmol) in THF (10 mL) and water (5 mL) is added lithium hydroxide monohydrate (132 mg, 3.14 mmol) in a single portion. The mixture is stirred until conversion is judged to be complete. The solvents are removed at reduced pressure to afford product as a white solid, contaminated with residual lithium hydroxide. MS(ESI) *m/z* = 351.2 (M+1).

123-D. 4-[3-(3-Isopropylcarbamoyl-phenyl)-isoxazol-5-yl]-(2-diethylamino-ethyl)-benzamide.



To a stirring solution of compound **123-C** (50 mg, 0.14 mmol) in DMF (2 mL) are added DIPEA (29 uL, 0.17 mmol), N,N-Diethylethylenediamine (82 uL, 0.57 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (217 mg, 0.57 mmol). The mixture is stirred at ambient temperature until conversion is judged to be complete. Water (10 mL) is added and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by RP-HPLC to give product as a white powder. MS(ESI) *m/z* = 449.2549 (M+1). HPLC R_t = 10.82 min.

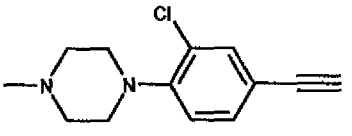
Example 124. 4-[3-(3-Isopropylcarbamoyl-phenyl)-isoxazol-5-yl]-(2-dimethylamino-ethyl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **123-D**. MS(ESI) *m/z* = 421.2239 (M+1). HPLC R_t = 10.02 min.

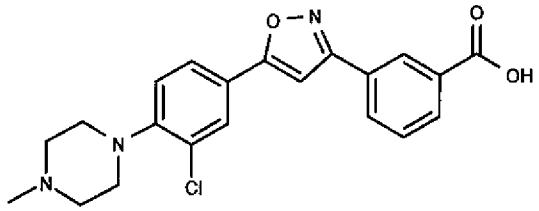
Example 125. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-N-(cyano-methyl-methyl)-benzamide.

125-A. 1-(2-Chloro-4-ethynyl-phenyl)-4-methyl-piperazine.



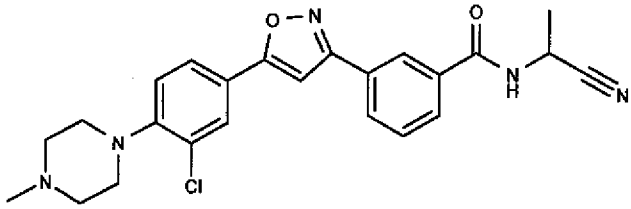
To a solution of LDA (3.1 mmol) in THF (2.5 M), which is precooled in a bath of dry ice in acetone, is added a solution of 3-chloro-4-(4-Methylpiperazino)acetophenone (713 mg, 2.8 mmol) in tetrahydrofuran dropwise. The resulting solution is stirred for 1 hour. To this mixture is added diethyl chlorophosphate (0.45 mL, 3.1 mmol) dropwise. The resulting dark brown mixture is stirred for 5 min, then allowed to warm to ambient temperature and stirred for an additional 15 min. The solution is returned to the cooling bath, and added via a cannula to a 2.5 M solution of LDA (6.25 mmol) in THF, which is also precooled in a bath of dry ice in acetone. The resulting mixture is stirred for 40 min then allowed to warm to ambient temperature and stirred for an additional 20 min. The reaction is quenched by addition of 1 N aqueous HCl, and the aqueous phase is extracted with ether four times. The combined organic layers are washed with saturated aqueous sodium bicarbonate solution. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product is separated by flash column chromatography with 0% to 100% ethyl acetate in hexanes to afford product as an oil. MS(ESI) *m/z* = 235, 237 (M+1).

125-B. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzoic acid.



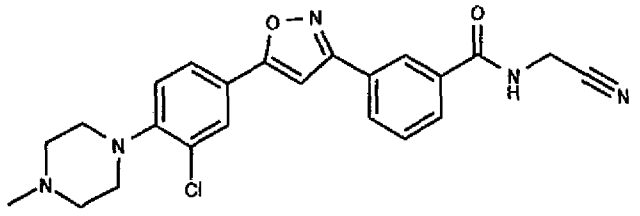
To a solution of compound **125-A** (340 mg, 1.44 mmol) and compound **108-B** (577 mg, 2.9 mmol) in DCM (4 mL), which is precooled in an ice water bath, is slowly added DIPEA (1.01 mL, 5.8 mmol). The mixture is allowed to warm to ambient temperature and is stirred for 3 hours. Saturated aqueous sodium carbonate solution (10 mL) is added to the mixture and the aqueous phase is adjusted to pH = 3 with aqueous HCl. The mixture is extracted with EtOAc (100 mL x 3). The organic layers are combined and dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford product as a white solid. MS(ESI) *m/z* = 398.3, 400.3 (M+1).

125-C. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-N-(cyano-methyl-methyl)-benzamide.



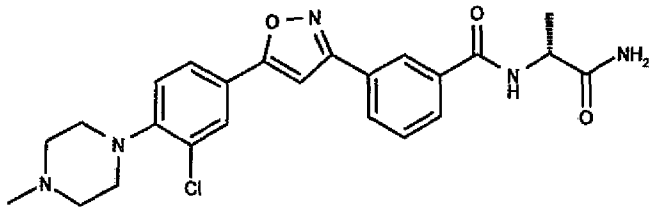
To a solution of **125-B** (100 mg, 0.25 mmol) in DMF (3 mL) is added DIPEA (218 uL, 1.25 mmol), 2-aminopropanenitrile hydrochloride (80 mg, 0.75 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (285 mg, 0.75 mmol). The mixture is stirred at room temperature until conversion is judged to be complete. Water (5 mL) is added, and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 450.1699 (M+1). HPLC R_t = 11.27 min.

Example 126. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-N-cyanomethyl-benzamide.



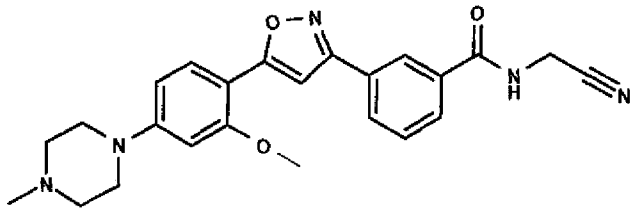
The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 436.1530 (M+1). HPLC R_t = 10.82 min.

Example 127. N-((R)-1-Carbamoyl-ethyl)-3-{5-[3-chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



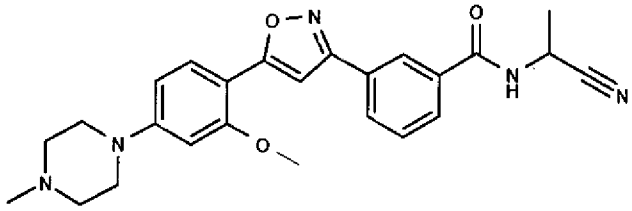
The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 468.1813 (M+1). HPLC R_t = 9.83 min.

Example 128. N-Cyanomethyl-3-{5-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



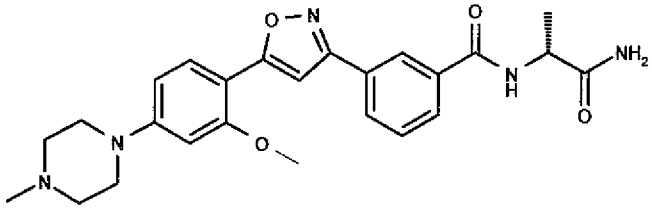
The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 432.2036 (M+1). HPLC R_t = 10.44 min.

Example 129. N-(Cyano-methyl-methyl)-3-{5-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



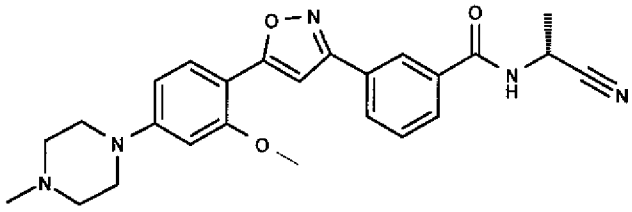
The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 446.2196 (M+1). HPLC R_t = 10.62 min.

Example 130. N-((R)-1-Carbamoyl-ethyl)-3-{5-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



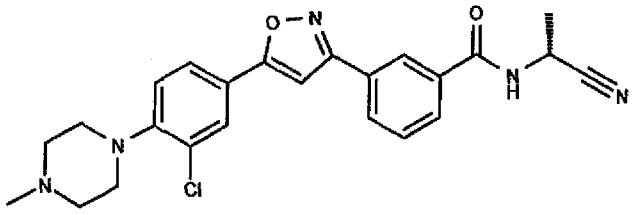
The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 464.2318 (M+1). HPLC R_t = 8.76 min.

Example 131. N-((R)-Cyano-methyl-methyl)-3-{5-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



To a solution of the compound of **Example 130** (185 mg, 0.4 mmol) in anhydrous THF (3 mL), which is precooled in an ice water bath, is added dropwise triethyl amine (0.14 mL, 1.0 mmol) followed by trifluoroacetic anhydride (0.11 mL, 0.8 mmol). When conversion is judged to be complete, saturated aqueous sodium bicarbonate solution (5 mL) is added to the mixture and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 446.2192 (M+1). HPLC R_t = 10.81 min.

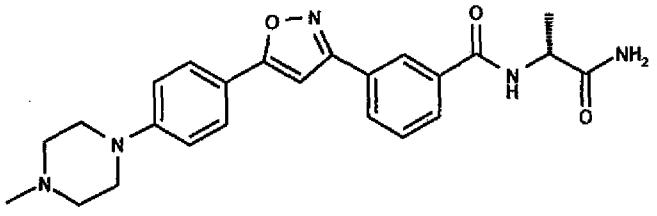
Example 132. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-N-((R)-cyano-methyl-methyl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound of **Example 131**. MS(ESI) *m/z* = 450.1703 (M+1). HPLC R_t = 11.20 min.

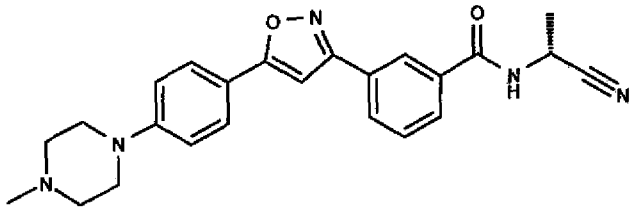
Example 133. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.

133-A. N-((R)-1-Carbamoyl-ethyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 434.4 (M+1).

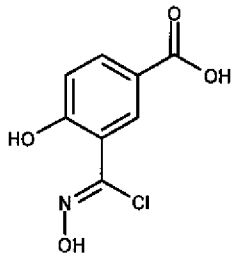
133-B. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound of **Example 131**. MS(ESI) *m/z* = 416.2071 (M+1). HPLC R_t = 12.06 min.

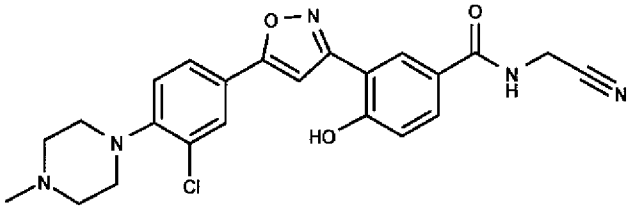
Example 134. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-N-cyanomethyl-4-hydroxy-benzamide

134-A. 3-[Chloro(hydroxyimino)methyl]-4- Hydroxy-benzoic acid



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-B**.

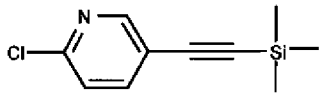
134-B. 3-{5-[3-Chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-isoxazol-3-yl}-N-cyanomethyl-4-hydroxy-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 452.1491 (M+1). HPLC R_t = 10.64 min.

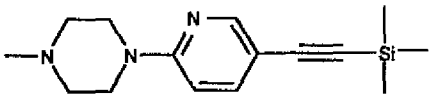
Example 135. N-Cyanomethyl-3-{5-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-isoxazol-3-yl}-benzamide.

135-A. 2-Chloro-5-trimethylsilanylethynyl-pyridine.



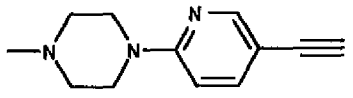
The title compound is prepared by methods similar to those utilized for the preparation of compound **102-A**. MS(ESI) *m/z* = 210.3 (M+1).

