

NOVEL INHIBITORS OF CHYMASE

FIELD OF THE INVENTION

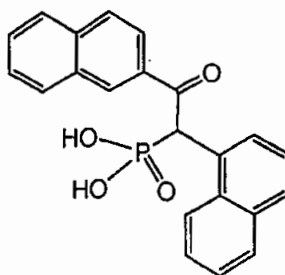
5 The present invention relates to certain novel compounds, methods for preparing compounds, compositions, intermediates and derivatives thereof and methods for treating inflammatory and serine protease mediated disorders. More particularly, the compounds of the present invention are serine protease inhibitors useful for treating inflammatory and serine protease mediated disorders.

10 BACKGROUND OF THE INVENTION

Serine proteases represent a broad class of proteolytic enzymes that are involved in physiological processes such as blood coagulation, complement activation, phagocytosis and turnover of damaged cell tissue. Human chymase (EC.3.4.21.39) is a glycosylated monomeric chymotrypsin-like serine protease (MW = 30 kDa) localized mainly in mast cell secretory granules. Chymase is thought to have a variety of functions, including degradation of extracellular matrix proteins, cleavage of angiotensin I to angiotensin II, (except in the rat), and activation of matrix proteases and cytokines. Endogenously, chymase is regulated by the serpins α 1-antichymotrypsin and α 1-proteinase.

20 Although the precise patho-physiological roles of chymase have yet to be determined, chymase has been implicated in microvascular leakage, neutrophil accumulation, the stimulation of mucus secretion, and the modulation of cytokines. A potent, chymase-selective inhibitor may be indicated in mast cell-mediated diseases such as asthma, pulmonary inflammation, and chronic obstructive pulmonary diseases (COPD). Because chymase can play a role in the generation of cardiac and vascular wall angiotensin II, an inhibitor may have potential use as an antihypertensive treatment for vascular wall injury and inflammation (atherosclerosis/restenosis), as well as cardiac hypertrophy. Thus, small molecule inhibitors of chymase are likely to represent useful therapeutic agents.

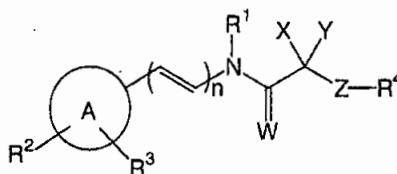
30 US Patent 5,508,273 to Beers, et al. and *Bioorganic & Med. Chem. Lett.*, 1995, 5 (16), 1801-1806 describe phosphonic acid compounds useful in treating bone wasting diseases. In particular, 1-naphthylmethylphosphonic acid derivatives have been described as osteoclastic acid phosphatase inhibitors of the formula:



Accordingly, it is an object of the present invention to provide phosphonic acid and phosphinic acid compounds that are serine protease inhibitors, in particular, inhibitors of chymase, useful for treating inflammatory and serine protease mediated disorders. It is another object of the invention to provide a process for preparing phosphonic or phosphinic acid compounds, compositions, intermediates and derivatives thereof. It is a further object of the invention to provide methods for treating inflammatory and serine protease mediated disorders.

10 SUMMARY OF THE INVENTION

The present invention is directed to a compound of Formula (I)



Formula (I)

15 wherein

R^1 is selected from the group consisting of hydrogen and C_{1-4} alkyl;



is selected from the group consisting of aryl, heteroaryl, benzo fused heterocyclyl, cyclopropyl when n is 0 and one of R^2 or R^3 is phenyl, and benzo fused cycloalkyl, and ring A is optionally substituted with R^2 and R^3 ;

R^2 is one to two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, C_{2-6} alkoxy, C_{1-6} alkylthio, $-OCF_3$, $-NH_2$, $-NH(C_{1-6})$ alkyl, $-N(C_{1-6})$ dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, and nitro; furthermore, R^2 is optionally oxo when ring A is heteroaryl or benzo fused heterocyclyl; and, wherein any aryl-containing substituent of R^2 is optionally substituted with a substituent independently selected from the group consisting of

C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆ alkenyl, C₁₋₆alkylthio, -NH₂, -NH(C₁₋₆)alkyl, -N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, and nitro;

and, wherein any of the foregoing C₁₋₆alkyl or C₂₋₆ alkoxy containing substituents of R² are optionally substituted with a substituent independently selected from the group consisting of -NR¹¹R¹², aryl, heteroaryl, one to three halogens and hydroxy; wherein R¹¹ and R¹² are independently hydrogen; C₁₋₆ alkyl optionally substituted with hydroxy, aryl, -C(=O)C₁₋₄alkoxy, or -NR¹⁵R¹⁶; or aryl;

R¹⁵ and R¹⁶ are substituents independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and aryl, and said R¹⁵ and R¹⁶ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

R³ is one to three substituents independently selected from the group consisting of C₁₋

₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkylthio, -OCF₃, -OCH₂(C₂₋
₆)alkenyl, -NH₂, -NH(C₁₋₆)alkyl, -N(C₁₋₆)dialkyl, -NHC(=O)Cy, -N(C₁₋
₆alkyl)C(=O)Cy, -(NC(=O))₂NH₂, -C(=O)C₁₋₄alkoxy, -C(=O)NR¹⁷R¹⁸,
 -C(=O)NHcycloalkyl, -C(=O)N(C₁₋₆alkyl)cycloalkyl, -C(=O)NHCy, -C(=O)N(C₁₋
₆alkyl)Cy, -C(=O)Cy, -OC(=O)C₁₋₆alkyl, -OC(=O)NR¹⁹R²⁰, -C(=O)Oaryl,
 -C(=O)Oheteroaryl, -CO₂H, ureido, halogen, hydroxy, nitro, cyano, aryl,
 heteroaryl, heteroaryloxy, and aryloxy;

wherein any of the foregoing C₁₋₆alkyl or C₁₋₆alkoxy containing substituents of R³ are optionally substituted with one to three substituents independently selected from the group consisting of -NR²¹R²², -NH(cycloalkyl), -N(C₁₋₆alkyl)(cycloalkyl), -
 NHCy, -N(C₁₋₆alkyl)Cy, aryl, heteroaryl, hydroxy, halogen, -C(=O)NR²³R²⁴, -
 OC(=O)NR²⁵R²⁶, -C(=O)C₁₋₄alkoxy, and -C(=O)Cy;

wherein said R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶ are substituents independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and aryl, wherein C₁₋₆ alkyl is optionally substituted with hydroxy, aryl, -
 C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆)dialkyl; and R¹⁷ and R¹⁸, R¹⁹
 and R²⁰, R²¹ and R²², R²³ and R²⁴, and R²⁵ and R²⁶ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

Cy is a heterocyclyl optionally substituted with a substituent selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, -C₁₋₆alkylC(=O)C₁₋₆alkoxy, C₁₋
₆alkylC(=O)aryl, -C(=O)(C₁₋₆)alkyl, -C(=O)(C₁₋₆)alkoxy, -C(=O)aryl, -SO₂aryl, aryl,

heteroaryl, and heterocyclyl; wherein the aryl portion of any aryl-containing substituent of Cy is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylthio, halogen, hydroxy, NH₂, NH(C₁₋₆alkyl), and -N(C₁₋₆)dialkyl; and
5 wherein heterocyclyl is optionally substituted with aryl, one to three halogen atoms, or one to three oxo substituents; and heterocyclyl is optionally spiro-fused to said Cy;

and wherein the C₁₋₆alkenyl and C₁₋₆alkynyl substituents of R³ are optionally
10 substituted with aryl or -C(=O)NR²⁷R²⁸; wherein said R²⁷ and R²⁸ are independently hydrogen; C₁₋₆ alkyl optionally substituted with hydroxy, aryl, -C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆)dialkyl; or aryl; and R²⁷ and R²⁸ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

15 wherein the aryl, heteroaryl, and cycloalkyl substituents of R³ are optionally substituted with one to three substituents independently selected from R¹⁴;

20 wherein R¹⁴ is independently hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₁₋₆alkylthio, -NH₂, -NH(C₁₋₆)alkyl, -N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, or nitro;

and any one of the foregoing C₁₋₆alkyl- or C₁₋₆alkoxy-containing substituents of R¹⁴ is optionally substituted on a terminal carbon atom with a substituent selected from -NR²⁹R³⁰, aryl, heteroaryl, one to three halogen atoms, or hydroxy; wherein R²⁹ and R³⁰ are
25 independently hydrogen; C₁₋₆ alkyl optionally substituted with hydroxy, aryl, -C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆)dialkyl; or aryl; and R²⁹ and R³⁰ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

n is 0 or 1;

30 W is O or S;

X is hydrogen or C₁₋₃alkyl;

35 Y is independently selected from the group consisting of C₁₋₆alkyl substituted with -OSO₂NH₂ or hydroxy; SO₃H, CO₂H, heteroaryl, -OC(=O)NH₂, and P(=O)OR⁵R⁶ provided that when Y is CO₂H, A and Z must both be bicyclic ring systems;

R^5 is selected from the group consisting of hydrogen; C_{1-6} alkyl optionally substituted with NH_2 , $-NH(C_{1-6})$ alkyl, $-N(C_{1-6})$ dialkyl, 1,3-dioxolan-2-yl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyloxy, C_{1-6} alkylcarbonylthio, (C_{1-6}) alkylaminocarbonyl, $di(C_{1-6})$ alkylaminocarbonyl, one to three halogens, or hydroxy; and aryl optionally substituted with C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{2-6} alkenyl, $-NH_2$, $-NH(C_{1-6})$ alkyl, $-N(C_{1-6})$ dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, or nitro; alternatively, when R^6 is C_{1-8} alkoxy, R^5 and R^6 are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring; provided that R^5 is other than C_{1-6} alkyl substituted with $di(C_{1-6})$ alkylamino-carbonyl when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is OH, and $Z-R^4$ is 5-chloro-benzothiophen-3-yl; and provided that R^5 is other than C_{1-6} alkyl substituted with C_{1-6} alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is CH_3 , and $Z-R^4$ is 5-chloro-benzothiophen-3-yl;

R^6 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{2-8} alkenyl, heteroaryl, aryl, and hydroxy; wherein C_{1-8} alkyl, C_{1-8} alkoxy, and C_{2-8} alkenyl are optionally substituted with a substituent selected from the group consisting of C_{1-6} alkoxy, aryl, heterocyclyl, heteroaryl, NH_2 , $-NH(C_{1-6})$ alkyl, $-N(C_{1-6})$ dialkyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylthio, C_{1-6} alkoxycarbonyloxy, (C_{1-6}) alkylaminocarbonyl, $di(C_{1-6})$ alkylaminocarbonyl, one to three halogen atoms, and hydroxy; and when R^6 is C_{1-8} alkyl, said C_{1-8} alkyl is optionally substituted with one to four additional halogen atoms such that one to three halogen atoms are optionally chlorine and one to seven of the halogen atoms are optionally fluorine; wherein the heteroaryl and aryl substituents of R^6 are optionally substituted with a substituent independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{1-6} alkylthio, $-NH_2$, $-NH(C_{1-6})$ alkyl, $-N(C_{1-6})$ dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, and nitro;

Z is a seven to fifteen membered monocyclic or polycyclic ring system selected from the group consisting aryl, heteroaryl, benzo fused heterocyclyl, or benzo fused cycloalkyl, optionally substituted with R^4 ;

R^4 is one to three substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkylthio, $aryl(C_{1-6})$ alkyl, $aryl(C_{2-6})$ alkenyl, halogen, $-C(=O)Cy$, $-C(=O)NR^{31}R^{32}$, aryl, $-CO_2H$, oxo, and cyano; wherein C_{1-6} alkyl, C_{1-6} alkenyl and C_{1-6} alkoxy are optionally substituted with $-NR^{33}R^{34}$, aryl, heteroaryl, cycloalkyl, one to three halogen atoms, or hydroxy; and aryl and heteroaryl are

each optionally substituted with a substituent independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆ alkenyl, C₁₋₆alkylthio, -NH₂, -NH(C₁₋₆)alkyl, -N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, one to three halogen atoms, hydroxy, and nitro;

5 wherein said R³¹, R³², R³³, and R³⁴ are substituents independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and aryl, wherein alkyl is optionally substituted with hydroxy, aryl, -C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆)dialkyl; and R³¹ with R³², and R³³ with R³⁴ are optionally taken together with the atoms to which they are attached to form a ring of
10 five to seven members;

and pharmaceutically acceptable salts thereof.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. An
15 illustration of the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Illustrating the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier.

The present invention is also directed to methods for producing the instant
20 compounds and pharmaceutical compositions and medicaments thereof.

The present invention is further directed to methods for treating or ameliorating a serine protease-mediated disorder. In particular, the method of the present invention is directed to treating or ameliorating a chymase mediated disorder such as, but not limited to, allergic rhinitis, viral rhinitis, asthma, chronic obstructive pulmonary diseases, bronchitis,
25 pulmonary emphysema, acute lung injury, psoriasis, arthritis, reperfusion injury, ischemia, hypertension, hypercardia myocardial infarction, heart failure damage associated with myocardial infarction, cardiac hypertrophy, arteriosclerosis, saroidosis, vascular stenosis or restenosis (e.g., associated with vascular injury, angioplasty, vascular stents or vascular grafts), pulmonary fibrosis, kidney fibrosis (e.g., associated with glomerulonephritis), liver
30 fibrosis, post surgical adhesion formation, systemic sclerosis, keloid scars, rheumatoid arthritis, bullous pemphigiod, and atherosclerosis. Additionally, these compounds can be used for modulating wound healing and remodeling (e.g., cardiac hypertrophy) as well as immune modulation.

35 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the percent change in specific lung resistance (SR_L) from baseline for Compound 17 when administered via aerosol inhalation compared to control in a

spontaneous *Ascaris suum* antigen-induced model of asthma in sheep over an 8 hour period.

Figure 2 shows the change in the cumulative carbachol dose required to increase SR_L 400% (PC 400) from a baseline value (BSL) measured at 24 hours post-dosing of

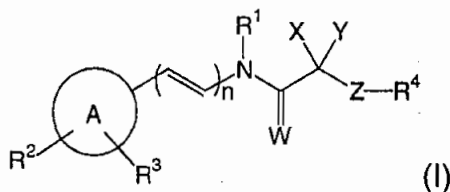
- 5 Compound 17 via aerosol inhalation delivery in the spontaneous *Ascaris suum* antigen-induced model of asthma in sheep compared to a 24 hour post-dosing challenge with carbachol (Post Antigen).

Figure 3 shows the percent change in specific lung resistance (SR_L) from baseline for Compound 17 when administered via oral administration compared to control in a
10 spontaneous *Ascaris suum* antigen-induced model of asthma in sheep over an 8 hour period.

Figure 4 shows the change in the cumulative carbachol dose required to increase SR_L 400% (PC 400) from a baseline value (BSL) measured at 24 hours post-dosing of
15 Compound 17 via oral administration in the spontaneous *Ascaris suum* antigen-induced model of asthma in sheep compared to a 24 hour post-dosing challenge with carbachol (Post Antigen).

DETAILED DESCRIPTION OF THE INVENTION

- 20 Preferred embodiments of the present invention include compounds of Formula (I) wherein:



R^1 is selected from the group consisting of hydrogen and C_{1-4} alkyl.

- 25 More preferably, R^1 is hydrogen.

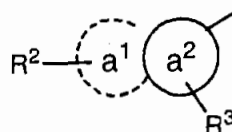
Preferred embodiments of the present invention include compounds of Formula (I) wherein:



is selected from the group consisting of aryl, heteroaryl, benzo fused heterocyclyl and benzo fused cycloalkyl optionally substituted with R^2 and R^3 .

- 30 Preferably, ring system A is selected from the group consisting of heteroaryl, benzo fused heterocyclyl, or aryl.

Preferably when A is a bicyclic ring system of the formula:



wherein the a^1 portion of said a^1a^2 is optionally substituted with R^2 ; and the a^2 portion is optionally substituted with R^3 .

Preferably a^2 is an aromatic ring.

- 5 Preferably, ring system A is selected from the group consisting of naphthyl, benzothiazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, dihydronaphthyl, indanyl, tetralinyl, and benzodioxolyl when n is equal to zero; and A is phenyl, pyridin-2-yl, or pyridin-3-yl when n is equal to one. In embodiments of the present invention wherein a bicyclic ring system is used for A, the a^2 ring will be aromatic. More preferably, ring system
- 10 A is selected from the group consisting of naphthyl, benzothiazolyl, and benzothiophenyl, when n is equal to zero, and A is selected from phenyl, pyridin-2-yl, and pyridin-3-yl when n is equal to one.

A preferred embodiment of the present invention includes compounds of Formula (I) wherein n is equal to one.

- 15 Preferred embodiments of the present invention include compounds of Formula (I) wherein R^2 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, methoxy, C_{2-6} alkoxy, $-NH_2$, $NH(C_{1-6}alkyl)$, $-N(C_{1-6})dialkyl$, aryl, heteroaryl, halogen, hydroxy, and nitro; wherein $C_{1-6}alkyl$ and $C_{2-6}alkoxy$ are optionally substituted with a substituent selected from $-NR^{11}R^{12}$, aryl, heteroaryl, one to three halogens, and hydroxy.

- 20 More preferably, R^2 is a substituent independently selected from the group consisting of $C_{1-4}alkyl$, methoxy, $C_{2-4}alkoxy$, hydroxy, halogen, and $-NH_2$.

Most preferably, R^2 is $C_{1-4}alkyl$, halogen, or $-NH_2$.

- Preferred embodiments of the present invention include compounds of Formula (I) wherein R^3 is one to three substituents independently selected from the group consisting of
- 25 $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{1-6}alkoxy$, $-OCH_2(C_{2-6})alkenyl$, NH_2 , $-NH(C_{1-6}alkyl)$, $-N(C_{1-6})dialkyl$, $-NHC(=O)Cy$, $-N(C_{1-6}alkyl)C(=O)Cy$, $-C(=O)C_{1-4}alkoxy$, $-C(=O)NR^{17}R^{18}$, $-C(=O)NHcycloalkyl$, $-C(=O)N(C_{1-6}alkyl)cycloalkyl$, $-C(=O)NHCy$, $-C(=O)N(C_{1-6}alkyl)Cy$, $-C(=O)Cy$, $-OC(=O)NR^{19}R^{20}$, halogen, hydroxy, nitro, cyano, aryl, and aryloxy; wherein alkyl and alkoxy are optionally substituted with one to three substituents independently
- 30 selected from the group consisting of $-NR^{21}R^{22}$, $-NHcycloalkyl$, $-N(C_{1-6}alkyl)cycloalkyl$, $-NHCy$, $-N(C_{1-6}alkyl)Cy$, aryl, heteroaryl, halogen, $-C(=O)NR^{23}R^{24}$, $-OC(=O)NR^{25}R^{26}$, $-C(=O)(C_{1-4})alkoxy$, and $-C(=O)Cy$; wherein alkenyl is optionally substituted on a terminal carbon with aryl and $-C(=O)NR^{27}R^{28}$; and wherein aryl and cycloalkyl are optionally substituted with one to three substituents independently selected from R^{14} .

More preferably, R^3 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{19}R^{20}$, $-NHC(=O)Cy$, $-C(=O)NR^{17}R^{18}$, $-C(=O)NH$ cycloalkyl, $-C(=O)N(C_{1-6}alkyl)$ cycloalkyl, halogen, and aryl; wherein alkyl and alkoxy are optionally substituted on a terminal carbon atom with one to three fluorine atoms, $-NH_2$, $-NHCy$, or $-N(C_{1-4}alkyl)Cy$; and wherein aryl and cycloalkyl are optionally substituted with a group independently selected from R^{14} .