135-B. 1-Methyl-4-(5-trimethylsilanylethynyl-pyridin-2-yl)-piperazine.



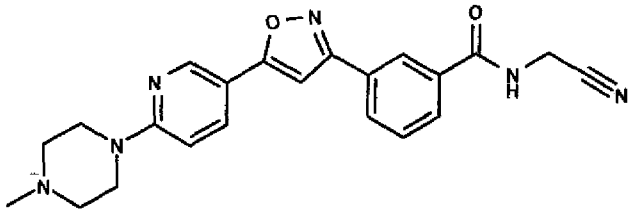
A solution of compound **135-A** (1.2 g, 5.72 mmol) in N-methyl piperazine (30 mL) are heated at reflux and stirred for 14 hours. Saturated aqueous ammonium chloride solution (100 mL) is added and the aqueous phase is extracted with ethyl acetate (150 mL x 2). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the product as a pale yellow solid.

135-C. 1-(5-Ethynyl-pyridin-2-yl)-4-methyl-piperazine.



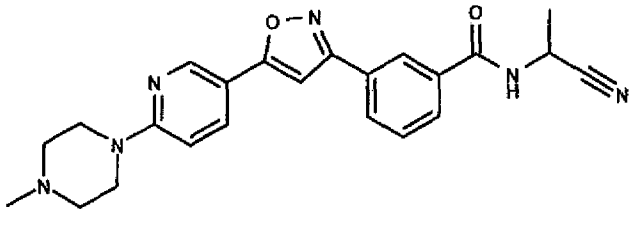
The title compound is prepared by methods similar to those utilized for the preparation of compound **102-B**.

135-D. N-Cyanomethyl-3-{5-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-isoxazol-3-yl}-benzamide.



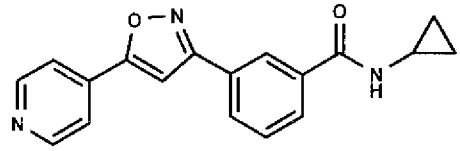
The title compound is prepared by methods similar to those utilized for the preparation of compound **125-C**. MS(ESI) *m/z* = 403.1884 (M+1). HPLC R_t = 9.31 min.

Example 136. N-(Cyano-methyl-methyl)-3-{5-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-isoxazol-3-yl}-benzamide.



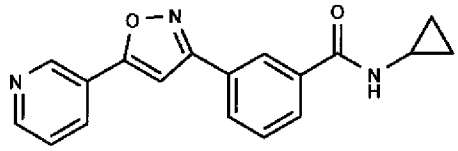
The title compound is prepared by methods similar to those utilized for the preparation of compound 135-D. MS(ESI) *m/z* = 417.2041 (M+1). HPLC R_t = 9.87 min.

Example 137. N-Cyclopropyl-3-(5-pyridin-4-yl-isoxazol-3-yl)-benzamide.



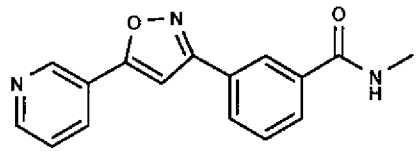
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-D**. MS(ESI) *m/z* = 306.1232 (M+1). HPLC R_t = 8.71 min.

Example 138. N-Cyclopropyl-3-(5-pyridin-3-yl-isoxazol-3-yl)-benzamide.



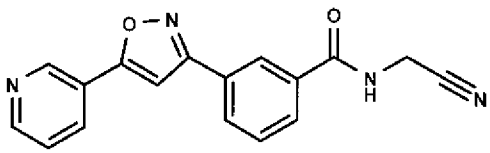
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-D**. MS(ESI) *m/z* = 306.1231 (M+1). HPLC R_t = 9.38 min.

Example 139. N-Methyl-3-(5-pyridin-3-yl-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-D**. MS(ESI) *m/z* = 280.1093 (M+1). HPLC R_t = 8.49 min.

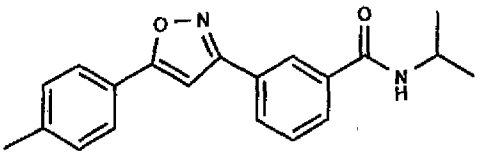
Example 140. N-Cyanomethyl-3-(5-pyridin-3-yl-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-D**. MS(ESI) *m/z* = 305.1035 (M+1). HPLC R_t = 9.00 min.

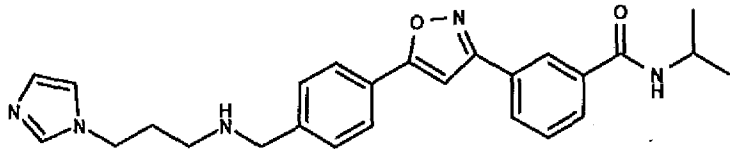
Example 141. 3-(5-{4-[(3-Imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-isopropyl-benzamide.

141-A.N-Isopropyl-3-(5-p-tolyl-isoxazol-3-yl)-benzamide.



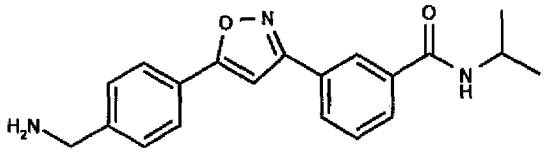
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-D**. MS(ESI) *m/z* = 321.3 (M+1).

141-B. 3-(5-{4-[(3-Imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-isopropyl-benzamide.



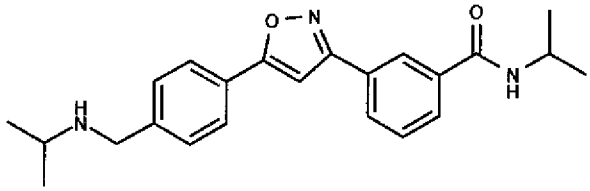
To a solution of compound **141-A** (100 mg, 0.312 mmol) in carbon tetrachloride (5 mL) are added NBS (83 mg, 0.468 mmol) and AIBN (5.1 mg, 0.0312 mmol). The mixture is stirred and heated in an 80°C oil bath until conversion is judged to be complete. The mixture is allowed to cool to ambient temperature and N-(3-aminopropyl)imidazole (0.37 mL, 3.12 mmol) is added. The mixture is stirred at ambient temperature until conversion of the intermediate bromide is judged to be complete. The mixture is concentrated under reduced pressure and the residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 444.2406 (M+1). HPLC R_t = 9.19 min.

Example 142. 3-[5-(4-Aminomethyl-phenyl)-isoxazol-3-yl]-N-isopropyl-benzamide.



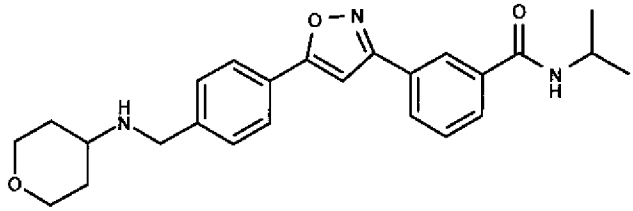
The title compound is prepared by methods similar to those utilized for the preparation of compound **141-B**. MS(ESI) *m/z* = 336.1718 (M+1). HPLC R_t = 9.77 min.

Example 143. N-Isopropyl-3-{5-[4-(isopropylamino-methyl)-phenyl]-isoxazol-3-yl}-benzamide.



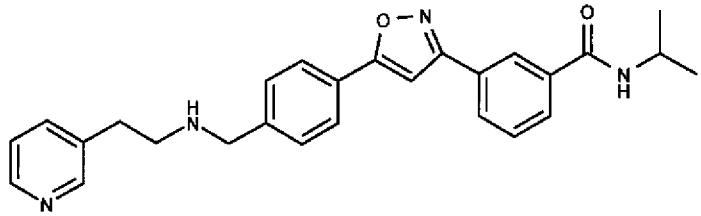
The title compound is prepared by methods similar to those utilized for the preparation of compound **141-B**. MS(ESI) *m/z* = 378.2181 (M+1). HPLC R_t = 10.67 min.

Example 144. N-Isopropyl-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



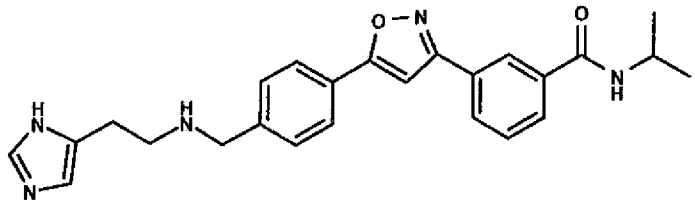
The title compound is prepared by methods similar to those utilized for the preparation of compound **141-B**. MS(ESI) *m/z* = 420.2295 (M+1). HPLC R_t = 10.36 min.

Example 145. N-Isopropyl-3-(5-{4-[(2-pyridin-3-yl-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **141-B**. MS(ESI) *m/z* = 441.2299 (M+1). HPLC R_t = 9.35 min.

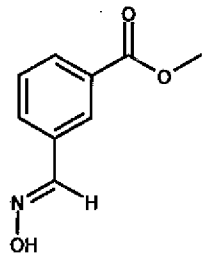
Example 146. 3-[5-(4-{[2-(3H-Imidazol-4-yl)-ethylamino]-methyl}-phenyl)-isoxazol-3-yl]-N-isopropyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **141-B**. MS(ESI) *m/z* = 430.2242 (M+1). HPLC R_t = 9.27 min.

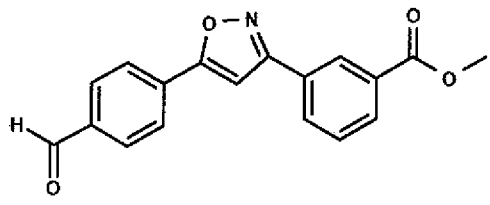
Example 147. N-Cyanomethyl-3-[5-(4-{[(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-phenyl)-isoxazol-3-yl]-benzamide.

147-A. 3-(Hydroxyimino-methyl)-benzoic acid methyl ester.



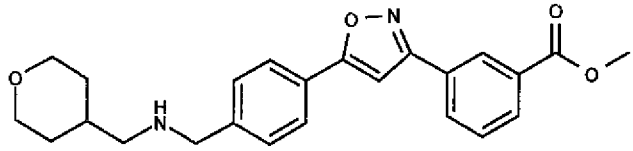
To a mixture of 3-formylbenzoate (5.0 g, 30 mmol) in water (280 mL) and ethanol (140 mL), which is precooled in an ice water bath, is added a 50% (w/w) aqueous hydroxylamine solution (2.2 g, 33 mmol) dropwise. The mixture is stirred for 3 hours. The resulting suspension is filtered, and the residue solid is washed with cold ethanol to afford product as a white solid. MS(ESI) *m/z* = 180.4 (M+1).

147-B. 3-[5-(4-Formyl-phenyl)-isoxazol-3-yl]-benzoic acid methyl ester.



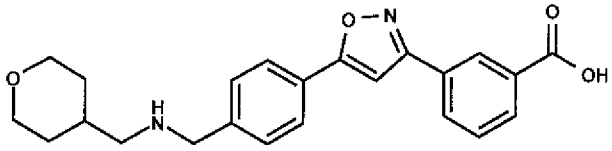
The title compound is prepared by methods similar to those utilized for the preparation of compound **108-C**. MS(ESI) *m/z* = 308.3 (M+1).

147-C. 3-[5-(4-{[(Tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-phenyl)-isoxazol-3-yl]-benzoic acid methyl ester.



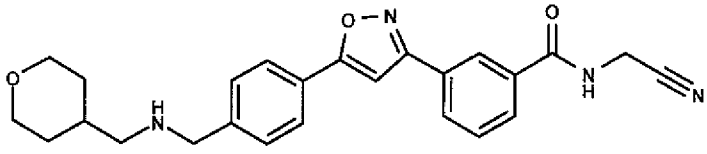
To a mixture of compound **147-B** (100 mg, 0.33 mmol) and 4-aminomethyltetrahydropyran (59 uL, 0.39 mmol) in 4 mL DCM, which is precooled in an ice water bath, is added sodium triacetoxyborohydride. The resulting suspension is allowed to warm to ambient temperature and stirred for 5 hours. Brine (10 mL) is added and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 to 10% MeOH in DCM to give the product as a white solid. MS(ESI) *m/z* = 407.32 (M+1).

147-D. 3-[5-(4-{[(Tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-phenyl)-isoxazol-3-yl]-benzoic acid.



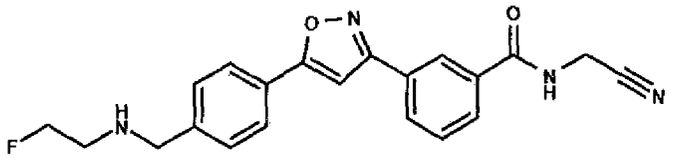
To a micture of **147-C** (82 mg, 0.20 mmol) in THF (2 mL) and water (1 mL) is added lithium hydroxide monohydrate (17 mg, 0.40 mmol) in one portion. The mixture is stirred at ambient temperature until conversion is judged to be complete. The solvents are evaporated at reduced pressure to afford product as a white solid, contaminated with residual lithium hydroxide. MS(ESI) *m/z* = 393.31 (M+1).

147-E. N-Cyanomethyl-3-[5-(4-{[(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-phenyl)-isoxazol-3-yl]-benzamide.



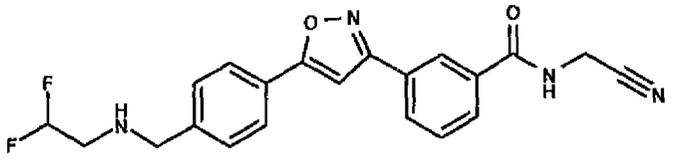
The title compound is prepared by methods similar to those utilized for the preparation of compound 125-C. MS(ESI) *m/z* = 431.2075 (M+1). HPLC R_t = 13.43 min.

Example 148. N-Cyanomethyl-3-(5-{4-[(2-fluoro-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



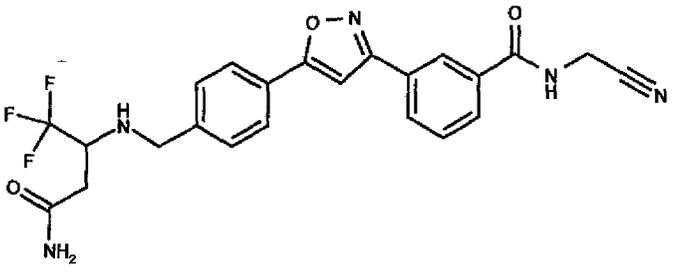
The title compound is prepared by methods similar to those utilized for the preparation of compound **147-E**. MS(ESI) *m/z* = 379.1571 (M+1). HPLC R_t = 9.62 min.

Example 149. N-Cyanomethyl-3-(5-{4-[(2,2-difluoro-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



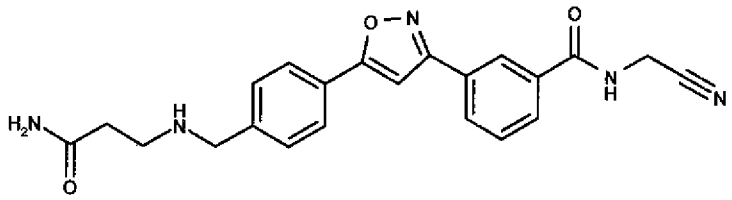
The title compound is prepared by methods similar to those utilized for the preparation of compound **147-E**. MS(ESI) *m/z* = 397.1471 (M+1). HPLC R_t = 10.01 min.

Example 150. 3-(5-{4-[(1-Carbamoylmethyl-2,2,2-trifluoro-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-cyanomethyl-benzamide.



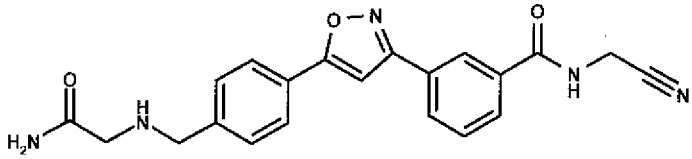
The title compound is prepared by methods similar to those utilized for the preparation of compound **147-E**. MS(ESI) *m/z* = 472.1594 (M+1). HPLC R_t = 11.08 min.

Example 151. 3-(5-{4-[(2-Carbamoyl-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-cyanomethyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **147-E**. MS(ESI) *m/z* = 404.1715 (M+1). HPLC R_t = 9.47 min.

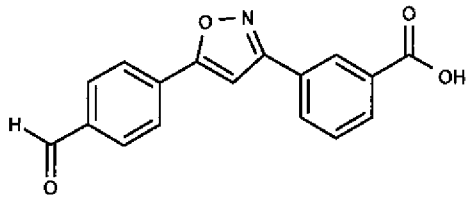
Example 152. 3-(5-{4-[(Carbamoylmethyl-amino)-methyl]-phenyl}-isoxazol-3-yl)-N-cyanomethyl-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **147-E**. MS(ESI) *m/z* = 390.1583 (M+1). HPLC R_t = 9.30 min.

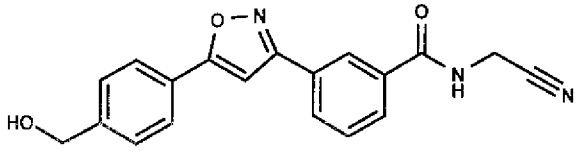
Example 153. N-Cyanomethyl-3-[5-(4-hydroxymethyl-phenyl)-isoxazol-3-yl]-benzamide.

153-A. 3-[5-(4-Formyl-phenyl)-isoxazol-3-yl]-benzoic acid.



The title compound is prepared by methods similar to those utilized for the preparation of compound **108-C**. MS(ESI) *m/z* = 294.3 (M+1).

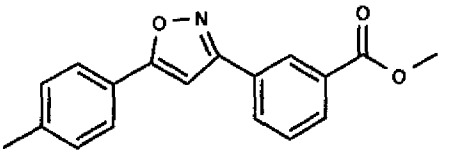
153-B. N-Cyanomethyl-3-[5-(4-hydroxymethyl-phenyl)-isoxazol-3-yl]-benzamide.



To a solution of **153-A** (200 mg, 0.65 mmol) in DMF (4 mL) is added DIPEA (113 uL, 0.65 mmol), aminoacetonitrile (55 uL, 0.785 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (296 mg, 0.78 mmol). The mixture is stirred at ambient temperature until conversion is judged to be complete. Water (5 mL) is added and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 334.1194 (M+1). HPLC R_t = 11.68 min.

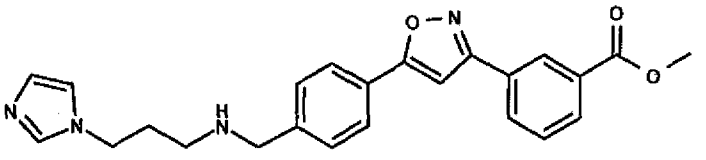
Example 154. N-(Cyano-methyl-methyl)-3-(5-{4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.

154-A. 3-(5-p-Tolyl-isoxazol-3-yl)-benzoic acid methyl ester



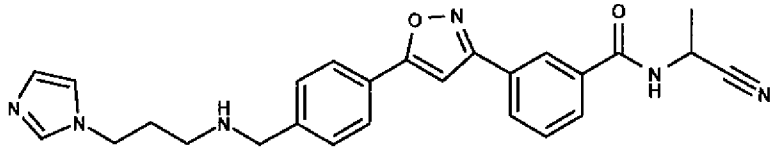
The title compound is prepared by methods similar to those utilized for the preparation of compound **147-B**. MS(ESI) *m/z* = 294.3 (M+1)

154-B. 3-(5-{4-[(3-Imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzoic acid methyl ester.



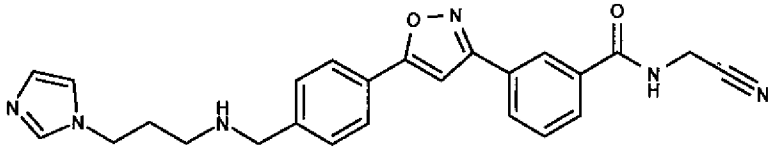
To a solution of **154-A** (1.32 g, 4.5 mmol) in carbon tetrachloride (8 mL) are added NBS (1.2 g, 6.8 mmol) and AIBN (74 mg, 0.45 mmol). The mixture is stirred and heated in an 80°C oil bath until conversion is judged to be complete. The mixture is allowed to cool to ambient temperature and N-(3-aminopropyl)imidazole (2.68 mL, 22.5 mmol) is added to the solution. The mixture is stirred overnight at ambient temperature until conversion of the intermediate benzylic bromide is judged to be complete. The mixture is concentrated under reduced pressure and the residue is purified by flash column chromatography with 0% to 6% MeOH in DCM to give the product as a white solid. MS(ESI) *m/z* = 417.3 (M+1).

154-C. N-(Cyano-methyl-methyl)-3-(5-{4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



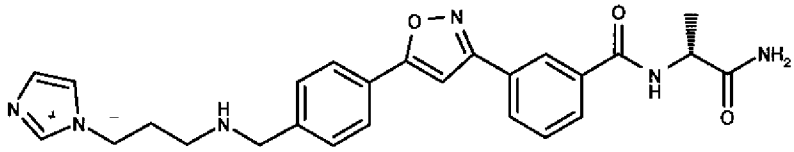
The title compound is prepared by methods similar to those utilized for the preparation of compound **147-E**. MS(ESI) *m/z* = 455.2206 (M+1). HPLC R_t = 9.88 min.

Example 155. N-Cyanomethyl-3-(5-{4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



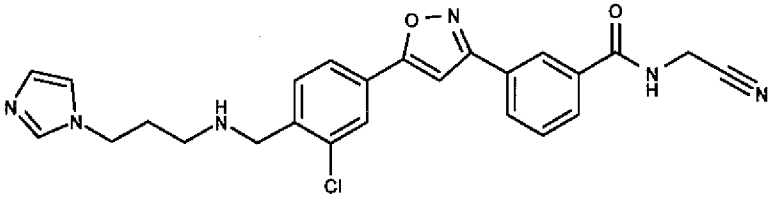
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 441.2045 (M+1). HPLC R_t = 8.67 min.

Example 156. N-((R)-1-Carbamoyl-ethyl)-3-(5-{4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



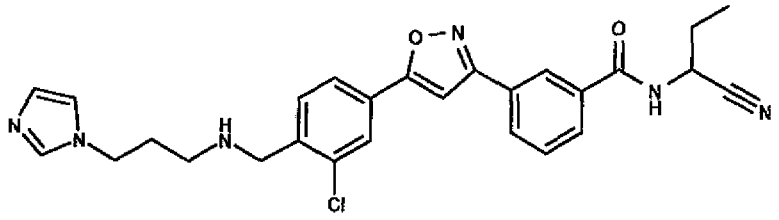
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 473.2320 (M+1). HPLC R_t = 7.89 min.

Example 157. 3-(5-{3-Chloro-4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-cyanomethyl-benzamide.



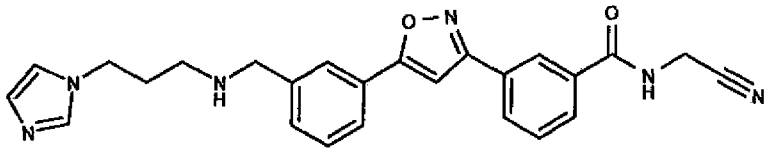
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 475.1654 (M+1). HPLC R_t = 9.00 min.

Example 158. 3-(5-{3-Chloro-4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-(1-cyano-propyl)-benzamide.



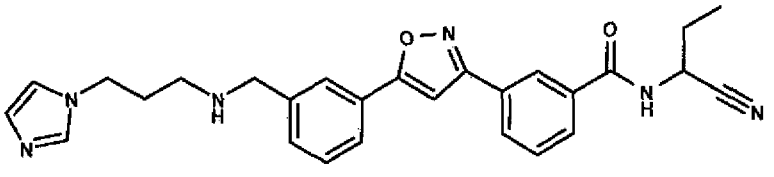
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 503.1955 (M+1). HPLC R_t = 9.99 min.

Example 159. N-Cyanomethyl-3-(5-{3-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



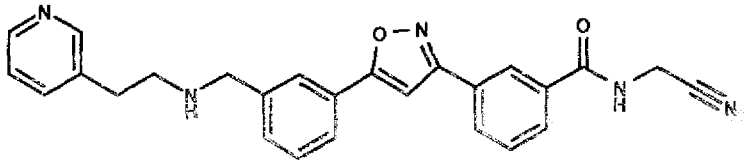
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 441.2039 (M+1). HPLC R_t = 8.91 min.