Even more preferably, R^3 is one to two substituents independently selected from trifluoromethyl, C_{1-4} alkoxy optionally substituted with one to three fluorine atoms, $-NH_2$, $-NHC(=O)Cy$, or halogen.

10 Preferably when R^3 is $NHC(=O)Cy$ then Cy is preferably piperadiny, and substituted with a substituent selected from the group consisting of C_{1-4} alkyl, $C_{1-4}alkylC(=O)C_{1-4}alkyl$, $-C_{1-4}alkylC(=O)C_{1-4}alkoxy$, $C_{1-4}alkylC(=O)aryl$, $-C(=O)(C_{1-4}alkyl)$, $-C(=O)(C_{1-4}alkoxy)$, $-C(=O)aryl$, $-SO_2aryl$, aryl, heteroaryl, and heterocycl; wherein aryl and the aryl portion of the $C_{1-4}alkylC(=O)aryl$, $-C(=O)aryl$, and $-SO_2aryl$ is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, hydroxy, NH_2 , $NH(C_{1-6}alkyl)$, and $-N(C_{1-4})dialkyl$; and wherein heterocycl is optionally substituted with aryl, one to three halogen atoms, or one oxo substituents.

Most preferably, R^3 is trifluoromethyl, one to two fluorine atoms, chloro, methoxy, trifluoromethoxy, or NH_2 ; furthermore, when A is naphthyl and n is equal to zero, R^3 is (4-[[1-(naphthalene-2-carbonyl)-piperadine-4-carbonyl]-amino]-naphthalene-2-yl.

Preferred embodiments of the present invention include compounds of Formula (I) wherein X is hydrogen or $C_{1-3}alkyl$.

More preferably, X is hydrogen.

25 Preferred embodiments of the present invention include compounds of Formula (I) wherein Y is independently selected from a group consisting of $C_{1-3}alkyl$, SO_3H , CO_2H , heteroaryl, $-OC(=O)NH_2$, and $P(=O)OR^5R^6$; wherein alkyl is substituted with a substituent selected from the group consisting of $-OSO_2NH_2$ and hydroxy.

More preferably, Y is independently SO_3H or $P(=O)OR^5R^6$.

30 Most preferably, Y is $P(=O)OR^5R^6$.

Preferred embodiments of the present invention include compounds of Formula (I) wherein R^5 is selected from the group consisting of hydrogen; $C_{1-3}alkyl$ optionally substituted with NH_2 , $-NH(C_{1-6}alkyl)$, $-N(C_{1-6})dialkyl$, $C_{1-6}alkyl$ carbonyloxy, $C_{1-6}alkoxy$ -carbonyloxy, $C_{1-6}alkyl$ carbonylthio, $(C_{1-6}alkyl)aminocarbonyl$, $di(C_{1-6}alkyl)amino$ -carbonyl, one to three halogens, or hydroxy; and aryl optionally substituted with $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $C_{1-6}alkyl$ thio, $C_{2-6}alkenyl$, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6})dialkyl$, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, or nitro; alternatively, when R^6 is $C_{1-6}alkoxy$, R^5 and R^6

are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring;

provided that R^5 is other than C_{1-6} alkyl substituted with $di(C_{1-6})$ alkylaminocarbonyl when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is OH, and $Z-R^4$ is 5-chloro-benzothiophen-3-yl; and provided that R^5 is other than C_{1-6} alkyl substituted with C_{1-6} alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is CH_3 , and $Z-R^4$ is 5-chloro-benzothiophen-3-yl.

More preferably, R^5 is selected from the group consisting of hydrogen, C_{1-3} alkyl optionally substituted with C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyloxy, C_{1-6} alkylcarbonylthio, (C_{1-6}) alkylaminocarbonyl, $di(C_{1-6})$ alkylaminocarbonyl, one to three halogens, or hydroxyl; and aryl; alternatively, when R^6 is C_{1-8} alkoxy, R^5 and R^6 are taken together with the atoms to which they are attached to form a 6-7 membered monocyclic ring; provided that R^5 is other than C_{1-3} alkyl substituted with $di(C_{1-6})$ alkylaminocarbonyl when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is OH, and $Z-R^4$ is 5-chloro-benzothiophen-3-yl; and provided that R^5 is other than C_{1-3} alkyl substituted with C_{1-6} alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is CH_3 , and $Z-R^4$ is 5-chloro-benzothiophen-3-yl.

Most preferably, R^5 is hydrogen or C_{1-3} alkyl optionally substituted with C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyloxy, C_{1-6} alkylcarbonylthio, (C_{1-6}) alkylamino-carbonyl, or $di(C_{1-6})$ alkylaminocarbonyl; and alternatively, when R^6 is C_{1-8} alkoxy, R^5 and R^6 are taken together with the atoms to which they are attached to form a 6-membered monocyclic ring; provided that R^5 is other than C_{1-3} alkyl substituted with $di(C_{1-6})$ alkylaminocarbonyl when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is OH, and $Z-R^4$ is 5-chloro-benzothiophen-3-yl; and provided that R^5 is other than C_{1-3} alkyl substituted with C_{1-6} alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is CH_3 , and $Z-R^4$ is 5-chloro-benzothiophen-3-yl.

Preferred embodiments of the present invention include compounds of Formula (I) wherein R^6 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{2-8} alkenyl, heteroaryl, aryl, and hydroxy; wherein alkyl, alkoxy, and alkenyl are optionally substituted on a terminal carbon atom with a substituent independently selected from the group consisting of C_{1-4} alkoxy, aryl, heteroaryl, heterocyclyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylthio, C_{1-6} alkoxycarbonyloxy, (C_{1-6}) alkylaminocarbonyl, $di(C_{1-6})$ alkylaminocarbonyl, and hydroxy; and wherein heteroaryl and aryl are optionally substituted with one to three substituents independently selected from the group consisting of aryl, hydroxy, C_{1-6} alkoxy, and halogen.

More preferably, R^6 is selected from the group consisting of C_{1-6} alkyl, C_{1-8} alkoxy, heteroaryl, aryl, and hydroxy; wherein alkyl and is optionally substituted on a terminal

carbon atom with a substituent selected from C₁₋₃alkoxy, aryl, or hydroxy; and alkoxy is optionally substituted on a terminal carbon with a substituent independently selected from the group consisting of C₁₋₆alkylcarbonyloxy, and di(C₁₋₆)alkyl-aminocarbonyl; and wherein heteroaryl and aryl are optionally substituted with one to three substituents independently selected from the group consisting of aryl, hydroxy, C₁₋₆alkoxy, and halogen.

Most preferably, R⁶ is selected from the group consisting of methyl, ethyl, methoxypropyl, phenethyl, benzo[1,3]dioxol-5-yl-propyl, hydroxy, and C₁₋₃alkoxy optionally substituted with C₁₋₆alkylcarbonyloxy, and di(C₁₋₆)alkylaminocarbonyl.

Preferred embodiments of the present invention include compounds of Formula (I) wherein Z is a bicyclic aryl or bicyclic heteroaryl; wherein aryl and heteroaryl are optionally substituted with the group R⁴; provided that when Y is CO₂H, A must be a bicycle.

More preferably, Z is selected from the group consisting of indolyl, benzothiophenyl, naphthalenyl, quinolinyl, isoquinolinyl and benzothiazolone.

Most preferably, Z is selected from the group consisting of indolyl, benzothiophenyl, and naphthalenyl.

Embodiments of the present invention include compounds of Formula (I) wherein R⁴ is one to three substituents selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkoxy, aryl(C₂₋₆)alkenyl, halogen, -C(=O)Cy, -C(=O)NR³¹R³², aryl, -CO₂H, oxo, and cyano; wherein alkyl and alkoxy are optionally substituted on a terminal carbon atom with a substituent selected from aryl, -NR³³R³⁴, one to three halogens, or hydroxy; wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, -NH₂, -NH(C₁₋₆)alkyl, -N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, and nitro.

Preferably, R⁴ is one to three substituents selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkoxy, aryl(C₂₋₆)alkenyl, halogen, -C(=O)Cy, -C(=O)NR³¹R³², aryl, -CO₂H, oxo, and cyano; wherein alkyl and alkoxy are optionally substituted with a substituent independently selected from -NR³³R³⁴, aryl, one to three halogen atoms, or hydroxy; wherein aryl is optionally substituted with a substituent independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, aryl, halogen, hydroxy, and nitro.

More preferably, R⁴ is one to three substituents selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkenyl, aryl(C₂₋₆)alkenyl, halogen, and -C(=O)Cy; wherein aryl is optionally substituted with a substituent selected from halogen and C₁₋₄alkoxy.

Most preferably, R⁴ is one to two substituents selected from the group consisting of fluorine, chlorine, bromine, methyl, phenyl(C₂₋₆)alkenyl, and -C(=O)(2-(4-phenyl-piperidin-1-ylcarbonyl)).

Embodiments of the phosphonic and phosphinic acids of the present invention include those compounds of Formula (Ia) wherein the substituents are as previously defined (including the previously listed preferred substitutions in any combination).

Examples of embodiments of the present invention are shown in Table I:

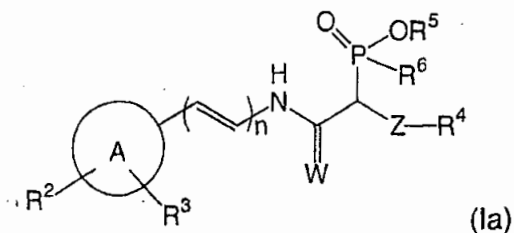
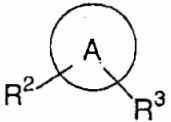
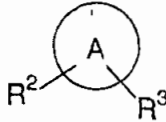
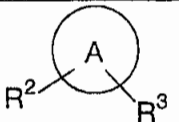
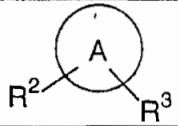


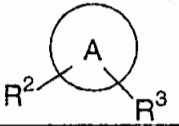
Table I

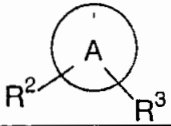
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
1	naphthalen-2-yl	H	CH ₃	0	O	5-Cl-N-methyl-indol-3-yl
2	3,4-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3	naphthalen-2-yl	H	OH	0	O	5-Cl-N-methyl-indol-3-yl
4	4-fluoro-phenyl	H	OH	1	O	5-Cl-N-methyl-indol-3-yl
5	naphthalen-2-yl	H	OH	0	O	5-Me-benzothiophen-2-yl
6	3-fluoro-phenyl	H	CH ₃	1	O	5-Cl-N-methyl-indol-3-yl
7	3,4-difluoro-phenyl	H	CH ₃	1	O	5-Cl-N-methyl-indol-3-yl
8	4-[[1-(naphthalen-2-ylcarbonyl)-piperidin-4-ylcarbonyl]-amino]naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
9	naphthalen-2-yl	H	OH	0	O	5-Cl-benzothiophen-3-yl
10	naphthalen-2-yl	H	OH	0	O	5-F-benzothiophen-3-yl
11	naphthalen-2-yl	H	OH	0	O	5-F-N-methyl-indol-3-yl

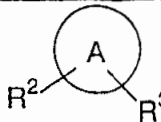
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
12	4-amino-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
13	naphthalen-2-yl	H	OH	0	O	5-Br-N-methyl-indol-3-yl
14	Phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
15	3-fluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
16	3,4-trifluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
17	3,4-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
18	phenyl	H	OH	1	O	5-Cl-benzothiophen-2-yl
19	4-fluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
20	naphthalen-2-yl	H	CH ₃	0	O	5-Cl-benzothiophen-3-yl
21	2-fluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
22	naphthalen-2-yl	H	OH	0	O	N-methyl-indol-3-yl
23	naphthalen-2-yl	H	OH	0	O	5-Br-benzothiophen-3-yl
24	4-fluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
25	pyridin-3-yl	H	OH	1	O	5-Cl-benzothiophen-3-yl
26	naphthalen-2-yl	H	OH	0	O	benzothiophen-3-yl
27	naphthalen-2-yl	H	OH	0	O	N-(3-phenyl-allyl)-indol-3-yl
28	naphthalen-2-yl	H	CH ₂ CH ₃	0	O	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
29	3,4-difluoro-phenyl	H	CH ₂ CH ₃	1	O	5-Cl-benzothiophen-3-yl
30	benzothiazol-6-yl	H	OH	0	O	5-Cl-benzothiophen-3-yl
31	naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
32	naphthalen-2-yl	H	CH ₃	0	O	2-(4-phenyl-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
33	naphthalen-2-yl	H	CH ₃	0	O	naphthalen-1-yl
34	naphthalen-2-yl	H	3-methoxy-propyl	0	O	5-Cl-benzothiophen-3-yl
35	naphthalen-2-yl	H	CH ₃	0	O	2-(4-(4-methoxyphenyl)-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
36	naphthalen-2-yl	H	phenethyl	0	O	5-Cl-benzothiophen-3-yl
37	phenyl	H	OH	1	O	naphthalen-1-yl
38	4-methoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
39	naphthalen-2-yl	H	3-(benzo [1,3]dioxol-5-yl)-propyl	0	O	5-Cl-benzothiophen-3-yl
40	naphthalen-2-yl	H	3-(naphthyl en-1yl) propyl	0	O	5-Cl-benzothiophen-3-yl
41	naphthalen-2-yl	H	CH ₃	0	O	2-(4-(Benzyloxycarbonyl)-piperazin-1-ylcarbonyl))-benzothiophen-3-yl
42	4-methyl-phenyl	H	OH	1	O	5-Cl-benzothiophen-2-yl
43	naphthalen-2-yl	H	3-(4-hydroxy phenyl) propyl	0	O	5-Cl-benzothiophen-3-yl

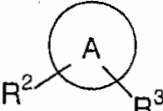
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
44	3-((N-benzoyl-piperidin-4-ylamino)-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
45	naphthalen-2-yl	H	OH	0	S	5-Cl-benzothiophen-3-yl
46	3-[(1-phenyl)-cyclohex-1-enyl-N-methyl-aminocarbonyl]-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
47	naphthalen-2-yl	H	CH ₃	0	O	2-((4-F-phenyl)-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
48	naphthalen-2-yl	H	(3-phenyl)propyl	0	O	5-Cl-benzothiophen-3-yl
49	3,4-dimethoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
51	naphthalen-2-yl	H	(4-phenyl)butyl	0	O	5-Cl-benzothiophen-3-yl
52	naphthalen-2-yl	H	OH	0	O	6-Cl-N-methyl-indol-3-yl
53	naphthalen-2-yl	H	3-(4-methoxy-phenyl)propyl	0	O	5-Cl-benzothiophen-3-yl
54	3-[4-((3-phenethyl)-pyrrolidin-1-ylcarbonyl)]-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
55	benzothiophen-5-yl	H	OH	0	O	5-Cl-benzothiophen-3-yl
56	naphthalen-2-yl	H	OH	0	O	5-carboxy-N-Me-indol-3-yl
57	quinolin-3-yl	H	OH	0	O	naphthalen-1-yl
58	naphthalen-2-yl	H	OH	0	O	7-Cl-N-methyl-indol-3-yl
59	benzo[b]thiophen-6-yl	H	OH	0	O	naphthalen-1-yl

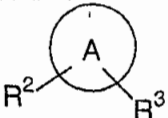
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
60	3-[4-(6-chloro-2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidin-1-ylcarbonyl]-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
61	4-biphenyl	H	OH	0	O	naphthalen-1-yl
62	naphthalen-2-yl	H	OH	0	O	<i>N</i> -cyclopropyl methyl-indol-3-yl
63	naphthalen-2-yl	H	OH	0	O	4-Cl- <i>N</i> -methyl-indol-3-yl
64	benzothiophen-2-yl	H	OH	0	O	naphthalen-1-yl
65	naphthalen-2-yl	H	OH	0	O	5-cyano- <i>N</i> -methyl-indol-3-yl
66	4-hydroxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
67	(6-Br)-naphthalen-2-yl	H	OH	0	O	5-Cl-benzothiophen-3-yl
68	naphthalen-2-yl	H	OH	0	O	Indol-3-yl
69	2-amino-benzothiazol-6-yl	H	OH	0	O	5-Cl-benzothiophen-3-yl
70	3-(Cyclohexylamino) methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
71	naphthalen-2-yl	H	OH	0	O	5-Ph-benzothiophen-3-yl
72	3-(<i>N</i> -benzyl-amino-carbonyloxymethyl) naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
73	3-(pyridin-4-yl-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
74	naphthalen-2-yl	H	OH	0	O	5-methoxy- <i>N</i> -methyl-indol-3-yl
75	3-(methoxycarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl

Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
76	naphthalen-2-yl	H	OH	0	O	6-Br-benzothiophen-3-yl
77	naphthalen-2-yl	H	OH	0	O	<i>N</i> -isopropyl-indol-3-yl
78	4-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
79	quinolin-6-yl	H	OH	0	O	naphthalen-1-yl
81	4-trifluoromethyl-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
82	naphthalen-2-yl	H	OH	0	O	<i>N</i> -phenyl-indol-3-yl
83	4-(1 <i>H</i> -indol-3-yl)-piperidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
85	indanyl	H	OH	0	O	naphthalen-1-yl
86	naphthalen-2-yl	H	OH	0	O	5-Cl-1,1-dioxo-benzothiophen-3-yl
87	((3-phenyl)pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
89	naphthalen-2-yl	H	Ph	0	O	5-Cl-benzothiophen-3-yl
90	((3-methyl)-cyclohexylamino)methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
91	3-(cyclopentyl- <i>N</i> -methylamino-carbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
92	3-((5-methoxycarbonyl)aminomethyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
93	3-(4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl

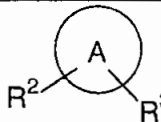
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
94	3-(phenylamino-carbonyloxy)methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
95	3-(phenylamino-carbonyl)methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
96	quinolin-2-yl	H	OH	0	O	naphthalen-1-yl
97	3-((4-phenoxy-phenyl)-aminocarbonyloxy methyl)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
98	naphthalen-2-yl	H	OH	0	O	5-(4-F-phenyl)-N-methyl-indol-3-yl
99	naphthalen-2-yl	H	OH	0	O	4-Br-benzo thiophen-3-yl
100	3-[(4-benzotriazol-1-yl-piperidin-1-ylcarbonyl)]-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
101	3-(4-phenyl)-piperidin-1-ylcarbonyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
102	3-((naphthalen-2-ylcarbonyl)piperidin-4-ylmethylamino-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
103	3-((3-benzenesulfonyl)-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
104	3-(N-[3-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]decane-8-carbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
105	3-(naphthalen-2-ylaminocarbonyloxy-methyl)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
106	2-fluorenyl	H	OH	0	O	naphthalen-1-yl
107	3-(benzylaminomethyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl

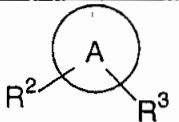
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
108	(3-OH)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
109	3-(<i>N</i> -benzyl-3-acrylamide)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
110	3-((5-phenyl)-pentylamino)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
111	3-(<i>N</i> -benzyl- <i>N</i> -methylaminocarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
112	3-[(5H-dibenzo-[a,d]cyclohepten-5-yl)-propyl]-methyl-amino-methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
113	3-(4-(benzothiazol-2-yl-piperidin-1-ylcarbonyl))-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
114	1-(2-oxo-2-(4-phenyl-piperidin-1-yl)-ethoxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
115	3-([2-(3,4-dimethoxy-phenyl)-ethyl]- <i>N</i> -methylaminocarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
116	naphthalen-2-yl	H	OH	0	O	1-Me-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine
117	3-((4-OH-cyclohexylamino)-methyl)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
118	naphthalen-2-yl	H	CH ₃	0	O	2-carboxy-benzothiophen-3-yl
119	3-(benzylaminocarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
121	3-(3-phenyl-allyloxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
122	3-(benzyloxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl

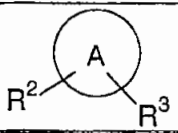
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
123	3-(methoxycarbonyl-methoxy)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
124	3-(cyclopentylamino-methyl)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
125	naphthalen-2-yl	H	OH	0	O	5-Cl-benzothiophen-2-yl
126	3-(phenethyl-methylaminomethyl)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
127	naphthalen-2-yl	H	CH ₃	0	O	2-(benzylaminocarbonyl)-benzothiophen-3-yl
128	naphthalen-2-yl	H	OH	0	O	N-phenyl-indol-4-yl
129	indol-5-yl	H	OH	0	O	naphthalen-1-yl
130	3-(3-phenyl-propylcarbamoyl)-methoxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
131	3-(2-phenyl-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
132	3-amino-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
133	3-((5-hydroxy-pentylamino)-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
134	1-(methoxycarbonyl-methoxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
135	benzo[1,3]dioxolyl	H	OH	0	O	naphthalen-1-yl
137	isoquinolin-3-yl	H	OH	0	O	naphthalen-1-yl
138	3-phenoxy-phenyl	H	OH	0	O	naphthalen-1-yl
139	3-(isopropoxy-carbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl

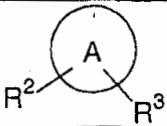
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
140	naphthalen-2-yl	H	OH	0	O	benzothiophen-2-yl
141	3-[[1-(naphthalen-2-ylcarbonyl)-piperidin-4-ylcarbonyl]-amino]-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
142	3-(benzylmethylaminomethyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
143	naphthalen-2-yl	H	OH	0	O	6-(4-butylphenyl)-benzothiophen-3-yl
144	trans 2-phenylcycloprop-1-yl	H	CH ₃	0	O	5-Cl-benzothiophen-3-yl
145	2-methoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
146	benzofuran-2-yl	H	CH ₃	0	O	5-Cl-benzothiophen-3-yl
147	2-nitro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
148	2-methylcarbonyloxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
149	2-hydroxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
150	pyridin-2-yl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
151	2-amino-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
152	3-trifluoromethyl-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
153	3-trifluoromethoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
154	3-methoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
155	2-methyl-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
156	2,6-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl

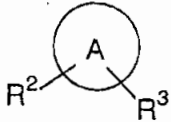
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
157	4-cyano-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
158	2-ureido-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
159	2-(NHC(=O)) ₂ NH ₂ -phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
160	2-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
161	3-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
162	3,5-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
163	2,3-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
164	2-bromo-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
165	2,3-dimethoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
166	3-nitro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
167	3-bromo-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
168	3,5-dimethoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
169	2,5-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
170	3,5-dichloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
171	2,4-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
172	3-amino-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
173	phenyl	-CH ₂ C(Me) ₂ CH ₂ O-		1	O	naphthalen-1-yl

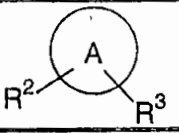
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
174	phenyl	3-methoxy-prop-1-yl	OH	1	O	naphthalen-1-yl
175	phenyl	3-methoxy-prop-1-yl	3-methoxy-prop-1-yl-oxy	1	O	naphthalen-1-yl
176	phenyl	2-(1,3-dioxolan-2-yl)-eth-1-yl	OH	1	O	naphthalen-1-yl
177	phenyl	-CH ₂ OC(=O)t-butyl	OH	1	O	naphthalen-1-yl
178	phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	naphthalen-1-yl
179	phenyl	(2-dimethylamino)-eth-1-yl	2-dimethylamino-ethoxy	1	O	naphthalen-1-yl
180	phenyl	-CH ₂ C(=O)NEt ₂	-OCH ₂ C(=O)NEt ₂	1	O	naphthalen-1-yl
181	phenyl	-(CH ₂) ₂ SC(=O)t-butyl	-O(CH ₂) ₂ SC(=O)t-butyl	1	O	naphthalen-1-yl
182	3,4-difluoro-phenyl	-CH ₂ OC(=O)t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
183	3,4-difluoro-phenyl	(2-dimethylamino)-eth-1-yl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
184	3,4-difluoro-phenyl	(2-amino)-eth-1-yl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
185	3,4-difluoro-phenyl	-CH ₂ C(=O)NEt ₂	CH ₃	1	O	5-Cl-benzothiophen-3-yl
186	3,4-difluoro-phenyl	-CH ₂ OC(=O)t-butyl	-OCH ₂ OC(=O)t-butyl	1	O	5-Cl-benzothiophen-3-yl
187	3,4-difluoro-phenyl	-CH ₂ OC(=O)t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
188	3,4-difluoro-phenyl	-CH ₂ C(=O)NEt ₂	-OCH ₂ C(=O)NEt ₂	1	O	5-Cl-benzothiophen-3-yl
189	3,4-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
190	3,4-difluoro-phenyl	-CH ₂ OC(=O)methyl	OH	1	O	5-Cl-benzothiophen-3-yl

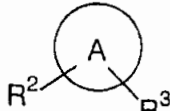
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
191	3,4-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
192	2-methoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
193	pyridin-2-yl	H	OH	1	O	5-Cl-benzothiophen-3-yl
194	3-trifluoromethoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
195	3-methoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
196	2,6-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
197	2-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
198	3-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
199	3,5-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
200	2,3-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
201	2-bromo-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
202	2,3-dimethoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
203	3-nitro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
204	3-bromo-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
205	3,5-dimethoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
206	2,5-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
207	3,5-dichloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl

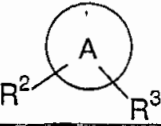
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
208	2,4-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
209	3-amino-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
210	2-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
211	pyridin-2-yl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
212	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
213	3-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
214	2,6-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
215	2-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
216	3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
217	3,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
218	2,3-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
219	2-bromo-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
220	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
221	3-nitro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
222	3-bromo-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
223	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
224	2,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl

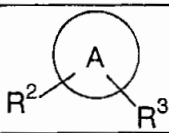
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
225	3,5-dichloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
226	2,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
227	3-amino-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
228	2-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
229	pyridin-2-yl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
230	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
231	3-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
232	2,6-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
233	2-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
234	3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
235	3,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
236	2,3-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
237	2-bromo-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
238	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
239	3-nitro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
240	3-bromo-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl

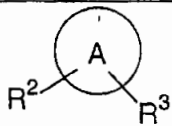
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
241	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
242	2,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
243	3,5-dichloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
244	2,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
245	3-amino-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
246	2-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
247	pyridin-2-yl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
248	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
249	3-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
250	2,6-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
251	2-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
252	3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
253	3,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
254	2,3-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
255	2-bromo-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
256	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
257	3-nitro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl

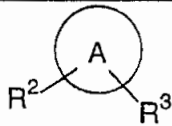
Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
258	3-bromo-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
259	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
260	2,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
261	3,5-dichloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
262	2,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
263	3-amino-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
264	2-methoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
265	pyridin-2-yl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
266	3-trifluoromethoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
267	3-methoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
268	2,6-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
269	2-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
270	3-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
271	3,5-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
272	2,3-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
273	2-bromo-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
274	2,3-dimethoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
275	3-nitro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
276	3-bromo-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
277	3,5-dimethoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
278	2,5-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
279	3,5-dichloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
280	2,4-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
281	3-amino-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
282	2-methoxy-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
283	pyridin-2-yl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
284	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
285	3-methoxy-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
286	2,6-difluoro-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
287	2-chloro-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
288	3-chloro-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
289	3,5-difluoro-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
290	2,3-difluoro-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl
291	2-bromo-phenyl	-CH ₂ OC(=O) isopropyloxy	OH	1	O	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
292	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
293	3-nitro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
294	3-bromo-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
295	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
296	2,5-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
297	3,5-dichloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
298	2,4-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
299	3-amino-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
300	3-fluoro-5-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
301	2-fluoro-3-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
302	4-fluoro-3-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
303	2-fluoro-5-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
304	3,5-dibromo-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
305	3-cyano-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
306	2-cyano-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
307	3-fluoro-5-trifluoromethyl-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
308	3-fluoro-5-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
309	2-fluoro-3-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
310	4-fluoro-3-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
311	2-fluoro-5-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
312	3,5-dibromo-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
313	3-cyano-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
314	2-cyano-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
315	3-fluoro-5-trifluoromethyl-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
316	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
317	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
318	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
319	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
320	3,5-dibromo-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
321	3-cyano-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
322	2-cyano-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
323	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
324	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
325	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
326	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
327	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
328	3,5-dibromo-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
329	3-cyano-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
330	2-cyano-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
331	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
332	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
333	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
334	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
335	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
336	3,5-dibromo-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
337	3-cyano-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
338	2-cyano-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
339	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
340	3-fluoro-5-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
341	2-fluoro-3-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
342	4-fluoro-3-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	n	W	Z-R ⁴
343	2-fluoro-5-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
344	3,5-dibromo-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
345	3-cyano-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
346	2-cyano-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
347	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ CH ₂ CH ₂ O-		1	O	5-Cl-benzothiophen-3-yl
348	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
349	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
350	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
351	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
352	3,5-dibromo-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
353	3-cyano-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
354	2-cyano-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
355	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl

Embodiments of the present invention include those compounds of Formula (II) shown in Table II:

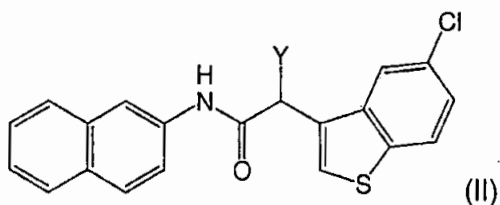
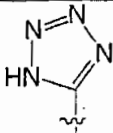


Table II

Cpd	Y
50	-SO ₃ H
80	-OC(=O)NH ₂
84	-CO ₂ H
88	
120	-CH ₂ OSO ₂ NH ₂
136	-CH ₂ OH

Preferred embodiments of the phosphonic and phosphinic acids of the present invention include those compounds of Formula (Ib) wherein the substituents are as previously defined (including any combinations of the preferred embodiments). Examples of some of these embodiments are shown in Table III:

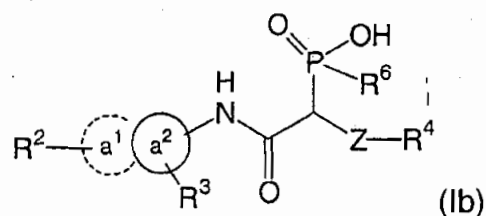
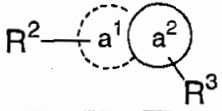
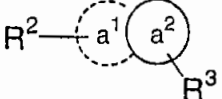
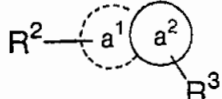
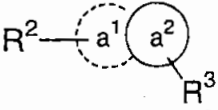


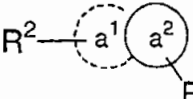
Table III

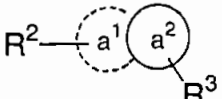
Cpd		R ⁶	Z-R ⁴
1	naphthalen-2-yl	CH ₃	5-Cl-N-methyl-indol-3-yl
3	naphthalen-2-yl	OH	5-Cl-N-methyl-indol-3-yl
5	naphthalen-2-yl	OH	5-Me-benzothiophen-2-yl
8	4-[[1-(naphthalen-2-carbonyl)-piperidin-4-ylcarbonyl]-amino]-naphthalen-2-yl	OH	naphthalen-1-yl

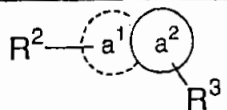
Cpd		R^6	$Z-R^4$
9	naphthalen-2-yl	OH	5-Cl-benzothiophen-3-yl
10	naphthalen-2-yl	OH	5-F-benzothiophen-3-yl
11	naphthalen-2-yl	OH	5-F- <i>N</i> -methyl-indol-3-yl
13	naphthalen-2-yl	OH	5-Br- <i>N</i> -methyl-indol-3-yl
20	naphthalen-2-yl	CH ₃	5-Cl-benzothiophen-3-yl
22	naphthalen-2-yl	H	<i>N</i> -methyl-indol-3-yl
23	naphthalen-2-yl	H	5-Br-benzothiophen-3-yl
26	naphthalen-2-yl	OH	benzothiophen-3-yl
27	naphthalen-2-yl	OH	<i>N</i> -(3-phenyl-allyl)-indol-3-yl
28	naphthalen-2-yl	CH ₂ CH ₃	5-Cl-benzothiophen-3-yl
30	benzothiazol-6-yl	OH	5-Cl-benzothiophen-3-yl
31	naphthalen-2-yl	OH	naphthalen-1-yl
32	naphthalen-2-yl	CH ₃	2-(4-phenyl-piperidine-1-carbonyl)-benzothiophen-3-yl
33	naphthalen-2-yl	CH ₃	naphthalen-1-yl
34	naphthalen-2-yl	3-methoxy-propyl	5-Cl-benzothiophen-3-yl
35	naphthalen-2-yl	CH ₃	2-(4-(4-methoxyphenyl)-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
36	naphthalen-2-yl	phenethyl	5-Cl-benzothiophen-3-yl

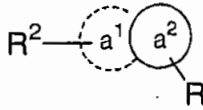
Cpd		R^6	$Z-R^4$
39	naphthalen-2-yl	3-(benzo [1,3]dioxol-5-yl)-propyl	5-Cl-benzothiophen-3-yl
40	naphthalen-2-yl	3-(naphthylen-1-yl)propyl	5-Cl-benzothiophen-3-yl
41	naphthalen-2-yl	CH ₃	2-(4-(Benzyloxycarbonyl)-piperazin-1-ylcarbonyl))-benzothiophen-3-yl
43	naphthalen-2-yl	3-(4-hydroxy phenyl) propyl	5-Cl-benzothiophen-3-yl
44	3-((benzoyl-piperidin-4-yl-amino)-methyl)-naphthalen-2-yl	OH	naphthalen-1-yl
45	naphthalen-2-yl	OH	5-Cl-benzothiophen-3-yl
46	3-[(1-phenyl)-cyclohex-1-enyl-4-N-methylamino-carbonyl]]-naphthalen-2-yl	OH	naphthalen-1-yl
47	naphthalen-2-yl	CH ₃	2-((4-F-phenyl)-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
48	naphthalen-2-yl	(3-phenyl) propyl	5-Cl-benzothiophen-3-yl
51	naphthalen-2-yl	(4-phenyl) butyl	5-Cl-benzothiophen-3-yl
52	naphthalen-2-yl	OH	6-Cl-N-methyl-indol-3-yl
53	naphthalen-2-yl	3-(4-methoxy phenyl) propyl	5-Cl-benzothiophen-3-yl
54	3-[4-((3-phenethyl)-pyrrolidin-1-ylcarbonyl)]-naphthalen-2-yl	OH	naphthalen-1-yl

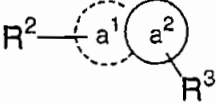
Cpd		R ⁶	Z-R ⁴
55	benzothiophen-5-yl	OH	5-Cl-benzothiophen-3-yl
56	naphthalen-2-yl	OH	5-carboxy- <i>N</i> -Me-indol-3-yl-
57	quinolin-3-yl	OH	naphthalen-1-yl
58	naphthalen-2-yl	OH	7-Cl- <i>N</i> -methyl-indol-3-yl
59	benzo[b]thiophen-6-yl	OH	naphthalen-1-yl
60	3-[4-(6-Chloro-2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidin-1-ylcarbonyl]-naphthalen-2-yl	OH	naphthalen-1-yl
61	<i>p</i> -biphenyl	OH	naphthalen-1-yl
62	naphthalen-2-yl	OH	<i>N</i> -cyclopropylmethyl-indol-3-yl
63	naphthalen-2-yl	OH	4-Cl- <i>N</i> -methyl-indol-3-yl
64	benzothiophen-2-yl	OH	naphthalen-1-yl
65	naphthalen-2-yl	OH	5-cyano- <i>N</i> -methyl-indol-3-yl
67	(6-Br)-naphthalen-2-yl	OH	5-Cl-benzothiophen-3-yl
68	naphthalen-2-yl	OH	Indol-3-yl
69	2-amino-benzothiazol-6-yl	OH	5-Cl-benzothiophen-3-yl
70	3-(cyclohexylamino)methyl-naphthalen-2-yl	OH	naphthalen-1-yl
71	naphthalen-2-yl	OH	5-Ph-benzothiophen-3-yl

Cpd		R^6	$Z-R^4$
72	3-(N-benzyl-aminocarbonyloxy methyl) naphthalen-2-yl	OH	naphthalen-1-yl
73	3-(pyridin-4-yl-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
74	naphthalen-2-yl	OH	5-methoxy- <i>N</i> -methyl-indol-3-yl
75	3-(methoxycarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
76	naphthalen-2-yl	OH	6-Br-benzothiophen-3-yl
77	naphthalen-2-yl	OH	<i>N</i> -isopropyl-indol-3-yl
79	quinolin-6-yl	OH	naphthalen-1-yl
82	naphthalen-2-yl	OH	<i>N</i> -phenyl-indol-3-yl
83	(4-(1 <i>H</i> -indol-3-yl)-piperidin-1-ylcarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
85	Indanyl	OH	naphthalen-1-yl
86	naphthalen-2-yl	OH	5-Cl-1,1-dioxo-benzothiophen-3-yl
87	((3-phenyl)pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
89	naphthalen-2-yl	Ph	5-Cl-benzothiophen-3-yl
90	((3-methyl)-cyclohexyl-amino)methyl-naphthalen-2-yl	OH	naphthalen-1-yl
91	3-(cyclopentyl- <i>N</i> -methylamino-carbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
92	3-((Hexanoic acid methyl ester)aminomethyl)-naphthalen-2-yl	OH	naphthalen-1-yl

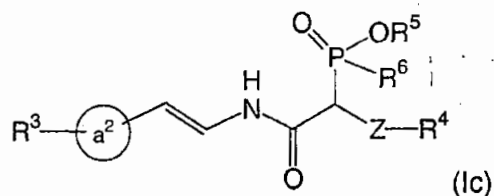
Cpd		R ⁵	Z-R ⁴
93	3-(4-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidin-1-ylcarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
94	3-(phenyl-aminocarbonyloxy-methyl)-naphthalen-2-yl	OH	naphthalen-1-yl
95	3-(phenyl-aminocarbonyl)-methyl-naphthalen-2-yl	OH	naphthalen-1-yl
96	quinolin-2-yl	OH	naphthalen-1-yl
97	3-((4-phenoxy-phenyl)-aminocarbonyloxymethyl)-naphthalen-2-yl	OH	naphthalen-1-yl
98	naphthalen-2-yl	OH	5-(4-F-phenyl)-N-methyl-indol-3-yl
99	naphthalen-2-yl	OH	4-Br-benzothiophen-3-yl
100	3-[(4-benzotriazol-1-yl-piperidin-1-ylcarbonyl)]-naphthalen-2-yl	OH	naphthalen-1-yl
101	3-(4-phenyl)-piperidin-1-ylcarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
102	3-((naphthalene-2-carbonyl)-piperidin-4-ylmethylamino-methyl)-naphthalen-2-yl	OH	naphthalen-1-yl
103	3-((3-benzenesulfonyl)-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
104	3-(N-[3-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]decane-8-carbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
105	3-(naphthalen-2-ylaminocarbonyloxy-methyl)-naphthalen-2-yl	OH	naphthalen-1-yl