Example 160. N-(1-Cyano-propyl)-3-(5-{3-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



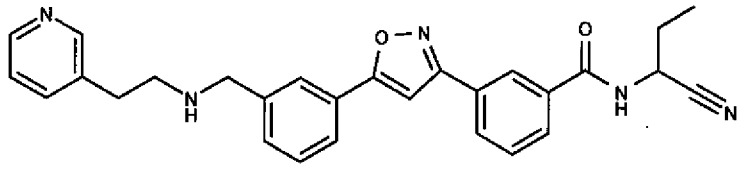
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 469.2362 (M+1). HPLC R_t = 10.10 min.

Example 161. N-Cyanomethyl-3-(5-{3-[(2-pyridin-3-yl-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



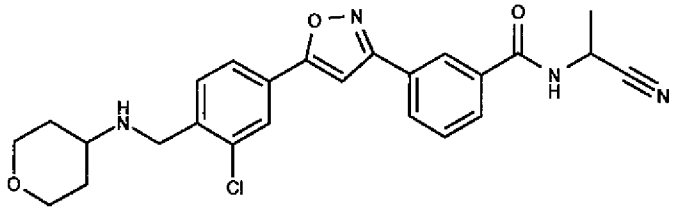
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 438.1939 (M+1). HPLC R_t = 8.93 min.

Example 162. N-(1-Cyano-propyl)-3-(5-{3-[(2-pyridin-3-yl-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



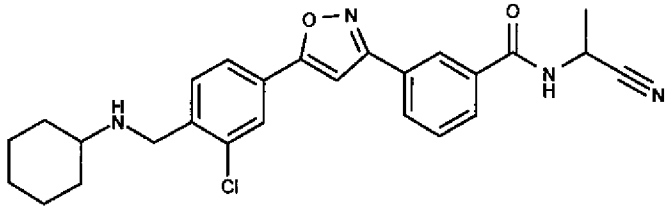
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 466.2257 (M+1). HPLC R_t = 9.81 min.

Example 163. 3-(5-{3-Chloro-4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-(cyano-methyl-methyl)-benzamide.



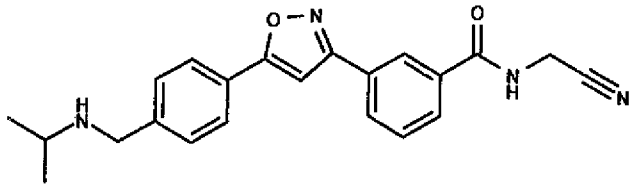
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 465.1711 (M+1). HPLC R_t = 11.74 min.

Example 164. 3-[5-(3-Chloro-4-cyclohexylaminomethyl-phenyl)-isoxazol-3-yl]-N-(cyano-methyl-methyl)-benzamide.



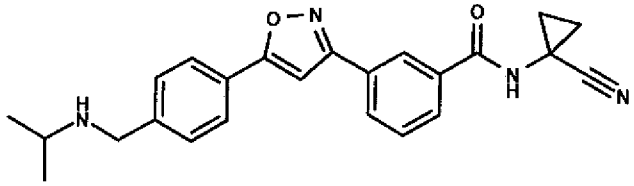
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 463.1902 (M+1). HPLC R_t = 13.39 min.

Example 165. N-Cyanomethyl-3-{5-[4-(isopropylamino-methyl)-phenyl]-isoxazol-3-yl}-benzamide.



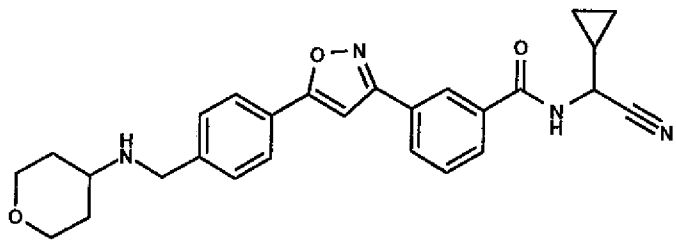
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 375.1825 (M+1). HPLC R_t = 12.01 min.

Example 166. N-(1-Cyano-cyclopropyl)-3-{5-[4-(isopropylamino-methyl)-phenyl]-isoxazol-3-yl}-benzamide.



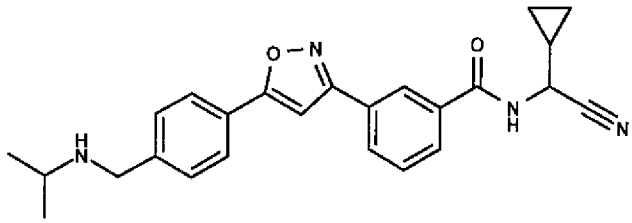
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 401.1970 (M+1). HPLC R_t = 12.20 min.

Example 167. N-(Cyano-cyclopropyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



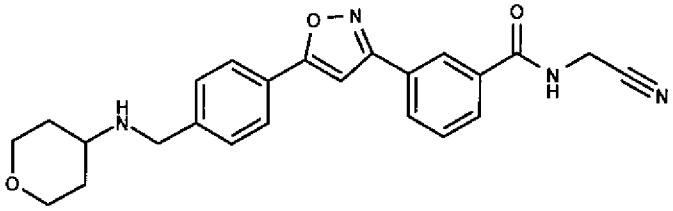
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 471.2396 (M+1). HPLC R_t = 13.80 min.

Example 168. N-(Cyano-cyclopropyl-methyl)-3-{5-[4-(isopropylamino-methyl)-phenyl]-isoxazol-3-yl}-benzamide.



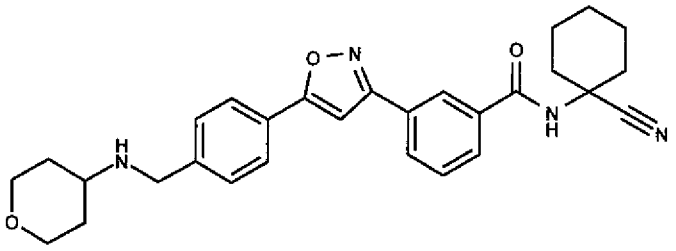
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 415.2130 (M+1). HPLC R_t = 13.80 min.

Example 169. N-Cyanomethyl-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



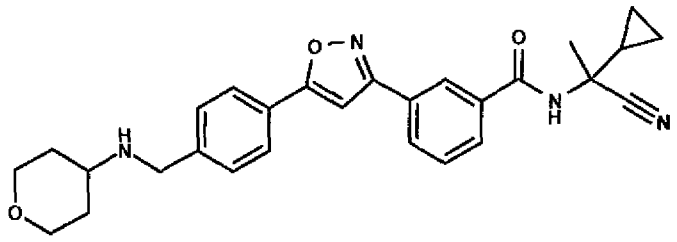
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 417.1931 (M+1). HPLC R_t = 9.43 min.

Example 170. N-(1-Cyano-cyclohexyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



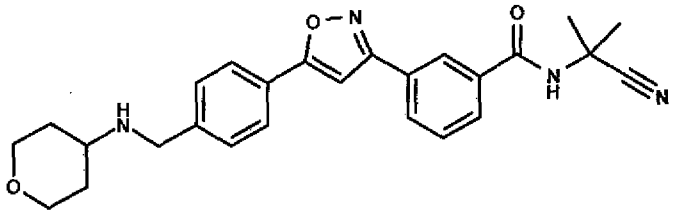
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 485.2545 (M+1). HPLC R_t = 11.46 min.

Example 171. N-(Cyano-cyclopropyl-methyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



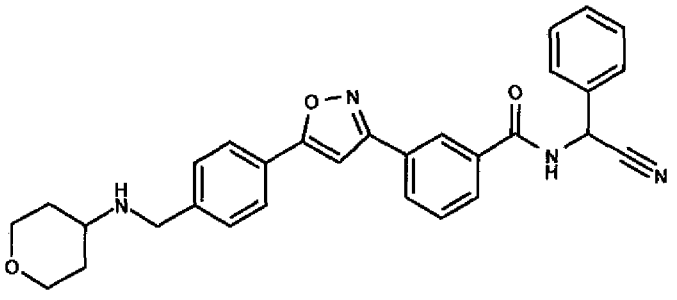
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 471.2397 (M+1). HPLC R_t = 10.98 min.

Example 172. N-(Cyano-dimethyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



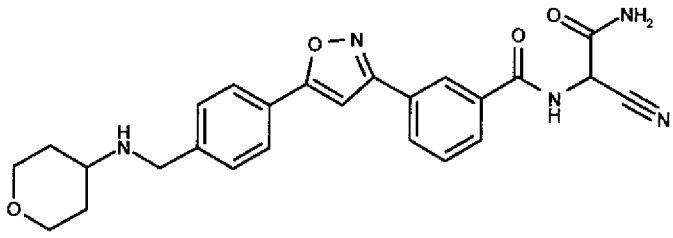
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 445.2220 (M+1). HPLC R_t = 10.23 min.

Example 173. N-(Cyano-phenyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



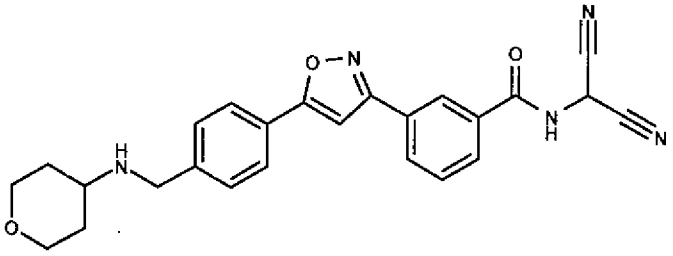
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 493.2236 (M+1). HPLC R_t = 11.72 min.

Example 174. N-(Carbamoyl-cyano-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



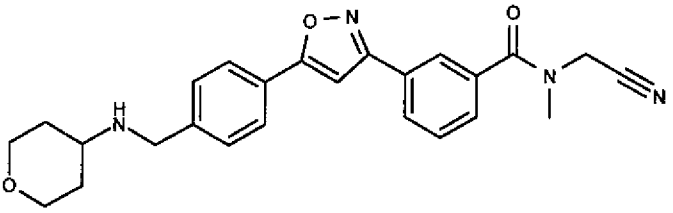
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 460.1989 (M+1). HPLC R_t = 8.78 min.

Example 175. N-Dicyanomethyl-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 442.1871 (M+1). HPLC R_t = 10.87 min.

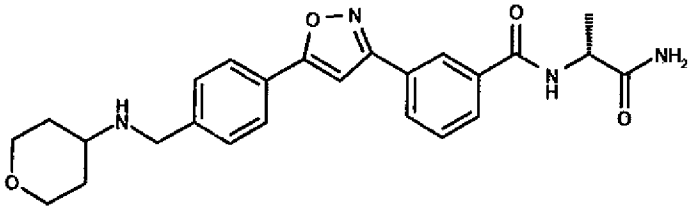
Example 176. N-Cyanomethyl-N-methyl-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 431.2079 (M+1). HPLC R_t = 9.63 min.

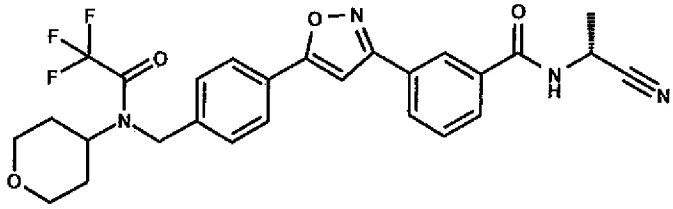
Example 177. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.

177-A. N-((R)-1-Carbamoyl-ethyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



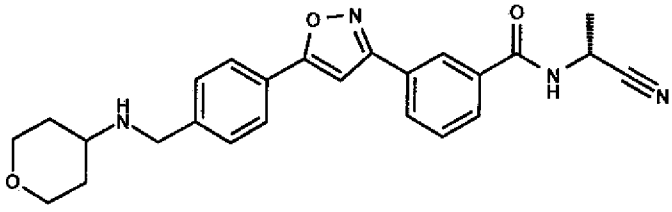
The title compound is prepared by methods similar to those utilized for the preparation of compound **154-C**. MS(ESI) *m/z* = 449.4 (M+1),

177-B. N-((R)-Cyano-methyl-methyl)-3-[5-(4-{[(tetrahydro-pyran-4-yl)-(2,2,2-trifluoro-acetyl)-amino]-methyl}-phenyl)-isoxazol-3-yl]-benzamide.



To a solution of compound **177-A** (74 mg, 0.19 mmol) in anhydrous THF (2 mL), which is pre-cooled in an ice water bath, are added dropwise triethyl amine (80 uL, 0.57 mmol) and trifluoroacetic anhydride (53 uL, 0.38 mmol). When conversion is judged to be complete, saturated aqueous sodium bicarbonate solution (5 mL) is added and the aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by flash column chromatography with 0 to 5% MeOH in DCM to give the product as an oil. MS(ESI) *m/z* = 527.4 (M+1)

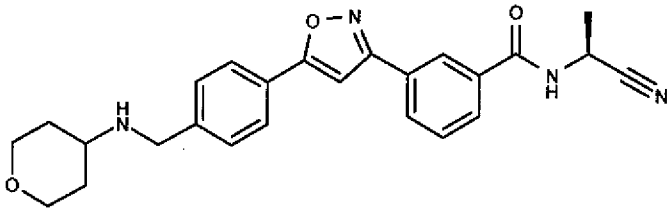
177-C. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



To a solution of compound **177-B** (63.7 mg, 0.12 mmol) in anhydrous methanol (1.5 mL), which is pre-cooled in an ice water bath, is added sodium borohydride (6 mg, 0.16 mmol).

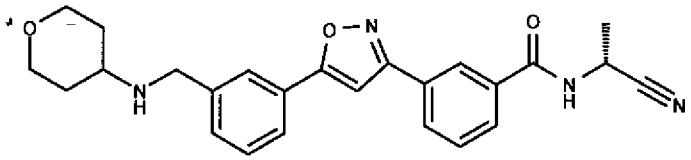
The mixture is stirred for two hours. Saturated aqueous sodium bicarbonate solution is added and the aqueous phase is extracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 431.2094 (M+1). HPLC R_t = 11.72 min, ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm: 9.35 (1H), 8.42 (1H), 8.13 (1H), 8.03 (1H), 7.88 (2H), 7.71 (1H), 7.65 (1H), 7.55 (2H), 5.04 (1H), 3.83 (2H), 3.81 (2H), 3.26 (2H), 2.61 (1H), 2.19 (1H), 1.79 (2H), 1.59 (3H), 1.29 (2H) ppm.

Example 178. N-((S)-Cyano-methyl-methyl)-3-(5-{4-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



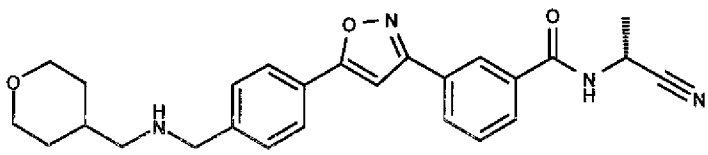
The title compound is prepared by methods similar to those utilized for the preparation of compound **177-C**. MS(ESI) *m/z* = 431.2083 (M+1). HPLC R_t = 12.10 min.

Example 179. N-((R)-Cyano-methyl-methyl)-3-(5-{3-[(tetrahydro-pyran-4-ylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



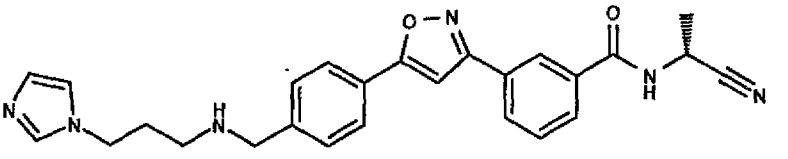
The title compound is prepared by methods similar to those utilized for the preparation of compound **177-C**. MS(ESI) *m/z* = 431.2077 (M+1). HPLC R_t = 12.34 min.

Example 180. N-((R)-Cyano-methyl-methyl)-3-[5-(4-{[(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-phenyl)-isoxazol-3-yl]-benzamide.



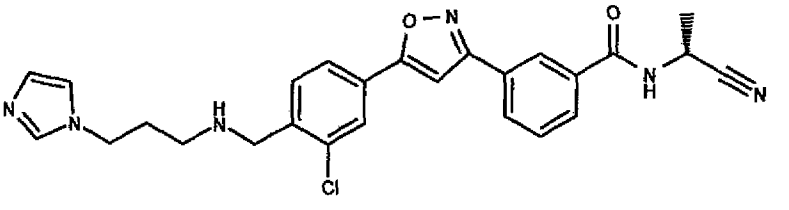
The title compound is prepared by methods similar to those utilized for the preparation of compound **177-C**. MS(ESI) *m/z* = 445.2234 (M+1). HPLC R_t = 10.19 min.

Example 181. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **177-C**. MS(ESI) *m/z* = 455.2205 (M+1). HPLC R_t = 9.94 min.

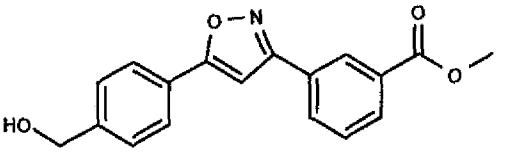
Example 182. 3-(5-{3-Chloro-4-[(3-imidazol-1-yl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-((R)-cyano-methyl-methyl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **177-C**. MS(ESI) *m/z* = 489.1801 (M+1). HPLC R_t = 9.87 min, ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm: 9.27 (1H), 8.35 (1H), 8.05 (1H), 7.96 (1H), 7.94 (1H), 7.82 (1H), 7.73 (1H), 7.65 (1H), 7.63 (1H), 7.53 (1H), 7.09 (1H), 6.80 (1H), 4.97 (1H), 3.98 (2H), 3.74 (2H), 3.22 (2H), 2.26 (1H), 1.82 (2H), 1.51 (3H) ppm.

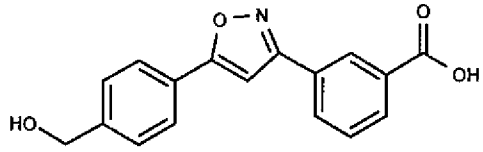
Example 183. N-((R)-Cyano-methyl-methyl)-3-[5-(4-hydroxymethyl-phenyl)-isoxazol-3-yl]-benzamide.

183-A. 3-[5-(4-Hydroxymethyl-phenyl)-isoxazol-3-yl]-benzoic acid methyl ester.



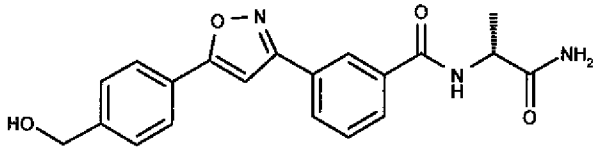
The title compound is prepared by methods similar to those utilized for the preparation of compound **147-B**. MS(ESI) *m/z* = 310.2 (M+1).

183-B. 3-[5-(4-Hydroxymethyl-phenyl)-isoxazol-3-yl]-benzoic acid.



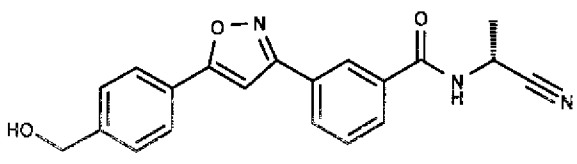
To a mixture of compound **183-A** (4.19 g, 13.60 mmol) in THF (100 mL) and water (10 mL) is added lithium hydroxide monohydrate (5.73 g, 136.6 mmol). The reaction is stirred at ambient temperature until conversion is judged to be complete. The reaction is diluted with 1N aqueous HCl solution (100 mL), and the mixture is concentrated under reduced pressure to 100 mL. The resulting suspension is centrifuged, and the supernatant discarded. The pelletted material is re-suspended in water and centrifuged, and the supernatant is discarded. The pelleted material is collected and dried under reduced pressure to provide product as a white solid. MS(ESI) *m/z* = 296.2 (M+1).

183-C. N-((R)-1-Carbamoyl-ethyl)-3-[5-(4-hydroxymethyl-phenyl)-isoxazol-3-yl]-benzamide.



To a mixture of compound **183-B** (4.04 g, 13.7 mmol), (R)-2-amino-propionamide hydrochloride (3.35 g, 26.9 mmol), and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (7.72 g, 20.3 mmol) in N,N-dimethylformamide (25 mL) is added DIPEA (7.0 mL, 40.3 mmol). The reaction is stirred at ambient temperature until conversion is judged to be complete. The mixture is diluted with water (100 mL) and 1N aqueous HCl solution (80 mL). The resulting precipitate is collected by centrifugation, and the supernatant is discarded. The pelleted solid is washed with water, 0.25 N aqueous NaOH solution, and water. The solid is dried under reduced pressure to provide product. MS(ESI) *m/z* = 366.3 (M+1).

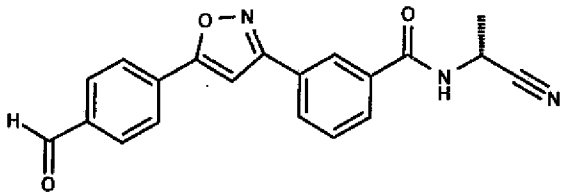
183-D. N-((R)-Cyano-methyl-methyl)-3-[5-(4-hydroxymethyl-phenyl)-isoxazol-3-yl]-benzamide.



To a solution of compound **183-C** (100 mg, 0.27 mmol) in anhydrous THF (3 mL), which is pre-cooled in an ice-water bath, is added dropwise triethyl amine (37 uL, 0.27 mmol) followed by trifluoroacetic anhydride (38 uL, 0.28 mmol). When conversion is judged to be complete the reaction is allowed to warm to ambient temperature and saturated aqueous sodium carbonate solution (1 mL) is added. The mixture is stirred for 10 min to deprotect the benzylic alcohol. The aqueous phase is extracted with ethyl acetate (20 mL x 3). The organic phases are combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 348.1342 (M+1). HPLC R_t = 11.53 min.

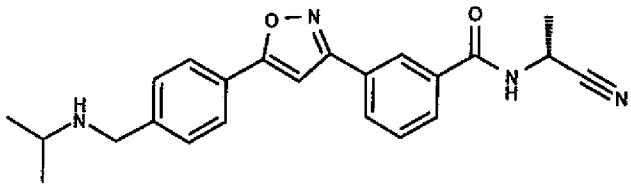
Example 184. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(isopropylamino-methyl)-phenyl]-isoxazol-3-yl}-benzamide.

184-A. N-((R)-Cyano-methyl-methyl)-3-[5-(4-formyl-phenyl)-isoxazol-3-yl]-benzamide.



To a solution of compound **183-D** (3.58 g, 9.8 mmol) in anhydrous DMSO (10 mL) is added triethyl amine (8.6 mL, 63 mmol) followed by sulfur trioxide-pyridine complex (4.7 g). The mixture is stirred at ambient temperature until conversion is judged to be complete. Water is added to the mixture, resulting in the formation of a white precipitate. The mixture is filtered and the solid residue is washed with water (3 x) followed by acetonitrile to afford product as a white solid. MS(ESI) *m/z* = 346.25 (M+1).

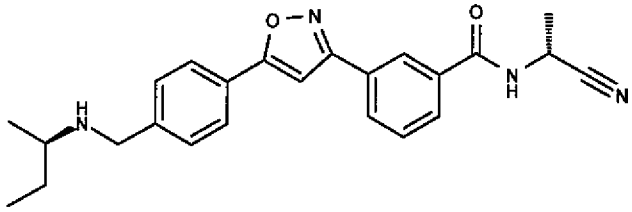
184-B. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(isopropylamino-methyl)-phenyl]-isoxazol-3-yl}-benzamide.



To a solution of **184-A** (2.93 g, 8.49 mmol) in anhydrous methanol (30 mL) is added isopropylamine (2.2 mL, 25.5 mmol) dropwise. The mixture is stirred at ambient temperature

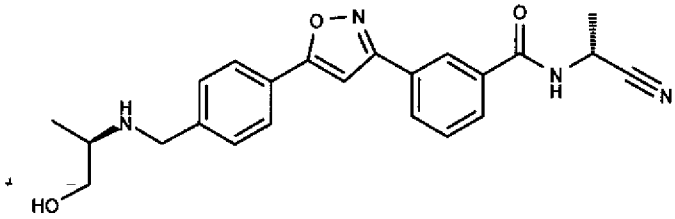
until imine formation is judged to be complete. The mixture is cooled in an ice water bath and sodium borohydride (516 mg, 13.6 mmol) is added. The mixture is allowed to warm to ambient temperature, and is stirred for one hour. Acetone is added to quench the reaction, and the mixture is purified by reversed phase HPLC to provide product as a white powder. MS(ESI) *m/z* = 389.1982 (M+1). HPLC R_t = 11.38 min.