Cpd		R ⁶	Z-R ⁴
106	2-fluorenyl	OH	naphthalen-1-yl
107	3-(benzylaminomethyl)-naphthalen-2-yl	OH	naphthalen-1-yl
108	(3-OH)naphthalen-2-yl	OH	naphthalen-1-yl
109	3-(N-benzyl-3-acrylamide)naphthalen-2-yl	OH	naphthalen-1-yl
110	3-((5-phenyl)pentylamino)-naphthalen-2-yl	OH	naphthalen-1-yl
111	3-(N-benzyl-N-methyl-amino-carbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
112	3-[(5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-methyl-amino-methyl-naphthalen-2-yl	OH	naphthalen-1-yl
113	3-(4-(benzothiazol-2-yl-piperidine-1-carbonyl))-naphthalen-2-yl	OH	naphthalen-1-yl
114	1-(2-oxo-2-(4-phenyl-piperidin-1-yl)-ethoxy)-naphthalen-2-yl	OH	naphthalen-1-yl
115	3-[2-(3,4-dimethoxy-phenyl)-ethyl]-N-methyl-aminocarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
116	naphthalen-2-yl	OH	1-Me-1H-pyrrolo[2,3-b]pyridine
117	3-((4-OH-cyclohexylamino)-methyl)-naphthalen-2-yl	OH	naphthalen-1-yl
118	naphthalen-2-yl	CH ₃	2-carboxy-benzothiophen-3-yl
119	3-(benzylaminocarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
121	3-(3-phenyl-allyloxy)-naphthalen-2-yl	OH	naphthalen-1-yl

Cpd		R ⁶	Z-R ⁴
122	3-(benzyloxy)-naphthalen-2-yl	OH	naphthalen-1-yl
123	3-(methoxycarbonyl-methoxy)-naphthalen-2-yl	OH	naphthalen-1-yl
124	3-(cyclopentylamino-methyl)-naphthalen-2-yl	OH	naphthalen-1-yl
125	naphthalen-2-yl	OH	5-Cl-benzothiophen-2-yl
126	3-(phenethyl-methylamino-methyl)naphthalen-2-yl	OH	naphthalen-1-yl
127	naphthalen-2-yl	CH ₃	2-(benzylaminocarbonyl)-benzothiophen-3-yl
128	naphthalen-2-yl	OH	N-phenyl-indol-4-yl
129	indol-5-yl	OH	naphthalen-1-yl
130	3-(3-phenyl-propylcarbamoyl)-methoxy)-naphthalen-2-yl	OH	naphthalen-1-yl
131	3-(2-phenyl-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
132	3-amino-naphthalen-2-yl	OH	naphthalen-1-yl
133	3-((5-hydroxypentylamino)-methyl)-naphthalen-2-yl	OH	naphthalen-1-yl
134	1-(1-oxy-acetic acid methyl ester)-naphthalen-2-yl	OH	naphthalen-1-yl
135	benzo[1,3]dioxolyl	OH	naphthalen-1-yl
137	isoquinolin-3-yl	OH	naphthalen-1-yl
138	3-phenoxy-phenyl	OH	naphthalen-1-yl

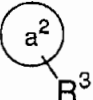
Cpd		R ⁶	Z-R ⁴
139	3-(isopropyloxycarbonyl)-naphthalen-2-yl	OH	naphthalen-1-yl
140	naphthalen-2-yl	OH	benzothiophen-2-yl
141	3-[[1-(naphthalen-2-ylcarbonyl)-piperidin-4-ylcarbonyl]-amino]-naphthalen-2-yl	OH	naphthalen-1-yl
142	3-(benzylmethyl aminomethyl)-naphthalen-2-yl	OH	naphthalen-1-yl
143	naphthalen-2-yl	OH	6-(4-butylphenyl)-benzothiophen-3-yl
146	benzofuran-2-yl	CH ₃	5-Cl-benzothiophen-3-yl

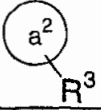
Preferred embodiments of the phosphonic and phosphinic acids of the present invention include those compounds of Formula (Ic) shown in Table IV:

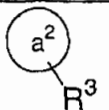


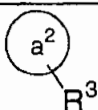
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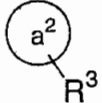
Table IV

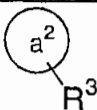
Cpd		R ⁵	R ⁶	Z-R ⁴
2	3,4-difluoro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
4	4-fluoro-phenyl	H	OH	5-Cl-N-methyl-indol-3-yl
6	3-fluoro-phenyl	H	CH ₃	5-Cl-N-methyl-indol-3-yl
7	3,4-difluoro-phenyl	H	CH ₃	5-Cl-N-methyl-indol-3-yl
12	4-amino-phenyl	H	OH	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	Z-R ⁴
14	phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
15	3-fluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
16	3,4-trifluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
17	3,4-difluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
18	phenyl	H	OH	5-Cl-benzothiophen-2-yl
19	4-fluoro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
21	2-fluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
24	4-fluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
25	pyridin-3-yl	H	OH	5-Cl-benzothiophen-3-yl
29	3,4-difluoro-phenyl	H	CH ₂ CH ₃	5-Cl-benzothiophen-3-yl
37	phenyl	H	OH	naphthalen-1-yl
38	4-methoxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl
42	4-methyl-phenyl	H	OH	5-Cl-benzothiophen-2-yl
49	3,4-dimethoxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl
66	4-hydroxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl
78	4-chloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
81	4-trifluoromethyl-phenyl	H	OH	5-Cl-benzothiophen-3-yl

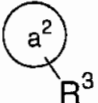
Cpd		R ⁵	R ⁶	Z-R ⁴
145	2-methoxy-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
146	benzofuran-2-yl	H	CH ₃	5-Cl-benzothiophen-3-yl
147	2-nitro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
148	2-methylcarbonyloxy-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
149	2-hydroxy-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
150	pyridin-2-yl	H	CH ₃	5-Cl-benzothiophen-3-yl
151	2-amino-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
152	3-trifluoromethyl-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
153	3-trifluoromethoxy-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
154	3-methoxy-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
155	2-methyl-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
156	2,6-difluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
157	4-cyano-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
158	2-ureido-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
159	2-(NHC(=O)) ₂ NH ₂ -phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
160	2-chloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
161	3-chloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	Z-R ⁴
162	3,5-difluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
163	2,3-difluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
164	2-bromo-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
165	2,3-dimethoxy-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
166	3-nitro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
167	3-bromo-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
168	3,5-dimethoxy-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
169	2,5-difluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
170	3,5-dichloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
171	2,4-difluoro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
172	3-amino-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
173	phenyl	-CH ₂ C(Me) ₂ CH ₂ O-		naphthalen-1-yl
174	phenyl	3-methoxy-prop-1-yl	OH	naphthalen-1-yl
175	phenyl	3-methoxy-prop-1-yl	3-methoxy-prop-1-yl-oxy	naphthalen-1-yl
176	phenyl	2-(1,3-dioxolan-2-yl)-eth-1-yl	OH	naphthalen-1-yl
177	phenyl	-CH ₂ OC(=O)t-butyl	OH	naphthalen-1-yl
178	phenyl	-CH ₂ CH ₂ CH ₂ O-		naphthalen-1-yl

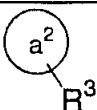
Cpd		R ⁵	R ⁶	Z-R ⁴
179	phenyl	(2-dimethylamino)-eth-1-yl	2-dimethyl amino-ethoxy	naphthalen-1-yl
180	phenyl	-CH ₂ C(=O)NEt ₂	-OCH ₂ C(=O)NEt ₂	naphthalen-1-yl
181	phenyl	-(CH ₂) ₂ SC(=O) t-butyl	-O(CH ₂) ₂ S C(=O) t-butyl	naphthalen-1-yl
182	3,4-difluoro-phenyl	1-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
183	3,4-difluoro-phenyl	(2-dimethylamino)-eth-1-yl	CH ₃	5-Cl-benzothiophen-3-yl
184	3,4-difluoro-phenyl	(2-amino)-eth-1-yl	CH ₃	5-Cl-benzothiophen-3-yl
185	3,4-difluoro-phenyl	-CH ₂ C(=O)NEt ₂	CH ₃	5-Cl-benzothiophen-3-yl
186	3,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
187	3,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
188	3,4-difluoro-phenyl	-CH ₂ C(=O)NEt ₂	-OCH ₂ C(=O)NEt ₂	5-Cl-benzothiophen-3-yl
189	3,4-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
190	3,4-difluoro-phenyl	-CH ₂ OC(=O) methyl	OH	5-Cl-benzothiophen-3-yl
191	3,4-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
192	2-methoxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl
193	pyridin-2-yl	H	OH	5-Cl-benzothiophen-3-yl
194	3-trifluoromethoxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl
195	3-methoxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl

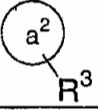
Cpd		R ⁵	R ⁶	Z-R ⁴
196	2,6-difluoro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
197	2-chloro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
198	3-chloro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
199	3,5-difluoro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
200	2,3-difluoro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
201	2-bromo-phenyl	H	OH	5-Cl-benzothiophen-3-yl
202	2,3-dimethoxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl
203	3-nitro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
204	3-bromo-phenyl	H	OH	5-Cl-benzothiophen-3-yl
205	3,5-dimethoxy-phenyl	H	OH	5-Cl-benzothiophen-3-yl
206	2,5-difluoro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
207	3,5-dichloro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
208	2,4-difluoro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
209	3-amino-phenyl	H	OH	5-Cl-benzothiophen-3-yl
210	2-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
211	pyridin-2-yl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
212	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl

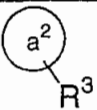
Cpd		R ⁵	R ⁶	Z-R ⁴
213	3-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
214	2,6-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
215	2-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
216	3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
217	3,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
218	2,3-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
219	2-bromo-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
220	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
221	3-nitro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
222	3-bromo-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
223	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
224	2,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
225	3,5-dichloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
226	2,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
227	3-amino-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
228	2-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
229	pyridin-2-yl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl

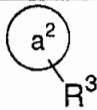
Cpd		R ⁵	R ⁶	Z-R ⁴
230	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
231	3-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
232	2,6-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
233	2-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
234	3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
235	3,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
236	2,3-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
237	2-bromo-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
238	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
239	3-nitro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
240	3-bromo-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
241	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
242	2,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
243	3,5-dichloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
244	2,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
245	3-amino-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
246	2-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl

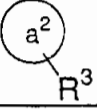
Cpd		R ⁵	R ⁶	Z-R ⁴
247	pyridin-2-yl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
248	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
249	3-methoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
250	2,6-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
251	2-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
252	3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
253	3,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
254	2,3-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
255	2-bromo-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
256	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
257	3-nitro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
258	3-bromo-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
259	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
260	2,5-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
261	3,5-dichloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
262	2,4-difluoro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
263	3-amino-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl

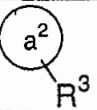
Cpd		R ⁵	R ⁶	Z-R ⁴
264	2-methoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
265	pyridin-2-yl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
266	3-trifluoromethoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
267	3-methoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
268	2,6-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
269	2-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
270	3-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
271	3,5-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
272	2,3-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
273	2-bromo-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
274	2,3-dimethoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
275	3-nitro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
276	3-bromo-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
277	3,5-dimethoxy-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
278	2,5-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
279	3,5-dichloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
280	2,4-difluoro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	Z-R ⁴
281	3-amino-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
282	2-methoxy-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
283	pyridin-2-yl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
284	3-trifluoromethoxy-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
285	3-methoxy-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
286	2,6-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
287	2-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
288	3-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
289	3,5-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
290	2,3-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
291	2-bromo-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
292	2,3-dimethoxy-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
293	3-nitro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
294	3-bromo-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
295	3,5-dimethoxy-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
296	2,5-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
297	3,5-dichloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	Z-R ⁴
298	2,4-difluoro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
299	3-amino-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
300	3-fluoro-5-chloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
301	2-fluoro-3-chloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
302	4-fluoro-3-chloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
303	2-fluoro-5-chloro-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
304	3,5-dibromo-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
305	3-cyano-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
306	2-cyano-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
307	3-fluoro-5-trifluoromethyl-phenyl	H	CH ₃	5-Cl-benzothiophen-3-yl
308	3-fluoro-5-chloro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
309	2-fluoro-3-chloro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
310	4-fluoro-3-chloro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
311	2-fluoro-5-chloro-phenyl	H	OH	5-Cl-benzothiophen-3-yl
312	3,5-dibromo-phenyl	H	OH	5-Cl-benzothiophen-3-yl
313	3-cyano-phenyl	H	OH	5-Cl-benzothiophen-3-yl
314	2-cyano-phenyl	H	OH	5-Cl-benzothiophen-3-yl

Cpd		R ⁵	R ⁶	Z-R ⁴
315	3-fluoro-5-trifluoromethyl-phenyl	H	OH	5-Cl-benzothiophen-3-yl
316	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
317	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
318	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
319	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
320	3,5-dibromo-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
321	3-cyano-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
322	2-cyano-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
323	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) t-butyl	CH ₃	5-Cl-benzothiophen-3-yl
324	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
325	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
326	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
327	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
328	3,5-dibromo-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
329	3-cyano-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
330	2-cyano-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl
331	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) t-butyl	-OCH ₂ OC(=O) t-butyl	5-Cl-benzothiophen-3-yl

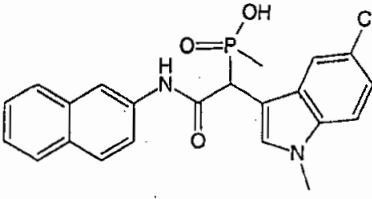
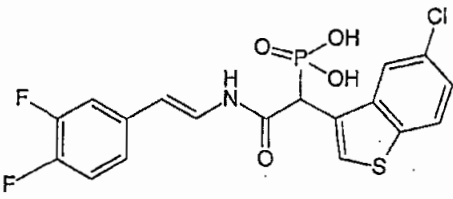
Cpd		R ⁵	R ⁶	Z-R ⁴
332	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
333	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
334	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
335	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
336	3,5-dibromo-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
337	3-cyano-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
338	2-cyano-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
339	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) t-butyl	OH	5-Cl-benzothiophen-3-yl
340	3-fluoro-5-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
341	2-fluoro-3-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
342	4-fluoro-3-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
343	2-fluoro-5-chloro-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
344	3,5-dibromo-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
345	3-cyano-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
346	2-cyano-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
347	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ CH ₂ CH ₂ O-		5-Cl-benzothiophen-3-yl
348	3-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl

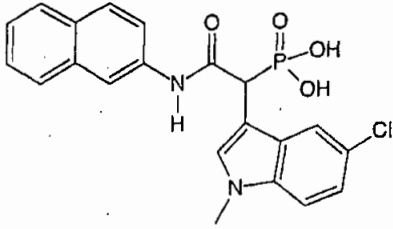
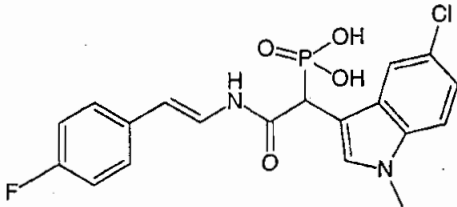
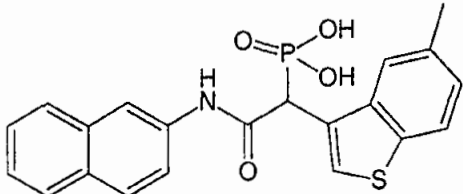
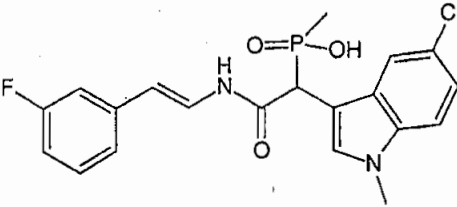
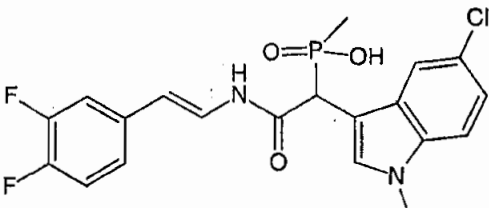
Cpd		R ⁵	R ⁶	Z-R ⁴
349	2-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
350	4-fluoro-3-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
351	2-fluoro-5-chloro-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
352	3,5-dibromo-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
353	3-cyano-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
354	2-cyano-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl
355	3-fluoro-5-trifluoromethyl-phenyl	-CH ₂ OC(=O) isopropoxy	OH	5-Cl-benzothiophen-3-yl

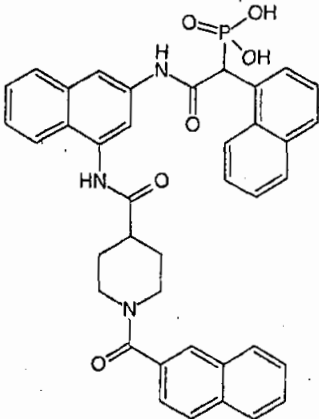
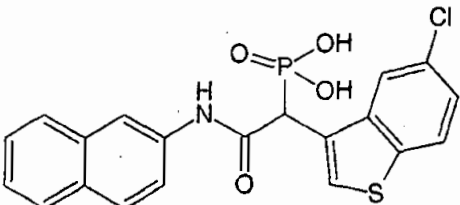
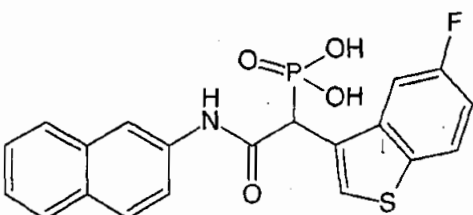
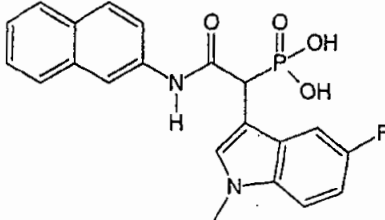
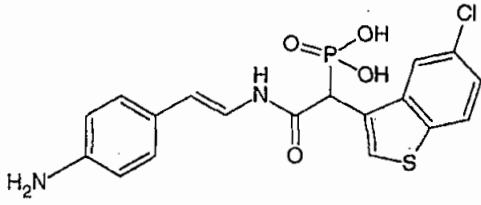
A preferred embodiment of the present invention includes the representative compounds presented in Table V.

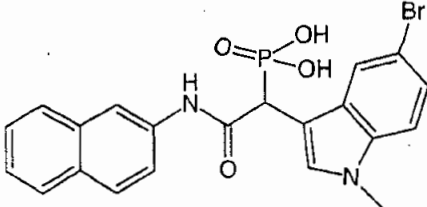
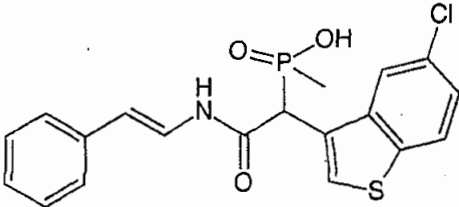
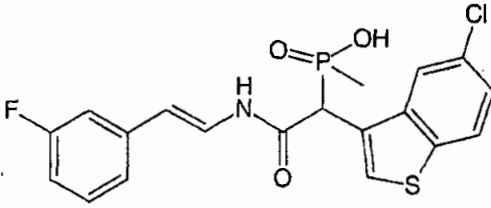
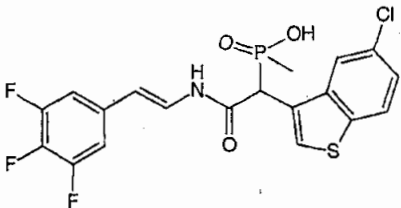
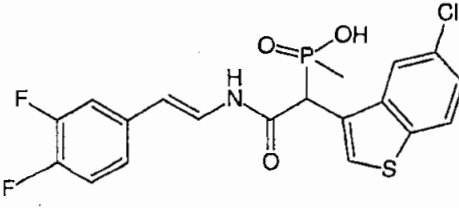
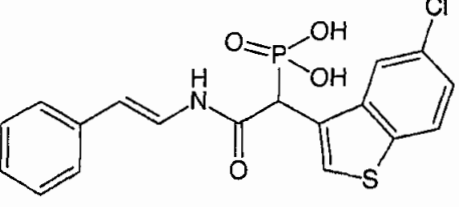
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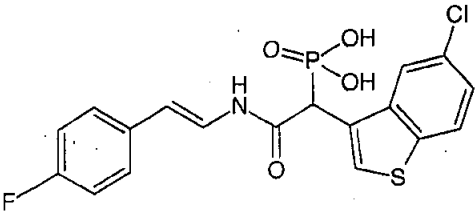
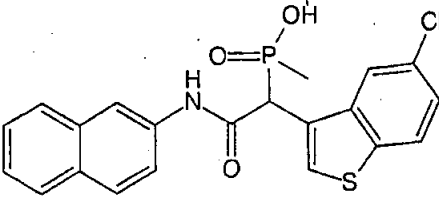
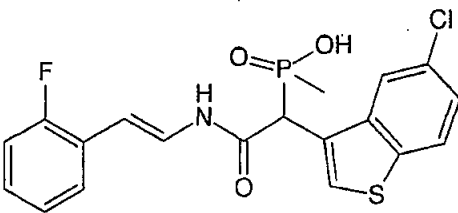
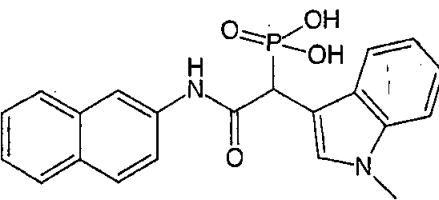
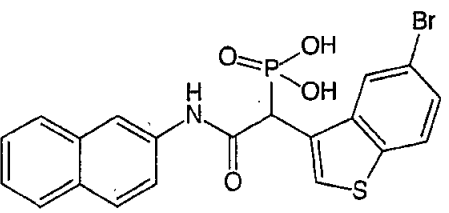
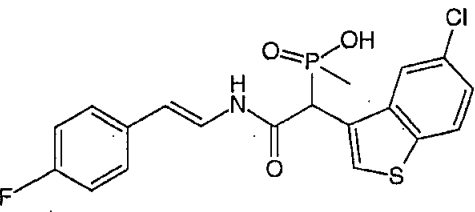
Table V

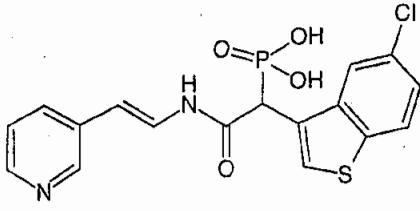
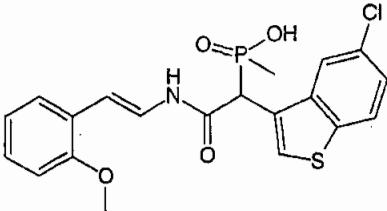
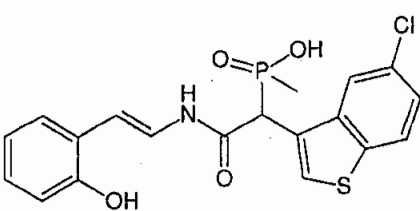
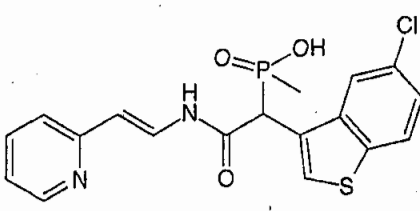
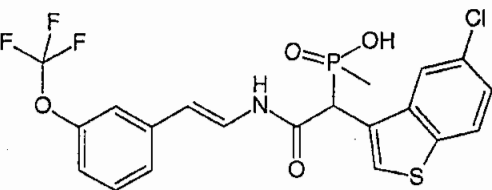
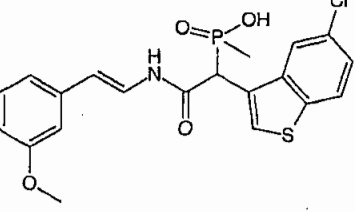
Cpd	
1	
2	

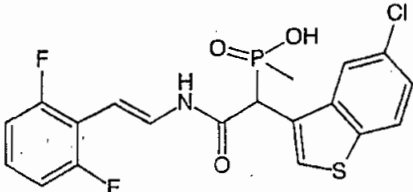
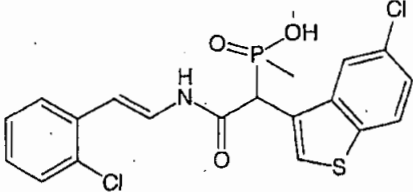
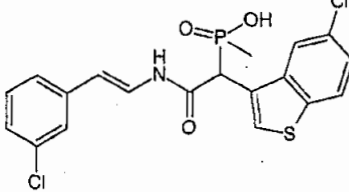
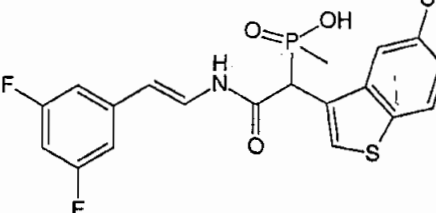
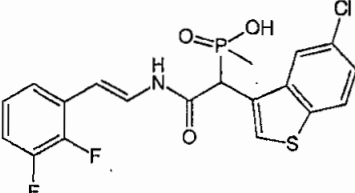
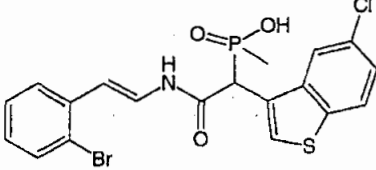
Cpd	
3	
4	
5	
6	
7	

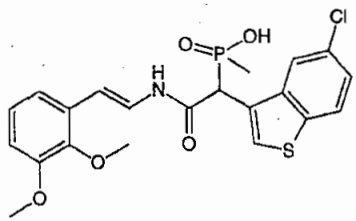
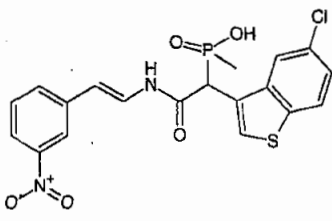
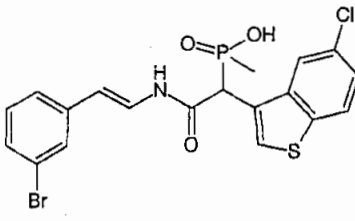
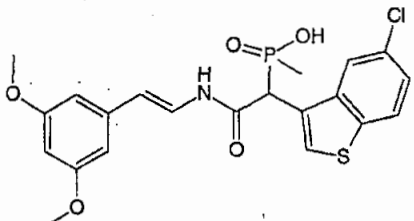
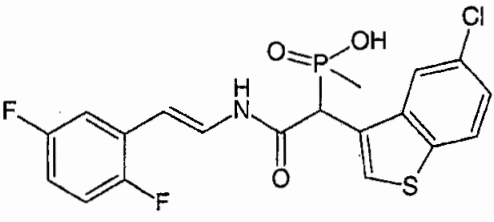
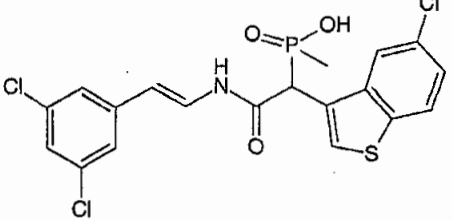
Cpd	
8	
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10	
11	
12	

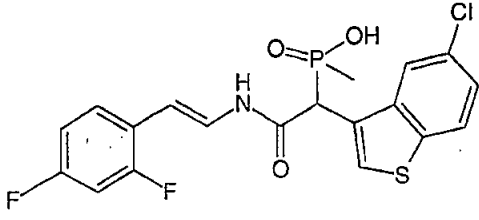
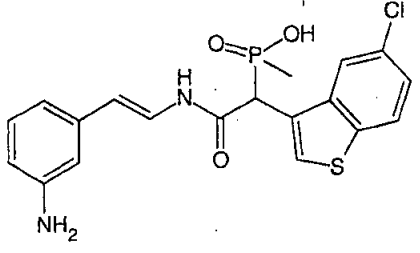
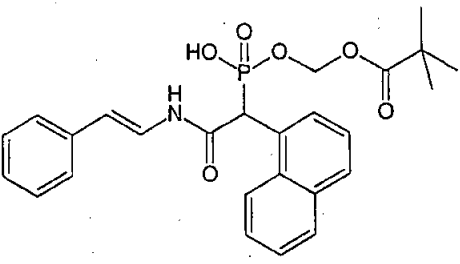
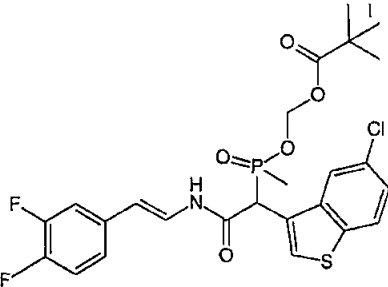
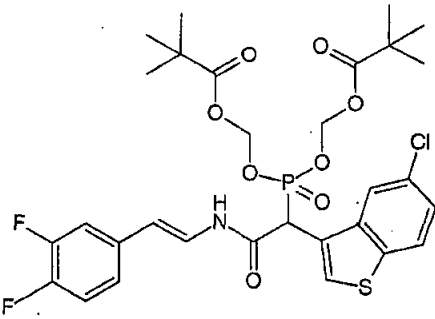
Cpd	
13	
14	
15	
16	
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18	

Cpd	
19	
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22	
23	
24	

Cpd	
25	 <chem>Clc1ccc2c(c1)sc(c2)C(=O)N/C=C/c3ccncc3</chem>
145	 <chem>COc1cccc(c1)/C=C/N/C(=O)C2(COP(=O)(O)O)c3cc(Cl)ccc3S2</chem>
149	 <chem>Clc1ccc2c(c1)sc(c2)C(=O)N/C=C/c3ccccc3O</chem>
150	 <chem>Clc1ccc2c(c1)sc(c2)C(=O)N/C=C/c3ccncc3</chem>
153	 <chem>Clc1ccc2c(c1)sc(c2)C(=O)N/C=C/c3ccc(OC(F)(F)F)cc3</chem>
154	 <chem>COc1ccc(cc1)/C=C/N/C(=O)C2(COP(=O)(O)O)c3cc(Cl)ccc3S2</chem>

Cpd	
156	
160	
161	
162	
163	
164	

Cpd	
165	
166	
167	
168	
169	
170	

Cpd	
171	
172	
177	
182	
186	

Cpd	
187	
189	
191	

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." FDA approved

5 pharmaceutically acceptable salt forms (*Ref. International J. Pharm.* **1986**, 33, 201-217; *J. Pharm. Sci.*, **1977**, Jan, 66(1), p1) include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

Pharmaceutically acceptable acidic/anionic salts include, and are not limited to

10 acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate,

15 polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate,

teoclate, tosylate, and triethiodide. Organic or inorganic acids also include, and are not limited to, hydriodic, perchloric, sulfuric, phosphoric, propionic, glycolic, methanesulfonic, hydroxyethanesulfonic, oxalic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, saccharinic, and trifluoroacetic acid.

- 5 Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, tris(hydroxymethyl)methylamine, tromethamine), ammonia, benzathine, *t*-butylamine, calcium, chlorprocaine, choline, cyclohexylamine, diethanolamine, ethylenediamine, lithium, L-lysine, magnesium, meglumine, NH₃, NH₄OH, 10 N-methyl-D-glucamine, piperidine, potassium, procaine, quinine, SEH, sodium, triethanolamine (TEA), imidazole, and zinc.

- Compounds of the present invention may be contacted with a pharmaceutically acceptable cation selected from the group consisting of aluminum, 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, 15 tris(hydroxymethyl)methylamine, tromethamine), ammonia, benzathine, *t*-butylamine, calcium, chlorprocaine, choline, cyclohexylamine, diethanolamine, ethylenediamine, lithium, L-lysine, magnesium, meglumine, NH₃, NH₄OH, N-methyl-D-glucamine, piperidine, potassium, procaine, quinine, SEH, sodium, triethanolamine (TEA), imidazole, and zinc to form a salt.

- 20 Preferred cations for use with the instant compounds are selected from the group consisting of benzathine, *t*-butylamine, calcium, choline, cyclohexylamine, diethanolamine, ethylenediamine, L-lysine, NH₃, NH₄OH, N-methyl-D-glucamine, piperidine, potassium, procaine, quinine, sodium, triethanolamine, imidazole, and tris(hydroxymethyl)methylamine (tromethamine).

- 25 More preferably, cations for use with the instant compounds are selected from the group consisting of *t*-butylamine, NH₄OH, imidazole, sodium, and tris(hydroxymethyl)methylamine (tromethamine).

 Most preferably, the cations for use with the instant compounds are tromethamine and sodium.

- 30 The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds, which are readily convertible *in vivo* into an active compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or a prodrug 35 compound which would be obviously included within the scope of the invention although not specifically disclosed. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H.

Bundgaard, Elsevier, 1985. Phosphonic acid prodrugs (as described in De Lombaert S., et al, Non-Peptidic Inhibitors of Neutral Endopeptidase 24.11; Design and Pharmacology of Orally Active Phosphonate Prodrugs, *Bioorganic and Medicinal Chemistry Letters*, **1995**, 5(2), 151-154; and, De Lombaert S., et al, N-Phosphonomethyl Dipeptides and Their
5 Phosphonate Prodrugs, a New Generation Neutral Endopeptidase (NEP, EC 3.424.11) Inhibitors, *J. Med. Chem.*, **1994**, 37, 498-511) and phosphinic acid prodrugs are intended to be included within the scope of the present invention.

The compounds according to this invention may have at least one chiral center and thus may exist as enantiomers. In addition, the compounds of the present invention may
10 also possess two or more chiral centers and thus may also exist as diastereomers. Where the processes for the preparation of the present compounds give rise to a mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. Accordingly, the compounds may be prepared as a racemic mixture or, by either enantiospecific synthesis or resolution, as individual enantiomers. The
15 compounds may, for example, be resolved from a racemic mixture into their component racemates by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active base, followed by fractional crystallization and regeneration of the compounds of this invention. The racemic mixture may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic
20 separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on
25 any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

30 Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

35 As used herein, unless otherwise noted, "alkyl" whether used alone or as part of a substituent group refers to straight and branched carbon chains having 1 to 8 carbon atoms or any number within this range. The term "alkoxy" refers to an -Oalkyl substituent

group, wherein alkyl is as defined *supra*. Similarly, the terms "alkenyl" and "alkynyl" refer to straight and branched carbon chains having 2 to 8 carbon atoms or any number within this range, wherein an alkenyl chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. An alkyl and alkoxy chain may be substituted on a terminal carbon atom or, when acting as a linking group, within the carbon chain.

The term "cycloalkyl" refers to saturated or partially unsaturated, monocyclic or polycyclic hydrocarbon rings of from 3 to 20 carbon atom members (preferably from 3 to 14 carbon atom members). Further, a cycloalkyl ring may optionally be fused to one or more cycloalkyl rings. Examples of such rings include, and are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl.

The term "heterocyclyl" refers to a nonaromatic cyclic ring of 5 to 10 members in which 1 to 4 members are nitrogen or a nonaromatic cyclic ring of 5 to 10 members in which zero, one or two members are nitrogen and up to two members is oxygen or sulfur; wherein, optionally, the ring contains zero, one or two unsaturated bonds. Alternatively, the heterocyclyl ring may be fused to a benzene ring (benzo fused heterocyclyl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl or cycloalkenyl ring, a 5 to 7 membered heterocyclyl ring (of the same definition as above but absent the option of a further fused ring) or fused with the carbon of attachment of a cycloalkyl, cycloalkenyl or heterocyclyl ring to form a spiro moiety. For instant compounds of the invention, the carbon atom ring members that form the heterocyclyl ring are fully saturated. Other compounds of the invention may have a partially saturated heterocyclyl ring. Additionally, the heterocyclyl can be bridged to form bicyclic rings. Preferred partially saturated heterocyclyl rings may have from one to two double bonds. Such compounds are not considered to be fully aromatic and are not referred to as heteroaryl compounds. Examples of heterocyclyl groups include, and are not limited to, pyrrolinyl (including 2*H*-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, and piperazinyl.

The term "aryl" refers to an unsaturated, aromatic monocyclic ring of 6 carbon members or to an unsaturated, aromatic polycyclic ring of from 10 to 20 carbon members. Examples of such aryl rings include, and are not limited to, phenyl, naphthalenyl and anthracenyl. Preferred aryl groups for the practice of this invention are phenyl and naphthalenyl.

The term "benzo fused cycloalkyl" refers to a bicyclic or tricyclic ring structure wherein at least one of the ring substituents is phenyl or naphthalenyl and at least one of the other substituents is a cycloalkyl ring (as cycloalkyl was previously defined). For the purpose of these definitions, the cycloalkyl rings may be fused to an additional benzene ring (to provide

fused multiple ring systems such as fluorene). Example of such benzo fused cycloalkyls include, but are not limited to, indanyl, 1,2,3,4-tetrahydronaphthalenyl and fluorenyl.

The term "heteroaryl" refers to an aromatic ring of 5 or 6 members wherein the ring consists of carbon atoms and has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen or sulfur. In the case of 5 membered rings, the heteroaryl ring contains one member of nitrogen, oxygen or sulfur and, in addition, may contain up to three additional nitrogens. In the case of 6 membered rings, the heteroaryl ring may contain from one to three nitrogen atoms. For the case wherein the 6 membered ring has three nitrogens, at most two nitrogen atoms are adjacent. Optionally, the heteroaryl ring is fused to a benzene ring (benzo fused heteroaryl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl ring or a 5 to 7 membered heterocyclo ring (as defined supra but absent the option of a further fused ring). Examples of heteroaryl groups include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl; fused heteroaryl groups include indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, quinoliziny, quinolinyl, isoquinolinyl, and quinazolinyl.

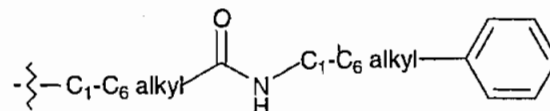
The term "arylalkyl" means an alkyl group substituted with an aryl group (e.g., benzyl and phenethyl). Similarly, the term "arylalkoxy" indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy).

The term "halogen" refers to fluorine, chlorine, bromine, and iodine. Substituents that are substituted with multiple halogens are substituted in a manner that provides compounds which are stable.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., arylalkyl and alkylamino), it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁-C₆) shall refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root. For alkyl, and alkoxy substituents the designated number of carbon atoms includes all of the independent member included in the range specified individually and all the combination of ranges within in the range specified. For example C₁₋₆ alkyl would include methyl, ethyl, propyl, butyl, pentyl and hexyl individually as well as sub-combinations thereof (e.g., C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₂₋₆, C₃₋₆, C₄₋₆, C₅₋₆, C₂₋₅, etc.). However, for clarity in the terms "C₉-C₁₄ benzo fused cycloalkyl", "C₉-C₁₄ benzo fused cycloalkenyl", "C₉-C₁₄ benzo fused aryl"; C₉-C₁₄ refers to the number of carbon atoms both in the benzene ring (6) and the number of atoms in the ring fused to the benzene ring, but does not include carbon atoms that may be pendent from these multiple ring systems. The amount

of substituents attached to a moiety "optionally substituted with one to five substituents" is limited to that amount of open valences on the moiety available for substitution.