Example 185. 3-(5-{4-[((R)-sec-Butylamino)-methyl]-phenyl}-isoxazol-3-yl)-N-((R)-cyano-methyl-methyl)-benzamide.



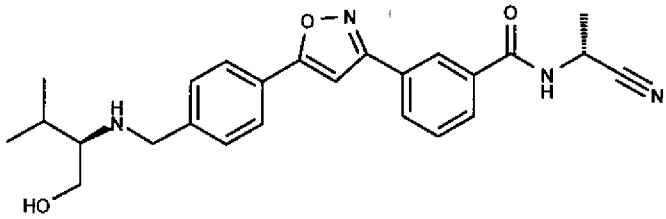
The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 403.2132 (M+1). HPLC R_t = 10.30 min.

Example 186. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[((R)-2-hydroxy-1-methyl-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



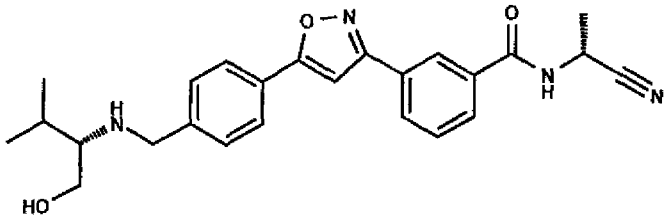
The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 405.1908 (M+1). HPLC R_t = 9.47 min.

Example 187. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[((R)-1-hydroxymethyl-2-methyl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



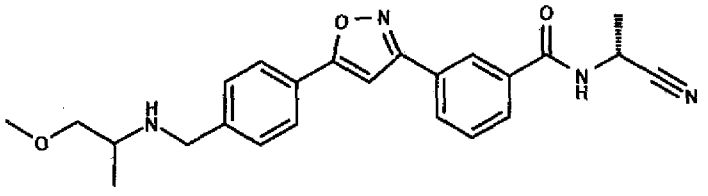
The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 433.2243 (M+1). HPLC R_t = 10.17 min.

Example 188. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[((S)-1-hydroxymethyl-2-methyl-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



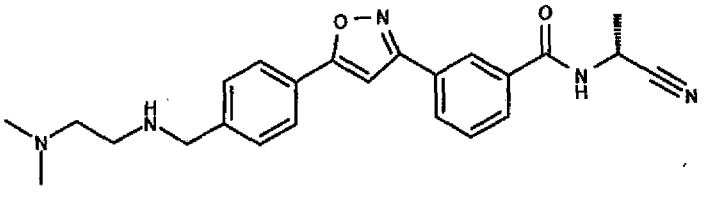
The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 433.2243 (M+1). HPLC R_t = 10.16 min.

Example 189. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(2-methoxy-1-methyl-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



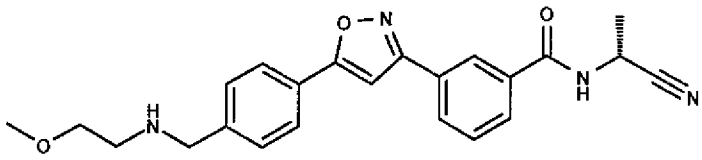
The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 419.2095 (M+1). HPLC R_t = 15.44 min (X-bridge RP-18, 4.6 mm x 150 mm, 3.5 um packing. 10% to 100% acetonitrile in 10 mM aqueous ammonia solution over 20 minutes, 1 mL/min).

Example 190. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(2-dimethylamino-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



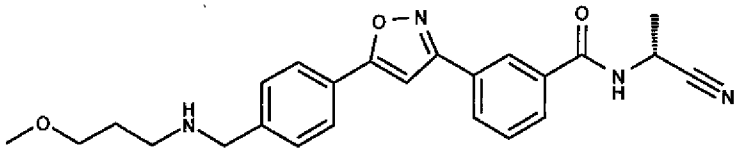
The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 418.2246 (M+1). HPLC R_t = 14.69 min (X-bridge RP-18, 4.6 mm x 150 mm, 3.5 um packing. 10% to 100% acetonitrile in 10 mM aqueous ammonia solution over 20 minutes, 1 mL/min).

Example 191. N-((R)-Cyano-methyl-methyl)-3-{5-{4-[(2-methoxy-ethylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 405.1924 (M+1). HPLC R_t = 14.50 min (X-bridge RP-18, 4.6 mm x 150 mm, 3.5 um packing. 10% to 100% acetonitrile in 10 mM aqueous ammonia solution over 20 minutes, 1 mL/min).

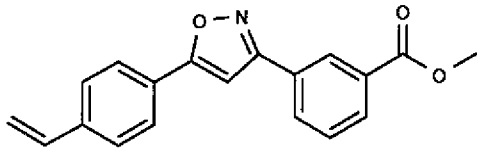
Example 192. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[(3-methoxy-propylamino)-methyl]-phenyl}-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **184-B**. MS(ESI) *m/z* = 419.2074 (M+1). HPLC R_t = 14.89 min (X-bridge RP-18, 4.6 mm x 150 mm, 3.5 um packing. 10% to 100% acetonitrile in 10 mM aqueous ammonia solution over 20 minutes, 1 mL/min).

Example 193. 3-{5-[4-(1-Hydroxy-2-isopropylamino-ethyl)-phenyl]-isoxazol-3-yl}-benzoic acid methyl ester.

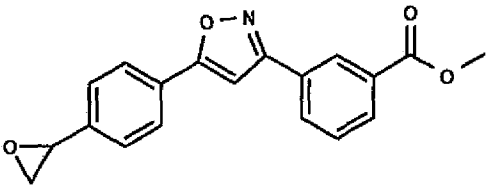
193-A. 3-[5-(4-Vinyl-phenyl)-isoxazol-3-yl]-benzoic acid methyl ester.



To a solution of **118-A** (0.4 g, 1.12 mmol) in dimethoxy ethane (15 mL) and water (3 mL) in a heavy walled glass vial, are added $Pd(dppf)_2Cl_2$ (0.08 g, 0.11 mmol), cesium carbonate (1.1g, 3.36 mmol) and potassium vinyltrifluoroborate (0.22 g, 1.68 mmol). The vial is sealed and inserted into a microwave reactor. The reaction is run under microwave irradiation for 15 min at 130 °C. When the reaction is complete, the mixture is filtered through celite and the

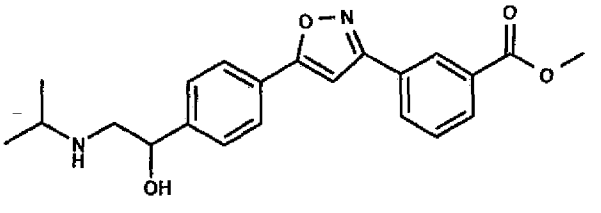
residue is washed with DCM. The combined filtrates are concentrated under reduced pressure and the residue is purified by flash column chromatography with 20% ethyl acetate in heptane to afford the product as a pale yellow solid. MS(ESI) *m/z* = 306.1 (M+1).

193-B. 3-[5-(4-Oxiranyl-phenyl)-isoxazol-3-yl]-benzoic acid methyl ester.



To a solution of **193-A** (0.10 g, 0.33 mmol) in DCM (3 mL), which is precooled in an ice water bath, is added MCPBA (0.084 g, 0.49 mmol). The mixture is allowed to warm to ambient temperature and stirred until conversion is judged to be complete. Aqueous sodium hydrogen sulfite solution is added to quench the reaction. The mixture is diluted with DCM and the organic layer is washed with sodium bicarbonate and brine. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford the product as a pale yellow solid. MS(ESI) *m/z* = 322.3 (M+1).

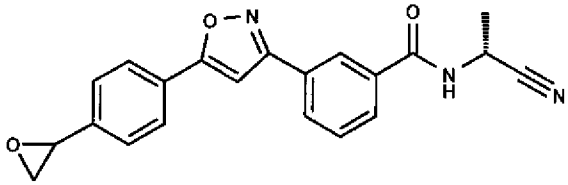
193-C. 3-{5-[4-(1-Hydroxy-2-isopropylamino-ethyl)-phenyl]-isoxazol-3-yl}-benzoic acid methyl ester.



To a solution of **193-B** (0.14 g, 0.44 mmol) in THF (3 mL) are added isopropylamine (78 uL, 0.88 mmol) and lithium perchlorate (94 mg, 0.88 mmol) . The mixture is stirred at ambient temperature for two days. The reaction is diluted with water and dichloromethane. The organic phase is washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue is purifed by RP-HPLC to provide product as a white solid. MS(ESI) *m/z* = 381.1814 (M+1). HPLC R_t = 11.75 min.

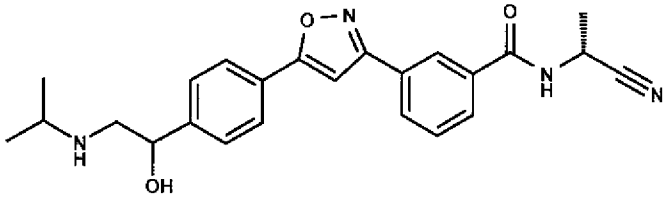
Example 194. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(1-hydroxy-2-isopropylamino-ethyl)-phenyl]-isoxazol-3-yl}-benzamide.

194-A. N-((R)-Cyano-methyl-methyl)-3-[5-(4-oxiranyl-phenyl)-isoxazol-3-yl]-benzamide.



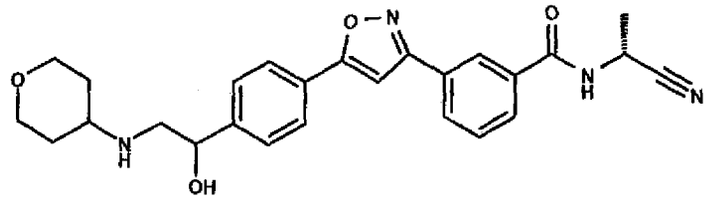
To a suspension of sodium hydride (40 mg, 1.67 mmol) in dimethylsulfoxide (1 mL) is added trimethylsulfonium iodide (225 mg, 1.10 mmol), followed by dimethylsulfoxide (2 mL). The reaction is stirred at ambient temperature for 30 min. Compound **184-A** (270 mg, 0.78 mmol) is added, followed by dimethylsulfoxide (2 mL). When conversion is judged to be complete, water (100 mL) and saturated aqueous ammonium chloride solution (100 mL) are added. The aqueous suspension is extracted with ethyl acetate (4 x 150 mL). The combined organic extracts are divided into two portions, each of which is washed with saturated sodium chloride solution (2 x 200 mL). The organics are recombined, dried over sodium sulfate, and filtered. The filtrate is concentrated under reduced pressure to provide product as a pale yellow solid. MS(ESI) *m/z* = 360.3 (M+1)

194-B. N-((R)-Cyano-methyl-methyl)-3-{5-[4-(1-hydroxy-2-isopropylamino-ethyl)-phenyl]-isoxazol-3-yl}-benzamide



Compound **194-A** (45 mg) is taken into isopropylamine (2.0 mL). The reaction vessel is sealed and the reaction is stirred at ambient temperature. When the reaction reaches 80% conversion by LCMS analysis, dimethylsulfoxide (8 mL) is added and the mixture is purified by RP-HPLC to provide product as a white solid. MS(ESI) *m/z* = 419.2083 (M+1). HPLC R_t = 9.89 min, ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm: 9.33 (1H), 8.42 (1H), 8.13 (1H), 8.02 (1H), 7.89 (2H), 7.70 (1H), 7.65 (1H), 7.56 (2H), 5.43 (1H), 5.04 (1H), 1.26 (1H), 2.74 (2H), 2.64 (2H), 1.58 (3H), 0.98 (6H).

Example 195. N-((R)-Cyano-methyl-methyl)-3-(5-{4-[1-hydroxy-2-(tetrahydro-pyran-4-ylamino)-ethyl]-phenyl}-isoxazol-3-yl)-benzamide.



The title compound is prepared by methods similar to those utilized for the preparation of compound **194-B**. MS(ESI) *m/z* = 461.2188 (M+1). HPLC R_t = 9.67 min.