In general, under standard nomenclature rules used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent
 5 functionality toward the point of attachment. Thus, for example, a "phenylC₁-C₆ alkylamidoC₁-C₆alkyl" substituent refers to a group of the formula:



It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood
 10 that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

Illustrative of the invention is a composition comprising a pharmaceutically acceptable
 15 carrier and any of the compounds described above. Also illustrative of the invention is a composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. A further illustration of the invention is a process for making a composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. The present invention also provides compositions comprising one or more
 20 compounds of this invention in association with a pharmaceutically acceptable carrier.

The compounds of the present invention are useful serine protease inhibitors (in particular, inhibitors of chymase) useful for treating inflammatory, and serine protease mediated disorders. Serine proteases such as chymase produced by mast cells have been recognized to be involved in a variety of inflammatory and wound healing events (e.g.,
 25 angiogenesis, collagen deposition and cell proliferation). Chymase plays these roles by activating a variety of pre-existing factors present in the microenvironment surrounding the mast cells. For example, just to name a few of these interactions chymase activates SCF, angiotensin I to angiotensin II, endothelin 1, type 1 procollagen, metalloproteinases, IL-1B, TGF-β, as well as, degrades the extracellular matrix (de Paulis *et al.* Int Arch Allerg
 30 Immunol 118 (1999) 422-425; Longley *et al.* Proc Natl Acad Sci USA 94 (1997) 9017-9021). Consequently, the release of chymase plays significant role in a variety of pathological conditions associated with vascular proliferation, fibrosis, tissue remodeling, inflammation, and the like.

Some of these, inflammatory and serine protease mediated disorders include, and are
 35 not limited to, allergic rhinitis, viral rhinitis, asthma, chronic obstructive pulmonary diseases,

bronchitis, pulmonary emphysema, acute lung injury (e.g. adult (acute) respiratory distress syndrome) psoriasis, arthritis, reperfusion injury, ischemia, hypertension, hypercardia myocardial infarction, heart failure damage associated with myocardial infarction, cardiac hypertrophy, arteriosclerosis, saroidosis, vascular stenosis or restenosis (e.g., associated with
5 vascular injury, angioplasty, vascular stents or vascular grafts), pulmonary fibrosis, kidney fibrosis (e.g., associated with glomerulonephritis), liver fibrosis, post surgical adhesion formation, systemic sclerosis, keloid scars rheumatoid arthritis, bullous pemphigoid and atherosclerosis. Additionally, these compounds can be used for modulating wound healing and remodeling (e.g., cardiac hypertrophy) as well as immune modulation. The utility of the
10 compounds to treat inflammatory and serine protease mediated disorders is illustrated by the following non-limiting discussions of the proposed mechanisms of actions of chymase. Other disorders that can be treated with chymase inhibitors can be determined according to the procedures described herein and the use of animal knock-out models and the like.

As mentioned above, chymase converts angiotensin I into angiotensin II, and this
15 activity has been associated with vascular proliferation. In human vascular extracts only about 8% of angiotensin II activity is inhibited with an angiotensin converting enzyme inhibitor (lisinopril) while 95% is inhibited by a chymase inhibitor. In vein grafts, vascular injury associated with catheter or balloon injury, chymase induces vascular hyperplasia and restenosis in dogs (Takai and Miyazaki, 21 (2003) 185-189). This same mechanism of
20 action would also be expected to apply to restenosis associated with the use of vascular stents. Pathological serine protease mediated disorders associated with angiotensin II, including but not limited to hypertension, hypercardia myocardial infarction, arteriosclerosis, saroidosis, vascular stenosis or restenosis (e.g., associated with vascular injury, angioplasty, vascular stents or vascular grafts), and the like.

25 Pathological fibrosis can be associated with the degeneration of organs (e.g., skin, heart, kidneys or liver) or as an undesirable outcome of surgery. Preventing the formation of pathological fibrosis would be beneficial in a variety of diseases. For example mast cell chymase has been implicated in pulmonary fibrosis, kidney fibrosis, liver fibrosis, post surgical adhesion formation, systemic sclerosis, keloid scars, and the like.

30 In the heart mast cells have been implicated in cardiac hypertrophy, which involves both fibrosis and remodeling. Cardiac hypertrophy develops to preserve its function by normalizing chamber wall stress. Mast cells have been implicated as being involved in the development of myocardial fibrosis and systolic pressure over load induced hypertrophy (Hara *et al.*, J. Exp. Med. 195 (2002) 375-381). The remodeling of the heart associated
35 under these conditions is believed to involve mast cell chymase, which activates endothelin 1, matrix metalloproteinases and TGF- β . Chymase inhibitors have been shown to exert

favorable cardioprotective action in a dog model of hypertrophy (Matsumoto *et al.*, Circulation 107 (2003) 2555-2558).

In the kidneys mast cell chymase has also been implicated in pathological fibrosis. For example, glomerulonephritis has also been reported to involve mast cells (Ehara and Shigematsu, Kidney Inter. 54 (1998) 1675-1683). The results of this found that mast cells
5 were one of the constitutive cell types in the interstitium of IgA nephritis patients and contributed to interstitial fibrosis resulting in deterioration of renal function. Similarly, liver fibrosis has been associated with mast cells (Yamashiro *et al.*, Virchows Arch. 433 (1998) 471-479). Although, the mechanisms for fibrosis in the kidney and liver have not been as
10 well defined as for coronary fibrosis, it is very likely that chymase is operating through similar signaling pathways to cause fibrosis (especially in liver fibrosis where fibrosis seem to be occurring more frequently where mast cells stained positive for chymase).

Chymase is also involved in the formation of fibrous adhesions associated with surgery. Chymase inhibitors have been tested in two different animals models and found
15 to reduce the number of adhesions (Okamoto *et al.*, J. Surg. Res. 107 (2002) 219-222 and Lucas *et al.*, J. Surg. Res. 65 (1999) 135). It has been suggested that the prevention of adhesions is associated with blocking the activation of latent TGF- β by chymase (Yoa *et al.*, J. Surg. Res. 92 (2000) 40-44).

Collagen induced arthritic mice show increased numbers of mast cells and
20 expression of chymase in fibroproliferative inflammation (Kakizoe *et al.*, Inflamm. Res. 48 (1999) 318-324). In human rheumatoid arthritis increased mast cell density in the superficial synovium is associated with the severity of the disease (Grotis-Graham and McNeil, Arthritis & Rheumatism 40 (1997) 479-489). It was theorized by these authors that chymase and its ability to activate metalloproteinases plays a significant role in the rapid
25 functional deterioration observed in rheumatoid arthritis.

Mast cell chymase has been implicated in atherosclerosis via its ability to cleave apolipoprotein B-100 of LDL which facilitates lipoprotein aggregation and uptake by macrophages (Paananen *et al.*, J. Biol. Chem. 269 (1994) 2023-2031). Chymase also
30 degrades apolipoprotein A of HDL, which would reduce cholesterol efflux and increases lipid deposition (Lindstedt *et al.*, J. Clin. Invest. 97 (1996) 2174-2182). Thus chymase is involved in two different pathways to atherosclerosis.

An embodiment of the invention is a method for treating inflammatory and serine protease mediated disorders in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of any of the compounds or compositions
35 described above. Also included in the invention is the use of a compound of Formula (I) for the preparation of a medicament for treating an inflammatory or serine protease mediated disorder in a subject in need thereof. The term "treating" as used herein refers to a method

for improving, halting, retarding or palliating an inflammatory or serine protease mediated disorder in the subject in need thereof. All such methods of treatment are intended to be within the scope of the present invention.

5 In accordance with the methods of the present invention, the individual components of the compositions described herein can also be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

10 The term "subject" as used herein, refers to an animal (preferably, a mammal; most preferably, a human) who has been the object of treatment, observation, or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical 15 doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified 20 amounts.

To prepare the compositions of this invention, one or more compounds of Formula (I) or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for 25 administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in The Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

Methods of formulating compositions have been described in numerous 30 publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1-3, edited by Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1-2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

35 In preparing a composition of the present invention in liquid dosage form for oral, topical, inhalation/insufflation and parenteral administration, any of the usual pharmaceutical media or excipients may be employed. Thus, for liquid dosage forms, such

as suspensions (i.e., colloids, emulsions and dispersions) and solutions; suitable carriers and additives include but are not limited to pharmaceutically acceptable wetting agents, dispersants, flocculation agents, thickeners, pH control agents (i.e., buffers), osmotic agents, coloring agents, flavors, fragrances, preservatives (i.e., to control microbial growth, etc.) and a liquid vehicle may be employed. Not all of the components listed above will be required for each liquid dosage form.

In solid oral preparations such as, for example, powders, granules, capsules, caplets, gelcaps, pills and tablets (each including immediate release, timed release and sustained release formulations), suitable carriers and additives include but are not limited to diluents, granulating agents, lubricants, binders, glidants, disintegrating agents, and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated, gelatin coated, film coated or enteric coated by standard techniques.

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, powders, granules, lozenges, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories for administration by oral, intranasal, sublingual, intraocular, transdermal, parenteral, rectal, vaginal, inhalation or insufflation means. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g., conventional tableting ingredients such as diluents, binders, adhesives, disintegrants, lubricants, antiadherents, and glidants. Suitable diluents include, but are not limited to, starch (i.e., corn, wheat, or potato starch, which may be hydrolized), lactose (granulated, spray dried or anhydrous), sucrose, sucrose-based diluents (confectioner's sugar; sucrose plus about 7 to 10 weight percent invert sugar; sucrose plus about 3 weight percent modified dextrans; sucrose plus invert sugar, about 4 weight percent invert sugar, about 0.1 to 0.2 weight percent cornstarch and magnesium stearate), dextrose, inositol, mannitol, sorbitol, microcrystalline cellulose (i.e., AVICEL™ microcrystalline cellulose available from FMC Corp.), dicalcium phosphate, calcium sulfate dihydrate, calcium lactate trihydrate, and the like. Suitable binders and

adhesives include, but are not limited to accacia gum, guar gum, tragacanth gum, sucrose, gelatin, glucose, starch, and cellulose (i.e. methylcellulose, sodium carboxymethylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and the like), water soluble or dispersible binders (i.e., alginic acid and salts thereof, magnesium aluminum silicate, hydroxyethylcellulose (i.e. TYLOSE™ available from Hoechst Celanese), polyethylene glycol, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates and pregelatinized starch), and the like. Suitable disintegrants include, but are not limited to, starches (corn, potato, etc.), sodium starch glycolates, pregelatinized starches, clays (magnesium aluminum silicate), celluloses (such as crosslinked sodium carboxymethylcellulose and microcrystalline cellulose), alginates, pregelatinized starches (i.e., corn starch, etc.), gums (i.e., agar, guar, locust bean, karaya, pectin, and tragacanth gum), cross-linked polyvinylpyrrolidone, and the like. Suitable lubricants and antiadherents include, but are not limited to, stearates (magnesium, calcium and sodium), stearic acid, talc waxes, stearowet, boric acid, sodium chloride, DL-leucine, carbowax 4000, carbowax 6000, sodium oleate, sodium benzoate, sodium acetate, sodium lauryl sulfate, magnesium lauryl sulfate, and the like. Suitable gildants include, but are not limited to, talc, cornstarch, silica (i.e., CAB-O-SIL™ silica available from Cabot, SYLOID™ silica available from W.R. Grace/Davison, and AEROSIL™ silica available from Degussa), and the like. Sweeteners and flavorants may be added to chewable solid dosage forms to improve the palatability of the oral dosage form. Additionally, colorants and coatings may be added or applied to the solid dosage form for ease of identification of the drug or for aesthetic purposes. These carriers are formulated with the pharmaceutical active to provide an accurate, appropriate dose of the pharmaceutical active with a therapeutic release profile.

Generally these carriers are mixed with the pharmaceutical active to form a solid preformulation composition containing a homogeneous mixture of the pharmaceutical active of the present invention, or a pharmaceutically acceptable salt thereof. Generally the preformulation will be formed by one of three common methods: (a) wet granulation, (b) dry granulation, and (c) dry blending. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from about 0.01 mg to about 500 mg of the active ingredient of the present invention. The tablets or pills containing the novel compositions may also be formulated in multilayer tablets or pills to provide a sustained or provide dual-release products. For example, a dual release tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in

the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric materials such as shellac, cellulose acetate, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, methacrylate and ethylacrylate copolymers, and the like. Sustained release tablets may also be made by film coating or wet granulation using slightly soluble or insoluble substances in solution (which for a wet granulation acts as the binding agents) or low melting solids in a molten form (which in a wet granulation may incorporate the active ingredient). These materials include natural and synthetic polymers waxes, hydrogenated oils, fatty acids and alcohols (i.e., beeswax, carnauba wax, cetyl alcohol, cetylstearyl alcohol, and the like), esters of fatty acids metallic soaps, and other acceptable materials that can be used to granulate, coat, entrap or otherwise limit the solubility of an active ingredient to achieve a prolonged or sustained release product.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, but are not limited to aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable suspending agents for aqueous suspensions, include synthetic and natural gums such as, acacia, agar, alginate (i.e., propylene alginate, sodium alginate, and the like), guar, karaya, locust bean, pectin, tragacanth, and xanthan gum, cellulose derivatives such as sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose, and combinations thereof, synthetic polymers such as polyvinyl pyrrolidone, carbomer (i.e., carboxypolyethylene), and polyethylene glycol; clays such as bentonite, hectorite, attapulgite or sepiolite; and other pharmaceutically acceptable suspending agents such as lecithin, gelatin, or the like. Suitable surfactants include but are not limited to sodium docusate, sodium lauryl sulfate, polysorbate, octoxynol-9, nonoxynol-10, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polyoxamer 188, polyoxamer 235, and combinations thereof. Suitable deflocculating or dispersing agent include pharmaceutical grade lecithins. Suitable flocculating agent include but are not limited to simple neutral electrolytes (i.e., sodium chloride, potassium, chloride, and the like), highly charged insoluble polymers and polyelectrolyte species, water soluble divalent or trivalent ions (i.e., calcium salts, alums or sulfates, citrates and phosphates (which can be used jointly in formulations as pH buffers and flocculating agents). Suitable preservatives include but are not limited to parabens (i.e., methyl, ethyl,

n-propyl and *n*-butyl), sorbic acid, thimerosal, quaternary ammonium salts, benzyl alcohol, benzoic acid, chlorhexidine gluconate, phenylethanol, and the like. There are many liquid vehicles that may be used in liquid pharmaceutical dosage forms, however, the liquid vehicle that is used in a particular dosage form must be compatible with the suspending agent(s). For example, nonpolar liquid vehicles such as fatty esters and oils liquid vehicles are best used with suspending agents such as low HLB (Hydrophile-Lipophile Balance) surfactants, stearylalkonium hectorite, water insoluble resins, water insoluble film forming polymers, and the like. Conversely, polar liquids such as water, alcohols, polyols and glycols are best used with suspending agents such as higher HLB surfactants, clays silicates, gums, water soluble cellulose, water soluble polymers, and the like. For parenteral administration, sterile suspensions and solutions are desired. Liquid forms useful for parenteral administration include sterile solutions, emulsions and suspensions. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Furthermore, compounds of the present invention can be administered in an intranasal dosage form via topical use of suitable intranasal vehicles or via transdermal skin patches, the composition of which are well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the administration of a therapeutic dose will, of course, be continuous rather than intermittent throughout the dosage regimen.

Compounds of the present invention can also be administered in a form suitable for intranasal or inhalation therapy. For such therapy, compounds of the present invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped or as an aerosol spray from a pressurized container or a nebulizer (such as, a metered dose inhaler, a dry powder inhaler or other conventional or non-conventional modes or devices for inhalation delivery) using a suitable propellant (such as, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (such as, those made from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, multilamellar vesicles and the like. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, phosphatidylcholines, and the like.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include, but are not limited to polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, and polyethyl eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, to homopolymers and copolymers (which means polymers containing two or more chemically distinguishable repeating units) of lactide (which includes lactic acid d-, l- and meso lactide), glycolide (including glycolic acid), ϵ -caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, δ -valerolactone, β -butyrolactone, γ -butyrolactone, ϵ -decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels and blends thereof.

The therapeutically effective amount of a compound or composition thereof may be from about 0.001 mg/kg/dose to about 300 mg/kg/dose. Preferably, the therapeutically effective amount may be from about 0.001 mg/kg/dose to about 100 mg/kg/dose. More preferably, the therapeutically effective amount may be from about 0.001 mg/kg/dose to about 50 mg/kg/dose. Most preferably, the therapeutically effective amount may be from about 0.001 mg/kg/dose to about 30 mg/kg/dose. Therefore, the therapeutically effective amount of the active ingredient contained per dosage unit (e.g., tablet, capsule, powder, injection, suppository, teaspoonful, and the like) as described herein will be in the range of from about 1 mg/day to about 21,000 mg/day for a subject, for example, having an average weight of 70 kg. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level. Advantageously, compounds of the present invention may be

administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily.

Representative IUPAC names for the compounds of the present invention were derived using the ACD/LABS SOFTWARE™ Index Name Pro Version 4.5 nomenclature software program provided by Advanced Chemistry Development, Inc., Toronto, Ontario, Canada or AutoNom Version 2.1 provided by Beilstein Informationssysteme.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

	Boc	=	<i>tert</i> -butoxycarbonyl
10	BOC-ON	=	2-(<i>tert</i> -butoxycarbonyloxyimino)-2-phenylacetonitrile
	BuLi	=	<i>n</i> -butyllithium
	<i>t</i> -BuOH	=	<i>tert</i> -butanol
	Cpd or Cpd	=	compound
	d	=	day/days
15	DCC	=	dicyclohexylcarbodiimide
	DIPEA	=	diisopropylethylamine
	EtOH	=	ethanol
	h	=	hour/hours
	HOBt	=	hydroxybenzotriazole
20	KH	=	potassium hydride
	LDA	=	lithium diisopropylamide
	M	=	molar
	Mel	=	methyl iodide
	MeOH	=	methanol
25	min	=	minutes
	NT	=	not tested
	PPA	=	polyphosphoric acid
	rt/RT	=	room temperature
	THF	=	tetrahydrofuran
30	TFA	=	trifluoroacetic acid
	TMSBr	=	bromotrimethylsilane.

GENERAL SYNTHETIC METHODS

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions

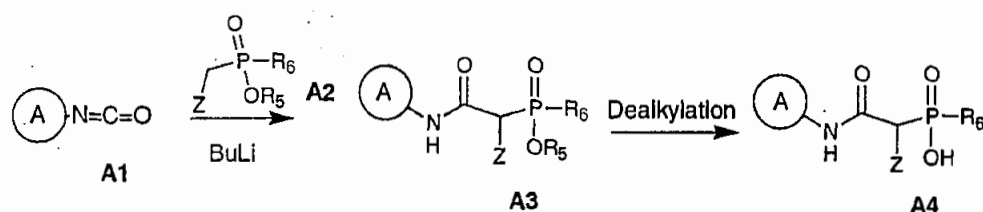
expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

The following schemes describe general synthetic methods whereby intermediate and target compounds of the present invention may be prepared. Additional representative compounds and stereoisomers, racemic mixtures, diastereomers and enantiomers thereof can be synthesized using the intermediates prepared in accordance to the general schemes and other materials, compounds and reagents known to those skilled in the art. All such compounds, stereoisomers, racemic mixtures, diastereomers and enantiomers thereof are intended to be encompassed within the scope of the present invention. Since the scheme is an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the scheme is well within the skill of persons versed in the art.