Example 196. *In Vitro* Assays for PKD Inhibition

196-A. PKD1 assay.

The assay to measure protein kinase D1 (PKD1) activity is a time-resolved fluorescence resonance transfer (TR-FRET) assay using PerkinElmer's LANCE™ technology. In this case, a biotinylated syntide-2 peptide is used as the substrate in this reaction. Phosphorylation of the syntide-2 substrate is detected by a specific antibody that recognizes the phosphorylated peptide. A second flurophore, APC, is conjugated to streptavidin that binds the biotinylated syntide-2 peptide. For detection, the europium fluorophore can be excited by 340nM light which then emits at 615 nM. Therefore, when the europium labeled secondary antibody binds on the phosphorylated peptide, it is brought into close contact with the APC and excites this fluorophore. ThE APC emission is at 665 nM and the 665 nM:615 nM ratio is a readout of PKD1 activity.

This assay is performed with full length wild-type enzyme that is expressed and purified from Sf9 insect cells. The reaction buffer consists of 35mM Tris-HCl pH7.5, 5mM $MgCl_2$, 0.02% Tween-20, 20 μM ATP, 1 mM DTT and 0.2 μg/mL PKD1 enzyme. The enzyme reaction is initiated by the addition of 2 μM syntide-2 peptide substrate and the reaction carried out for 50 minutes at room temperature. The reaction is stopped by a stop/detection buffer consisting of 50 mM EDTA, 0.18 mg/mL rabbit polyclonal anti-phospho Syntide-2 antibody, 0.5 nM europium labeled anti-rabbit IgG and 10 nM streptavidin conjugated APC. After a one hour incubation with the stop/detection buffer, the reaction is read on an Envision 2100 reader using a LANCE™ Eu/APC dual protocol. As described above, a 665 nM:615 nM ratio is determined to measure substrate phosphorylation and enzyme activity. Compounds are typically tested in an 11 point dose response fashion in triplicate for each concentration used. IC_{50} values are calculated using an activity base (IDBS) software program.

196-B. PKD2 assay.

The assay to measure protein kinase D2 (PKD2) activity is a time-resolved fluorescence resonance transfer (TR-FRET) assay using PerkinElmer's LANCE™ technology. In this case, a biotinylated syntide-2 peptide is used as the substrate in this reaction. Phosphorylation of the syntide-2 substrate is detected by a specific antibody that recognizes the phosphorylated peptide. A second flurophore, APC, is conjugated to streptavidin that binds the biotinylated syntide-2 peptide. For detection, the europium fluorophore can be excited by 340nM light which then emits at 615 nM. Therefore, when the europium labeled secondary antibody binds on the phosphorylated peptide, it is brought into close contact with the APC and excites this fluorophore. The APC emission Is at 665nM and the 665 nM:615 nM ratio is a readout of PKD2 activity.

This assay is performed with full length wild-type enzyme purchase from Invitrogen. The reaction buffer consists of 35 mM Tris-HCl pH7.5, 5 mM $MgCl_2$, 0.02% Tween-20, 20 μM atP, 1 mM DTT and 0.2 μg/mL PKD2 enzyme. The enzyme reaction is initiated by the addition of 2 μM syntide-2 peptide substrate and the reaction carried out for 50 minutes at room temperature. The reaction is stopped by a stop/detection buffer consisting of 50 mM EDTA, 0.18 mg/mL rabbit polyclonal anti-phospho Syntide-2 antibody, 0.5 nM europium labeled anti-rabbit IgG and 10 nM streptavidin conjugated APC. After a one hour incubation with the stop/detection buffer, the reaction is read on an Envision 2100 reader using a LANCE™ Eu/APC dual protocol. As described above, a 665 nM:615 nM ratio is determined to measure substrate phosphorylation and enzyme activity. Compounds are typically tested in an 11 point dose response fashion in triplicate for each concentration used. IC_{50} values are calculated using an activity base (IDBS) software program.

196-C. PKD3 assay.

The assay to measure protein kinase D3 (PKD3) activity is a time-resolved fluorescence resonance transfer (TR-FRET) assay using PerkinElmer's LANCE™ technology. In this case, a biotinylated syntide-2 peptide is used as the substrate in this reaction. Phosphorylation of the syntide-2 substrate is detected by a specific antibody that recognizes the phosphorylated peptide. A second flurophore, APC, is conjugated to streptavidin that binds the biotinylated syntide-2 peptide. For detection, the europium fluorophore can be excited by 340nM light which then emits at 615 nM. Therefore, when the europium labeled secondary antibody binds on the phosphorylated peptide, it is brought into

close contact with the APC and excites this fluorophore. The APC emission is at 665 nM and the 665 nM:615 nM ratio is a readout of PKD3 activity.

This assay is performed with full length wild-type enzyme that is purchased from Invitrogen. The reaction buffer consists oF 35 mM Tris-HCl pH7.5, 5mM $MgCl_2$, 0.02% Tween-20, 20 μM atP, 1 mM DTT and 0.2 μg/mL PKD3 enzyme. The enzyme reaction is initiated by the addition of 2 μM syntide-2 peptide substrate and the reaction carried out for 50 minutes at room temperature. The reaction is stopped by a stop/detection buffer consisting of 50 mM EDTA, 0.18 mg/mL rabbit polyclonal anti-phospho Syntide-2 antibody, 0.5 nM europium labeled anti-rabbit IgG and 10 nM streptavidin conjugated APC. After a one hour incubation with the stop/detection buffer, the reaction is read on an Envision 2100 reader using a LANCE™ Eu/APC dual protocol. As described above, a 665 nM:615 nM ratio is determined to measure substrate phosphorylation and enzyme activity. Compounds are typically tested in an 11 point dose response fashion in triplicate for each concentration used. IC_{50} values are calculated using an activity base (IDBS) software program.

196-D. HDAC5 nuclear export assay.

Compounds are evaluated in the HDAC5 nuclear export assay, a 384-well plate-based assay that enables high throughput screening (HTS) to identify small molecules that block agonist-dependent nuclear export of HDAC5. This assay employs the Cellomics High Content Imaging platform (Giuliano & Taylor 1998) and adenovirus encoding green fluorescent protein (GFP) tagged HDAC5. Neonatal rat ventricular myocytes (NRVMs) are infected with GFP-HDAC5 encoding virus and plated on gelatin-coated 384-well dishes. Cells are exposed to compound and stimulated with an prostaglandin (PGF2α), which is a potent stimulus for HDAC5 nuclear export. Following two hours of stimulation, cells are fixed and GFP-HDAC5 localization quantified using the Cellomics system, which provides a read-out of relative fluorescence intensity in the cytoplasmic versus nuclear compartment.

Table 1 Inhibitory Activity of Compounds

Compound of:	PKD1 (uM)	PKD2 (uM)	PKD3 (uM)	HDAC (uM)
Example 37	0.74	0.54	0.47	> 1.0
Example 105	0.64	0.42	0.50	> 1.0
Example 193	0.59	2.7	1.5	> 1.0
Example 108	0.50	0.53	0.45	> 1.0

Example 38	0.44	0.29	0.43	> 1.0
Example 26	0.34	0.76	0.82	> 1.0
Example 79	0.30	0.80	0.58	> 1.0
Example 106	0.27	0.41	0.41	> 1.0
Example 86	0.23	0.64	0.57	> 1.0
Example 126	0.21	0.72	0.75	> 1.0
Example 159	0.19	0.80	0.46	> 1.0
Example 122	0.14	0.20	0.29	
Example 91	0.084	0.23	0.25	> 1.0
Example 166	0.035	0.093	0.064	> 1.0
Example 182	0.026	0.15	0.057	0.42
Example 147	0.016	0.037	0.031	> 1.0
Example 194	0.014	0.065	0.037	0.35
Example 177	0.005	0.047	0.015	0.23
Example 69	0.006	0.052	0.014	0.35
Example 62	0.004	0.12	0.013	0.53

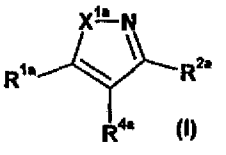
Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of the present invention and are covered by the following claims. The appropriate components, processes, and methods of those patents, applications and other documents may be selected for the present invention and embodiments thereof.

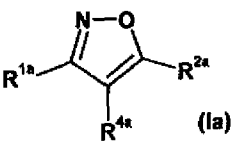
CLAIMS

We Claim:

1. The compound of formula (I) or (Ia):


(I)

or

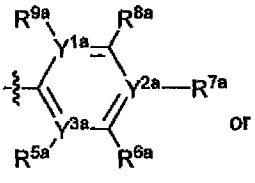

(Ia)

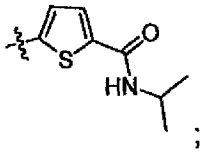
wherein:

X^{1a} is NR^{11a} or O;

R^{1a} is a substituted or unsubstituted aryl;

R^{2a} is:


or


;

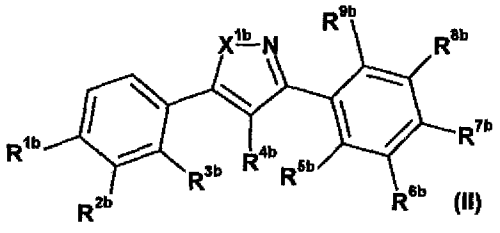
R^{5a}, R^{6a}, R^{7a}, R^{8a} and R^{9a} are each, independently, absent, hydrogen, halogen, alkyl, aminocarbonyl, carbonyl, heterocyclyl, hydroxyl, alkoxyl, amido or imino; R^{5a} and R^{6a} may be linked to form an aryl or heterocyclyl ring; R^{6a} and R^{7a} may be linked to form an aryl ring; R^{8a} and R^{9a} may be linked to form a lactam;

Y^{1a}, Y^{2a} and Y^{3a} are each, independently, N or C;

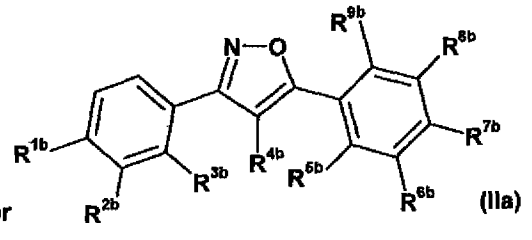
R^{11a} and R^{4a} are each, idependently, hydrogen, halogen or alkyl; and

pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

2. The compound of claim 1, wherein the compound is of formula (II) or (IIa):


(II)

or


(IIa)

wherein

X^{1b} is NR^{10b} or O;

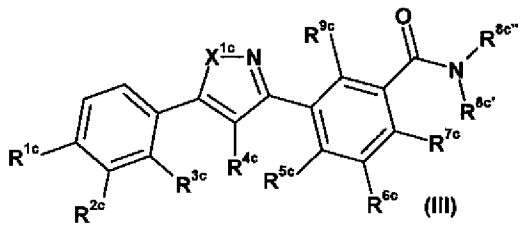
R^{1b} and R^{2b} are each independently hydrogen, alkyl, alkenyl, halogen, amino, amido, heterocyclyl or carbonyl;

R^{3b} is hydrogen or alkoxy;

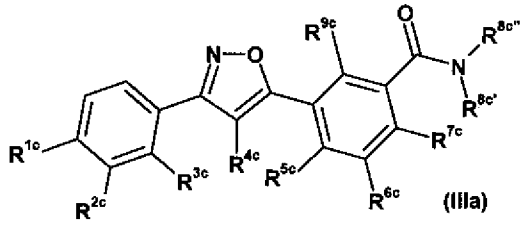
R^{5b} and R^{6b} are each hydrogen or R^{5b} and R^{6b} may be linked together to form an aryl or heterocyclyl ring;

R^{7b} and R^{8b} are each, independently, a hydrogen, aminocarbonyl, carbonyl or heterocyclyl or R^{6b} and R^{7b} may be linked together to form an aryl ring; R^{4b}, R^{9b} and R^{10b} are each, idependently, hydrogen, halogen, alkyl or alkoxy; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

3. The compound of any one of claims 1 or 2, wherein the compound is of formula (III):


(III)

or


(IIIa)

wherein

X^{1c} is NR^{10c} or O;

R^{1c} is heterocyclyl;