Scheme A illustrates the general method for the preparation of compounds of the present invention by the reaction of a phosphonate or phosphinate anion (prepared from its corresponding phosphonate or phosphinate Compound **A2** and an organometallic base such as *n*-butyllithium) to isocyanate **A1** in a solvent such as THF to afford an amidophosphonate or amidophosphinate compound **A3**. One versed in the art will recognize that conventional chemical transformations may be utilized to prepare certain R² and R³ substituents of the present invention. For example, for the preparation of a compound wherein R³ is amino, a nitro group may be reduced with hydrazine hydrate in the presence of a palladium catalyst; or, for the preparation of a compound wherein R³ is ureido, a compound in which R³ is an amino group may be reacted with a cyanate salt or the like.

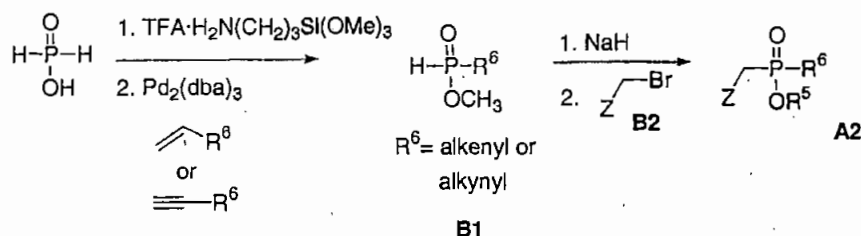
Compound **A2**, wherein R⁵ and R⁶ are as previously defined, may be made according to known methods (Katritzky *et al. Org. Prep. Proced. Int.*, **1990**, 22(2), 209-213; *J. Am. Chem. Soc.*, **2002**, 124, 9386-9387; and *Chem. Ber.*, **1963**, 96, 3184-3194). Fluorinated R⁶ compounds can be made following methods known in the art such as the methods similar those set forth in Garabadzhia *et al.*, Journal General Chemistry USSR, English translation, 1981, pages 1905-1910. Compound **A3** may be dealkylated with bromotrimethylsilane in a solvent such as pyridine, followed by treatment with dilute HCl to afford Compound **A4**.

Scheme A



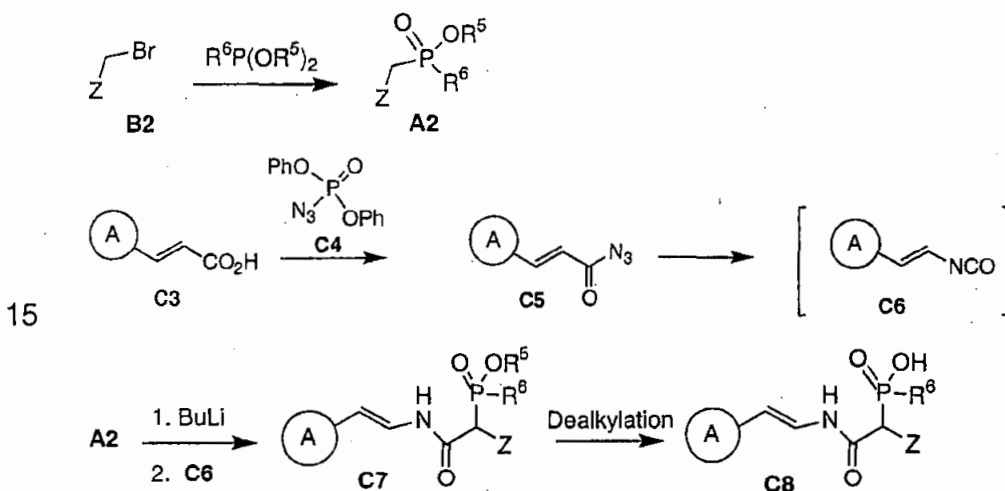
Compound **A2**, wherein Z is a heteroaryl or aryl ring, may be prepared from a commercially available or known haloalkyl substituted heteroaryl ring. Another method for preparing Compound **A2** uses a quaternary ammonium salt rather than an alkyl halide:

5 Scheme B



Scheme B shows a method for preparing Compound **A2** wherein R^6 is an alkyl or alkenyl substituent using methods described in the literature (*J. Organomet. Chem.* **2002**, 643-644, 154-163; *J. Amer. Chem. Soc.* **2002**, 124, 9386-9387). An alternate method for preparing such compounds is described in the literature (*Med. Chem.* **1995**, 38(17), 3297-3312; *Bioorg. Med. Chem.* **1999**, 7, 2697-2704).

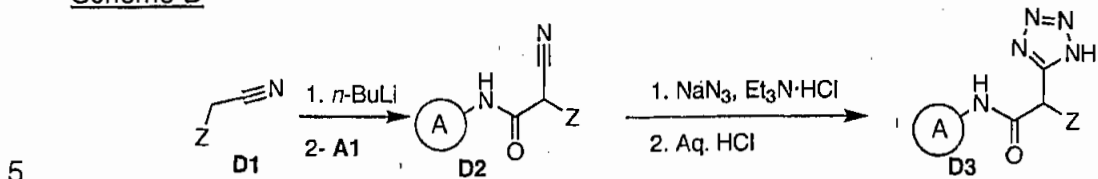
Scheme C



Scheme C illustrates a general method for the preparation of compounds of the present invention wherein ring system A of Formula (I) is an aryl substituent and n of Formula (I) is equal to 1. Reaction of an α/β -unsaturated carboxylic acid, Compound **C3**, with phosphorazidic acid dialkyl ester Compound **C4** provides Compound **C5**. Compound **C5** may subsequently undergo a Curtius rearrangement to afford an isocyanate intermediate, Compound **C6**. Compound **C6** may be treated with a phosphonate or phosphinate anion (as previously described in Scheme A) in an aprotic solvent such as THF to yield amidophosphonate or amidophosphinate Compound **C7**. Compound **C7** may

be dealkylated with bromotrimethylsilane, followed by treatment with dilute HCl to afford Compound **C8**.

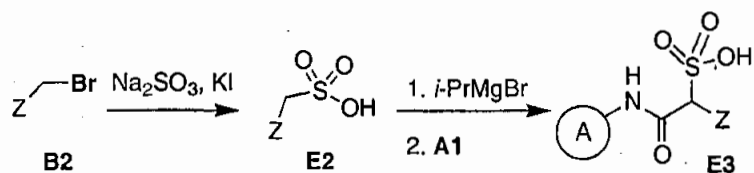
Scheme D



Scheme D further illustrates the preparation of compounds of the present invention wherein Y of Formula (I) is a heteroaryl substituent. Compound **D1** may be dissolved in an aprotic solvent, treated with an organometallic base such as *n*-BuLi, and subsequently reacted with isocyanate Compound **A1** to afford Compound **D2**. Compound **D2** may undergo a cycloaddition reaction with sodium azide to provide Compound **D3**.

10

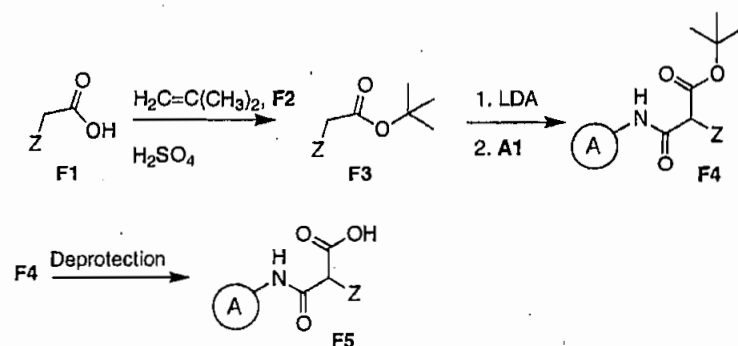
Scheme E



Scheme E shows the preparation of compounds of the present invention wherein Y of Formula (I) is a sulfonic acid. Compound **B2** may be treated with sodium sulfite to afford Compound **E2**. Compound **E2** may then be treated with an organometallic base such as isopropylmagnesium bromide and reacted with isocyanate Compound **A1** to yield Compound **E3**.

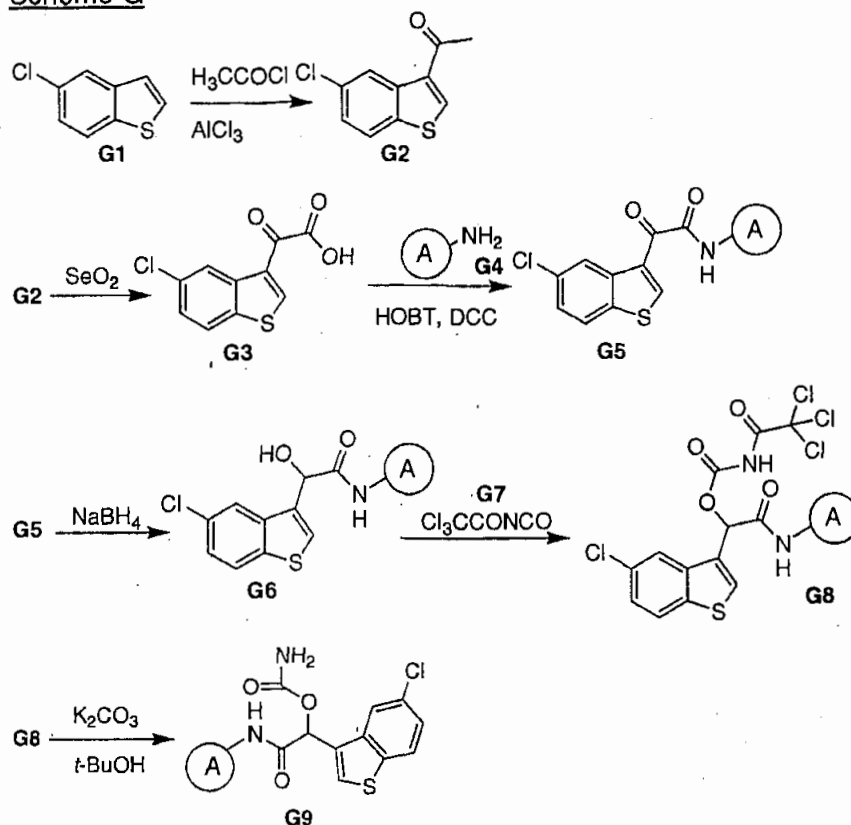
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Scheme F

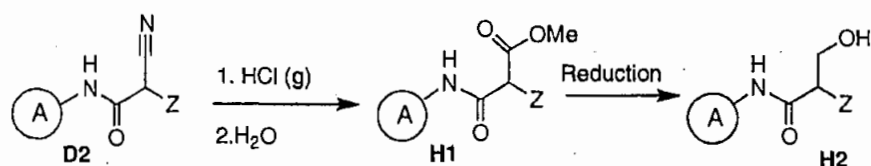


Scheme F illustrates the preparation of compounds of the present invention wherein Y of Formula (I) is a carboxylic acid. Compound **F1** may be reacted with isobutylene under acidic conditions to provide ester Compound **F3**. Compound **F3** may then be treated with a strong base such as lithium diethylamide and further reacted with isocyanate Compound **A1** to give Compound **F4**. Compound **F4** is converted into its corresponding carboxylic acid Compound **F5** by treatment with TFA.

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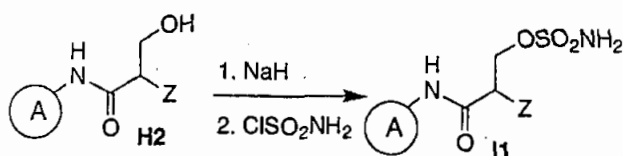
Scheme G

Scheme G illustrates the preparation of compounds of the present invention wherein Y of Formula (I) is a carbamate. Compound **G1** may be prepared by the methods described in the literature (*J. Med. Chem.* **1989**, 32(12), 2548-2554, *J. Het. Chem.* **1998**, 25, 1271). Compound **G1** may be converted to Compound **G2** by the method described in the literature (*Eur. J. Med. Chem.* **2001**, 36(1), 55-62). Compound **G2** may be oxidized using selenium dioxide to yield resultant carboxylic acid Compound **G3**. Compound **G3** may be coupled with amine Compound **G4** in the presence of an appropriate coupling agent, base, activating agent, and solvent to afford amide Compound **G5**. In the present invention, Compound **G3** is coupled to Compound **G4** in the presence of DCC and HOBt to form Compound **G5**. Compound **G5** may be reduced in the presence of a hydride source such as sodium borohydride to give alcohol Compound **G6**, which may be treated with isocyanate Compound **G7** to form Compound **G8**. Compound **G8** may be deprotected in the presence of *t*-butyl alcohol and potassium carbonate to yield carbamate Compound **G9**.

Scheme H

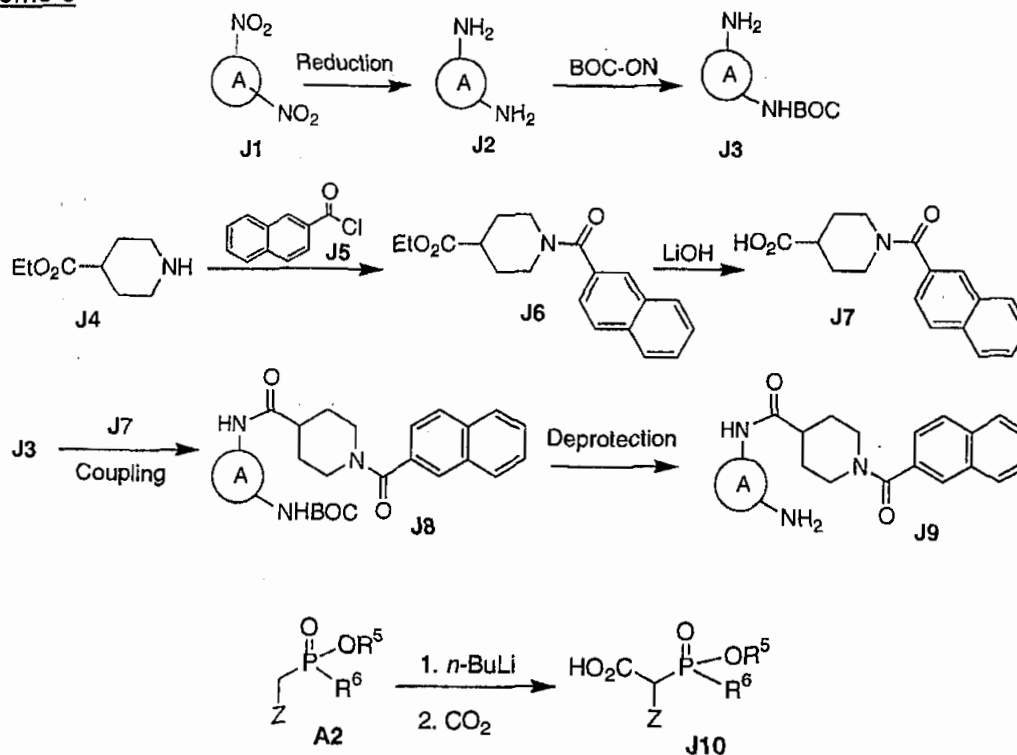
Scheme H illustrates the preparation of compounds of the present invention wherein Y of Formula (I) is hydroxymethyl. Nitrile Compound **D2** may be converted to an imidate in the presence of HCl gas, followed by hydrolysis to yield Compound **H1**. Compound **H1** may be reduced to a primary alcohol in the presence of hydride source, such as sodium borohydride, to give methyl alcohol Compound **H2**.

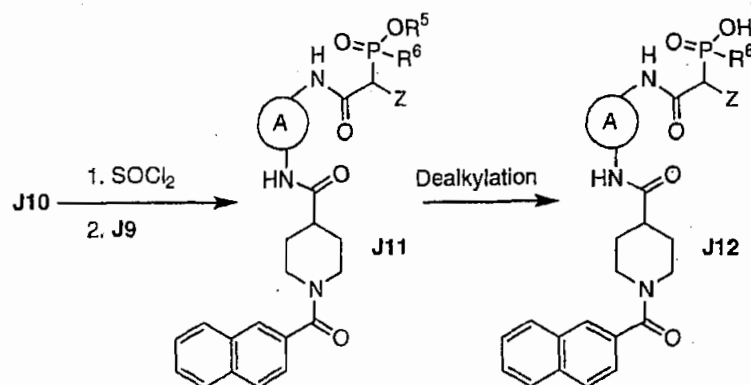
Scheme I



Scheme I illustrates the preparation of compounds of the present invention wherein Y of Formula (I) is a sulfamic acid methyl group. Compound **H2** may be treated with a base such as sodium hydride, followed by the addition of sulfamoyl chloride to yield Compound **I1**.

Scheme J



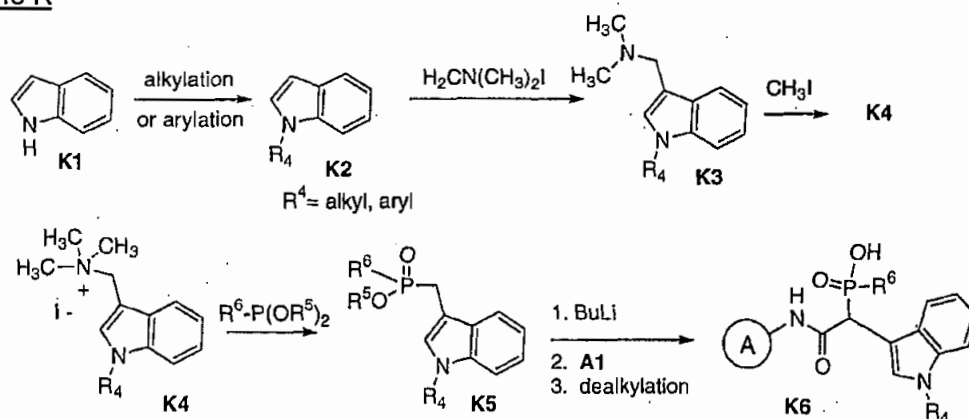


Scheme J illustrates the general method for the preparation of compounds of the present invention wherein R^3 is an amide substituent on ring A as defined by the invention. Dinitro-substituted Compound **J1** may be reduced by hydrogenation in the presence of a palladium catalyst to give Compound **J2** which then may be acylated with BOC-ON to provide Compound **J3**.

Compound **J4** may be acylated with acid chloride Compound **J5** to yield Compound **J6**, followed by saponification of Compound **J6** to provide carboxylic acid Compound **J7**. Compound **J8** may be prepared by coupling Compound **J3** to Compound **J7** using an appropriate coupling agent, activating agent, and solvent.

The Boc protecting group of Compound **J8** was removed under acidic conditions to afford the free amine, Compound **J9**. Treatment of Compound **A2** with an organometallic base such as *n*-butyllithium, followed by reaction with carbon dioxide afforded the carboxylated phosphonic ester, Compound **J10**. Compound **J10** was converted to its acid chloride by treatment with thionyl chloride followed by condensation with amine Compound **J9** to afford amide Compound **J11**. Compound **J11** was dealkylated using bromotrimethylsilane and treated with HCl to provide Compound **J12**.