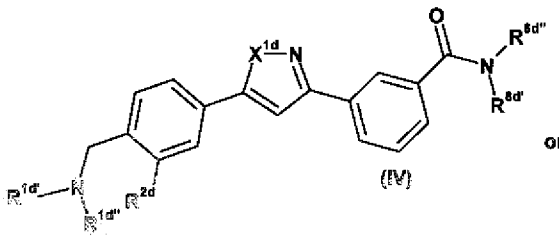
R^{2c}, R^{3c}, R^{4c}, R^{9c} and R^{10c} are each, independently, hydrogen, alkyl, halogen or alkoxy;

R^{5c}, R^{6c} and R^{7c} are each, independently, hydrogen, halogen or alkyl;

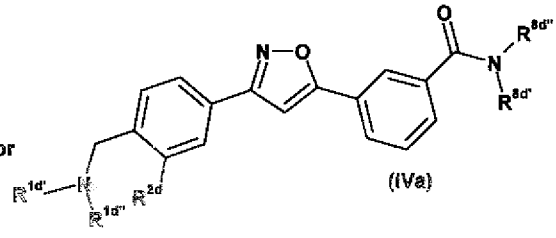
$R^{8c'}$ and $R^{8c''}$ are each, independently, a hydrogen, hydroxyl, alkyl, alkoxyl, amido or heterocyclyl;

R^{5c} and R^{6c} can be linked together to form an aryl or heterocyclyl ring; R^{6c} and R^{7c} can be linked together to form an aryl ring; $R^{8c''}$ and R^{9c} may be linked together to form a lactam; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

4. The compound of any one of claims 1 or 2, wherein the compound is of formula (IV) or (IVa):


(IV)

or


(IVa)

wherein:

X^{1d} is NH or O;

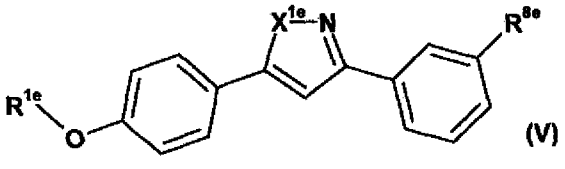
$R^{1d'}$ and $R^{1d''}$ are each, independently, hydrogen, alkyl, acyl, amido, amino or heterocyclyl;

R^{2d} is hydrogen or halogen;

$R^{8d'}$ and $R^{8d''}$ are each, independently, hydrogen, alkyl, amido or imino; and

$R^{1d'}$ and $R^{1d''}$ may be linked to form a heterocyclyl ring; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

5. The compound of claims 1 or 2, wherein the compound is of formula (V):



(V)

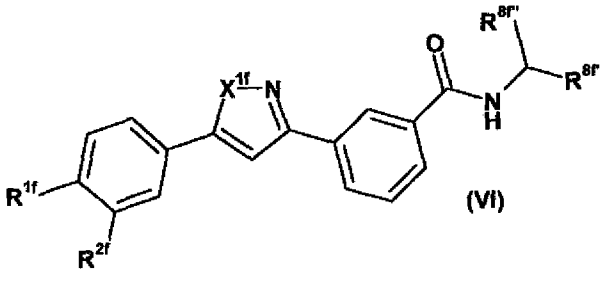
wherein:

X^{1e} is NH or O;

R^{1e} is hydrogen, alkyl, amino, amido, heterocyclyl or alkoxycarbonylalkyl;

R^{8e} is carbonyl or amido; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

6. The compound of claims 1 or 2, wherein the compound of formula (VI):



(VI)

wherein:

X^{1f} is NH or O;

R^{1f} is alkyl or heterocyclyl;

R^{2f} is hydrogen or halogen;

R^{8f} is alkyl or cyano;

$R^{8f'}$ is hydrogen or alkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs and enantiomers thereof.

7. A method of inhibiting PKD activity in a subject, comprising:

administering to the subject a therapeutically effective amount of the compound according to any one of claims 1-6.

8. A method of treating a disorder or a disease in a subject mediated by PKD, comprising:

administering to the subject a therapeutically effective amount of the compound according to any one of claims 1-6.

9. The method of claim 8, wherein the disorder or disease in a subject is characterized by an abnormal activity of PKD.

10. The method of claim 8 wherein the disorder or the disease is selected from heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, or hyperproliferative skin disorders.

11. A pharmaceutical composition, comprising:

a therapeutically effective amount of the compound of any one of claims 1-6 and

one or more pharmaceutically acceptable carriers.

12. A pharmaceutical composition, comprising:

a therapeutically effective amount of the compound according to any one of claims 1-6 and

one or more therapeutically active agents selected from (i) HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof; (ii) angiotensin II receptor antagonist or a pharmaceutically acceptable salt thereof; (iii) angiotensin converting enzyme (ACE) Inhibitor or a pharmaceutically acceptable salt thereof; (iv) calcium channel blocker (CCB) or a pharmaceutically acceptable salt thereof; (v) dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof; (vi) endothelin antagonist or a pharmaceutically acceptable salt thereof; (vii) renin inhibitor or a pharmaceutically acceptable salt thereof; (viii) diuretic or a pharmaceutically acceptable salt thereof; (ix) an ApoA-I mimic; (x) an anti-diabetic agent; (xi) an obesity-reducing agent; (xii)

an aldosterone receptor blocker; (xiii) an endothelin receptor blocker; and (xiv) CETP inhibitor.

13. A compound of any one of claims 1-6 for use as a medicament.

14. Use of a compound of any one of claims 1-6, for the preparation of a pharmaceutical composition for the treatment of a disorder or disease in a subject mediated by PKD.

15. Use of a compound of any one of claims 1-6, for the preparation of a pharmaceutical composition for the treatment of a disorder or disease in a subject characterized by an abnormal activity of PKD.

16. Use of a compound of any one of claims 1-6, for the preparation of a pharmaceutical composition for the treatment of a disorder or disease in a subject characterized by an abnormal expression of PKD.

17. Use of a pharmaceutical composition according to claim 12 or 13 for the preparation of a medicament for the treatment of a disorder or disease in a subject mediated by PKD.

18. Use of a pharmaceutical composition according to claim 12 or 13 for the preparation of a medicament for the treatment of a disorder or disease in a subject characterized by an abnormal activity of PKD.

19. Use of a pharmaceutical composition according to claim 12 or 13 for the preparation of a medicament for the treatment of a disorder or disease in a subject characterized by an abnormal expression of PKD.

20. The use of claim 15, wherein the disorder or disease is selected from heart failure, colorectal cancer, regulation of cell growth, autoimmune disorders, or hyperproliferative skin disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/059404

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/12 C07D261/08 C07D401/14 C07D403/10 C07D403/12
C07D405/12 C07D409/14 C07D413/04 C07D413/10 C07D413/12
A61K31/4155 A61K31/42 A61K31/4427 A61K31/496 A61P35/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. J. NYE, W. P. TANG: "Tautomerism of 4-hydroxypyrazoles and 4-hydroxyisoxazoles I" TETRAHEDRON, vol. 28, 1972, pages 455-462, XP002550884 Compounds 4b, 4e; 5b, 5e	1,2
X	H. KELLER, H. V. HALBAN: "Über die Photochemie des Tetrabenzoyl-äthylens III." HELVETICA CHIMICA ACTA, vol. 27, 1944, pages 1253-1275, XP002550885 page 1274	1,2

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2009	18/11/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rudolf, Manfred

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHONGJIAO REN, WEIGUO CAO, JIE CHEN, YU WANG, WEIYU DING: "A novel synthesis of 5-aryl-3-phenylpyrazole from 2-aryl-3-benzoyl-1,1-cyclopropanedicarbonitrile and hydrazine" J. HETEROCYCLIC CHEM., vol. 43, 2006, pages 495-497, XP002550886 table 1	1,2
X	H. HENNING: "Metallchelate des 3-Pyridyl(2)-5-phenyl-pyrazols" J. PRAKT. CHEM., vol. 34, 1966, pages 64-68, XP002550887 page 67	1,2
X	MUNEAKI IIZUKA, YOSHINORI KONDO: "Palladium-catalyzed alkynylcabonylation of aryl iodides with the use of Mo(CO)6 in the presence of tBu3P ligand" EUR. J. ORG. CHEM., vol. 2007, 2007, pages 5180-5182, XP002550888 table 4; compounds 2,5	1,2
X	MOHAMED S. MOHAMED AHMED, KEI KOBAYASHI, ATSUNORI MORI: "One-pot construction of pyrazoles and isoxazoles with palladium-catalyzed four-component coupling" ORGANIC LETTERS, vol. 7, no. 20, 2005, pages 4487-4489, XP002550889 table 2	1,2
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; XP002550899 Database accession no. brn 15857 abstract & CUSMANO, SPRIO: GAZZETTA CHIMICA ITALIANA, vol. 82, 1952, pages 420-426,	1,2
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; XP002550900 Database accession no. brn 4878590 abstract & P. RAJANI, D. ASHOK, P. N. SARMA: J. IND. CHEM. SOC., vol. 68, no. 1, 1991, pages 52-55,	1,2

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; XP002550901 Database accession no. BRN 795239 abstract & HAMID EL-BAYOUKI: EGYPTIAN JOURNAL OF CHEMISTRY, vol. 22, 1979, pages 37-46, -----	1,2
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; XP002550902 Database accession no. BRN 24950 abstract & V. AUWERS, BERGMANN: JUSTUS LIEBIGS ANNALEN DER CHEMIE, vol. 472, 1929, page 310, -----	1,2
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; XP002550903 Database accession no. BRN 1125016 abstract & KRISHNA MOHAN RAO, MARUTATMAJA RAO: PROCEEDINGS INDIAN ACADEMY OF SCIENCES, SECTION A, vol. 81, 1975, pages 262-269, -----	1,2
X	DATABASE CROSSFIRE BEILSTEIN BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; XP002550904 Database accession no. 568702 abstract & M. R. LANGELLA, P. GRUENANGER: GAZZETTA CHIMICA ITALIANA, vol. 91, 1961, pages 1449-1460, -----	1,2
X	A. BATTAGLIA, A. DONDONI, F. TADDEI: "Isoxazoles from nitrile oxides and acetylenes. Substituent effect on the PMR spectra of disubstituted isoxazoles" J. HETEROCYCLIC CHEM., vol. 7, 1970, pages 721-724, XP002550890 table 1 ----- -/--	1,2

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANNY BERGER, ADOLF EMIL SIEGRIST: "Anil-Synthese. Über die Herstellung von Stilbenyl-Derivaten des Isoxazols" HELVETICA CHIMICA ACTA, vol. 62, no. 80, 1979, pages 779-806, XP002550891 Table 36, compounds Z2, Z11	1,2
X	H. J. ROTH, M. SCHWARZ: "Zur Kondensation von Chalkonoxiden mit Hydroxylamin" ARCHIV DER PHARMAZIE, vol. 294, no. 12, 1961, pages 769-774, XP002550892 table 1	1,2
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 00/08001 A (CHIRON CORP [US]; HUEBNER VERENA D [US]; LIN XIAODONG [US]; JAMES IAN) 17 February 2000 (2000-02-17)	1,2,11, 13
A	compounds 4.1.2.134,4.1.2.139,4.1.2.140 page 3, lines 1-6; claim 1; compound 1	3
X	US 2005/239751 A1 (SINGH RAJINDER [US] ET AL) 27 October 2005 (2005-10-27)	1,2,11, 13
A	paragraphs [0002], [0046], [0094], [0095]; claim 1; compound 1044	3
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A	examples 22-24	5
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2009/059404

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1, 2; 7-10 partly
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1,2 partly
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 1, 2; 7-10 partly

Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 1,2 partly

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims 1 and 2 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1 and 2.

Moreover, numerous dependent claims are inconsistent with the parent claims to which they refer; e.g. claim 2 dependent on claim 1 includes "alkoxy" in the definition for substituent R4b, whereas the corresponding substituent R4a in formula (I) of claim 1 does not embrace "alkoxy". It is therefore unclear which compounds should be embraced by the claims, and also for this reason a meaningful search all over the claimed scope cannot be carried out.

The documents cited against novelty of the subject matter of claims 1 and 2 are illustrative only. Many more documents disclosing compounds prejudicial to the novelty of the subject matter of claims 1 and 2 exist.

The search was therefore restricted to: compounds of formula (I) and (Ia) as defined in claim 1 bearing the thiophene substituent as defined in claim 1, and to compounds of formula (I) and (Ia) as defined in claim 1, wherein the cyclic substituent R2a bears a (substituted) aminocarbonyl group for substituent R8a (cf. claim 3). The search is complete for these groups of compounds. Also the subject matter of claim 5 has been fully searched.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/059404

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