Scheme K

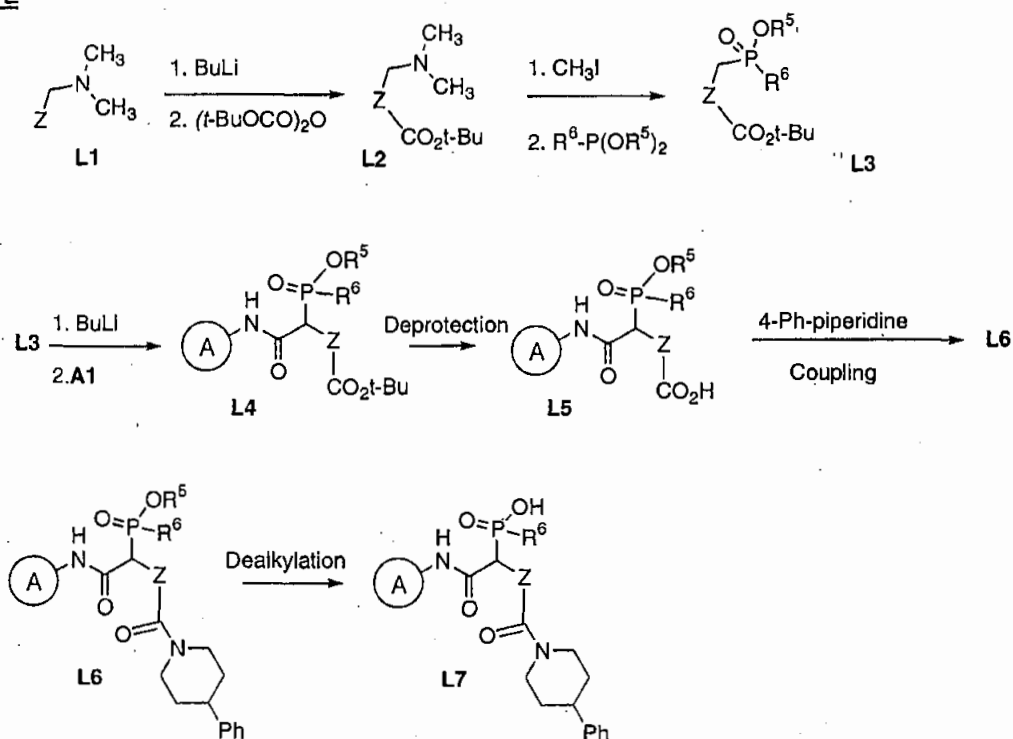


Scheme K illustrates a general method for the preparation of compounds of the present invention wherein Z is an N-substituted indole as previously defined. Compound

K1 may be reacted with an alkylating agent such as methyl iodide or an arylating agent such as bromobenzene with copper oxide, Compound **K2**. Compound **K2** may be treated with *N,N*-dimethylmethyleammonium iodide to afford Compound **K3**. Compound **K3** may be converted to Compound **K4** using methyl iodide, and then reacted with a phosphite or phosphonite to provide Compound **K5**. Compound **K5** may be reacted with Compound **A1** and dealkylated as previously described to yield Compound **K6**.

Optionally, the phenyl portion of Compound **K2** may be substituted with an alkoxy carbonyl. In this instance, the ester may be reduced to its corresponding methyl alcohol, and converted to a methyl halide using techniques and reagents known to those skilled in the art. The halide may then be converted to Compound **A2** wherein **Z** is an indole as previously defined in the present invention. Compound **A2** may be subsequently reacted according to Scheme A to form a compound of Formula (I) wherein the phosphonic attached through the aryl portion of indole **Z**.

15 Scheme L

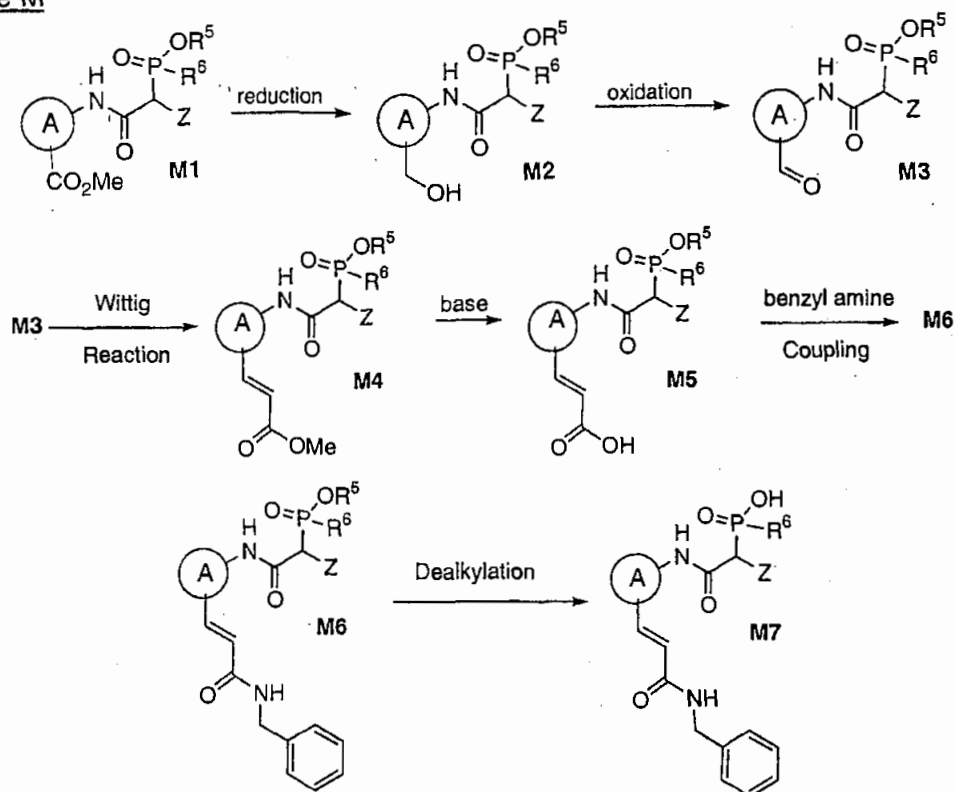


Scheme L illustrates the general method for the preparation of compounds of the present invention wherein R⁴ is a heterocyclylcarbonyl substituent. Compound **L1** may be made by the procedures described in *JACS* **1963**, 6, 711 - 716 and *JACS* **1971**, 93(12), 2897-2904.

Compound **L1** may be reacted with an organometallic base, such as butyllithium, followed by treatment with di-*tert*-butyldicarbonate to give Compound **L2**. Compound **L2** may be converted to Compound **L4** using the methods described previously. Compound

L4 may be deprotected under acidic conditions to afford Compound **L5**. The carboxylic acid group of Compound **L5** may be treated with an amine, such as 4-phenylpiperidine, in the presence of an appropriate coupling agent, base, activating agent, and solvent, to afford Compound **L6**. Dealkylation of Compound **L6** as described supra yields Compound **L7**.

Scheme M



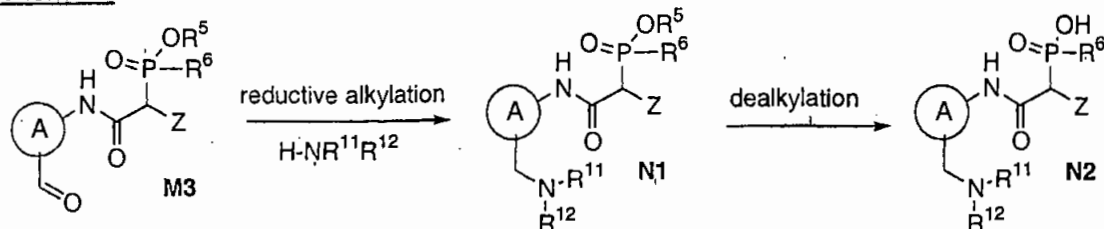
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Scheme M illustrates a general method for the preparation of compounds of the present invention. A Compound **M1**, wherein R^3 is an alkoxy carbonyl substituent, may be reduced in the presence of a hydride source to the corresponding alcohol, Compound **M2**. Compound **M2** may be oxidized to aldehyde Compound **M3**. Reaction of Compound **M3** with a Wittig reagent affords alkene Compound **M4**. Saponification of Compound **M4** provides carboxylic acid Compound **M5**, which may be coupled with an amine, such as benzyl amine, in the presence of an appropriate coupling agent as described supra, to give amide Compound **M6**. Compound **M6** may be dealkylated using the procedure previously described in Scheme A to yield Compound **M7**.

Alternatively, other compounds of the present invention wherein R^3 is alkoxy or $C(=O)NR^{11}R^{12}$ may be derived from Compound **M2**. The hydroxy group of Compound **M2** may be alkylated using reagents and methods known to one skilled in the art to afford compounds wherein R^3 is alkoxy. Alternatively, the hydroxy group of Compound **M2** may

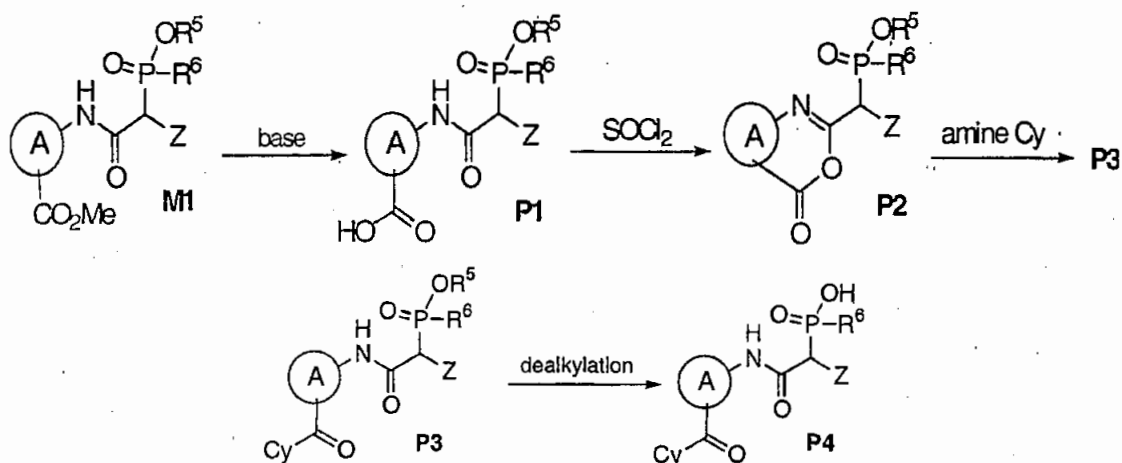
be reacted with a variety of acylating agents known to one skilled in the art, such as isocyanates, to arrive at compounds of the present invention wherein R^3 is a carbamate.

Scheme N



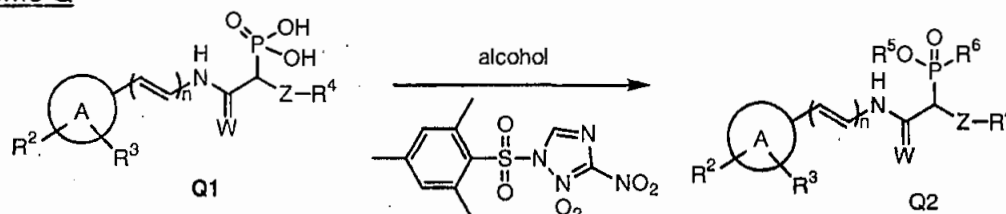
As shown in Scheme N, Compound **M3** may be reacted with a variety of amines in the presence of a hydride source under acidic conditions to yield Compound **N1**. Dealkylation of Compound **N1** by the method described in Scheme A affords Compound **N2**.

Scheme P



The preparation of compounds of the present invention wherein R^3 is $-C(=O)Cy$ as previously defined, and said **Cy** is attached through a nitrogen atom, is shown in Scheme P. Compound **M1** may be saponified under basic conditions to provide Compound **P1**, which may be treated with thionyl chloride to give Compound **P2**. Compound **P2** may be reacted with a heterocyclic amine to provide Compound **P3**. Dealkylation of Compound **P3** using methods previously described affords Compound **P4**.

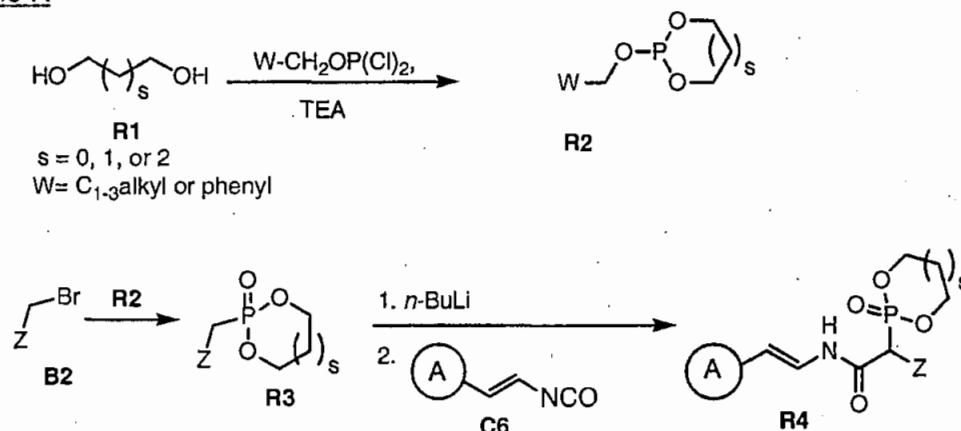
Scheme Q



Scheme Q illustrates a method for the preparation of compounds of the present invention wherein R^5 and R^6 are appropriately substituted alkoxy substituents as defined herein. A compound of formula **Q1** wherein R^5 is hydrogen and R^6 is hydroxyl may be coupled with an appropriately substituted alcohol in the presence of MSNT (1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole) to afford a compound of formula **Q2** wherein R^5 is a substituted alkyl and R^6 is a substituted alkoxy as defined herein.

Alternatively, compounds of formula **Q1** may be elaborated using an appropriately substituted alkylating agent to provide compounds of the present invention where either one or both hydroxyl groups of the phosphonic acid are alkylated. An alkylating agent in this instance is an alkyl substituent that is optionally substituted as defined for R^5 or R^6 , and said alkyl substituent is substituted with a leaving group. A leaving group is defined as a substituent that is activated toward nucleophilic displacement, including halides, tosylates, and the like.

15 Scheme R



Scheme R illustrates the preparation of compounds of the present invention wherein R^5 and R^6 (when R^6 is alkoxy) are taken together with the atoms to which they are both attached to form a monocyclic ring. A diol of formula **R1** may be treated with a benzyl- or lower alkyl-dichlorophosphite to form a cyclic phosphonate of formula **R2**. A compound of formula **R2** may be condensed under refluxing conditions with a compound of formula **B2** to form a compound of formula **R3**. The elaboration of a compound of formula **R3** to a compound of formula **R4** may be achieved using the methods described for Scheme A.

25 SPECIFIC SYNTHETIC EXAMPLES

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The depicted intermediates may also be used in

subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

5 All chemicals were obtained from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC[®] 300B (300 MHz proton) or a Bruker[®] AM-400 (400 MHz proton) spectrometer with Me_4Si as an internal standard (s = singlet, d = doublet, m = multiplet, t = triplet, br = broad). ES-MS were recorded on a Micromass[®] mass spectrometer or on an Agilent[®] HPLC mass spectrometer.

10 TLC was performed with Whatman[®] 250- μm silica gel plates. Preparative TLC was performed with Analtech[®] tapered silica gel GF plates. Preparative HPLC separations were carried out on a Gilson[®] HPLC using a Phenomenex[®] Kromasil 100A C18 column (25 cm x 50 mm, or 10 cm x 21.2 mm) using gradients of CH_3CN / water/ 0.2% TFA; Analytical HPLC separations were carried out on a Supelco[®] ABZ+Plus column (5 cm x 2.1 mm) or a

15 YMC[®] J'Sphere H80 S4 column (5 cm x 2 mm) with detection at 220 nm and 254 nm on a Hewlett Packard[®] 1100 UV detector. The gradient used was 10% to 90% CH_3CN /water/0.1% TFA in 6 min. Reported percent purity data is based on the 220 nm data. Microanalysis was performed by Robertson Microlit Laboratories, Inc.

Representative Chemical Abstracts Service (CAS) Index-like names for the

20 compounds of the present invention were derived using the Autonom Version 2.1 nomenclature software.

EXAMPLE 1

[(5-Chloro-benzo[*b*]thiophen-3-yl)- (naphthalen-2-ylcarbamoyl)-methyl]-phosphonic acid,

25 Cpd 9

A solution of Compound **1a** (5.01 g, 19.2 mmol) and Compound **1b** (10 mL) was refluxed for 105 min. The solution was concentrated under high vacuum at 90 °C to yield 6.01 g of Compound **1c** as a pale yellow viscous oil; HPLC: 3.51 min; MS (ES) m/z 319 (MH^+).

30 To a solution of 2.5 M *n*-BuLi in hexanes (4.73 mL, 12 mmol) in THF (30 mL) at -78°C was added dropwise a solution of Compound **1c** (3.77 g, 12 mmol) in THF (30 mL) over 15 min. After stirring for an additional 30 min, Compound **1d** (naphthalen-2-yl isocyanate) (2.0 g, 12 mmol) in THF (30 mL) was added dropwise to the mixture over 5 min. After the addition was complete, the solution was allowed to reach rt and stirred

35 overnight. Excess saturated NH_4Cl (aq) was added, and the layers were separated. The aqueous portion was extracted with EtOAc (3 x 20 mL). The combined organic extracts

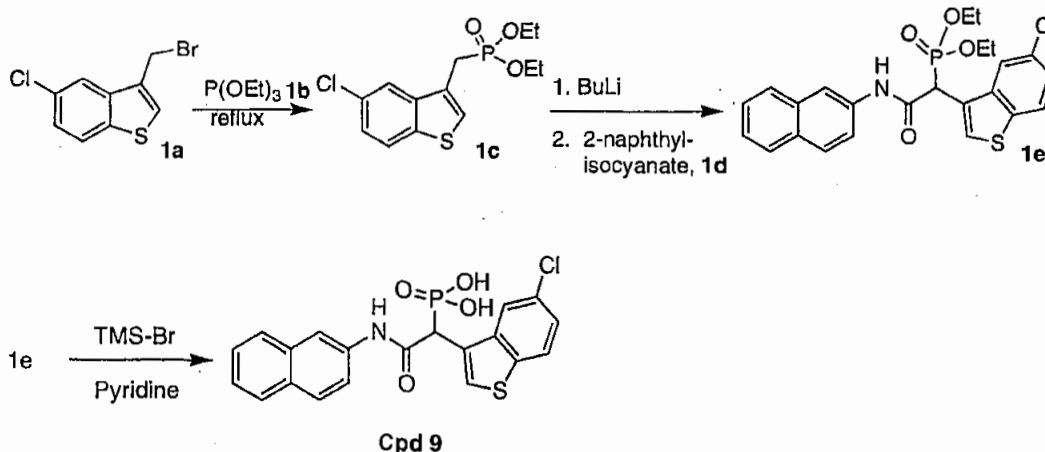
were dried (Na_2SO_4), filtered, and concentrated under reduced pressure at rt. The residue was taken up in CH_3CN (10 mL), the solid was collected and dried under N_2 /vacuum to afford Compound **1e** (4.3 g) as a white powder: HPLC: 4.25 min; MS (ES) m/z 488 (MH^+).

5 Procedure A: General Method for Deethylation of Phosphonates and Phosphinates

To a solution of the phosphonate or phosphinate (x mmol) in pyridine (5 mL/ mmol of phosphonate or phosphinate) is added excess bromotrimethylsilane (5x to 8x mmol) in three portions at 15 min intervals. The mixture is stirred for 60 min after the last addition, then concentrated under reduced pressure. The residue is stirred with excess 1N HCl (aq) for 60 min. The white precipitate is collected and rinsed sequentially with 1N HCl (aq) and water, then dried under N_2 /vacuum. The crude product may be purified by trituration with appropriate solvents, salt formation, recrystallization, or reverse phase chromatography.

Compound **1e** (4.3 g, 8.8 mmol) was deethylated according to Procedure A. The crude product was further purified: the white solid was stirred with CH_3CN for 60 min, collected, rinsed with CH_3CN , and dried under N_2 /vacuum to afford 3.2 g of **Cpd 9** as a white powder: HPLC 4.47 min; MS (ES) m/z 432 (MH^+).

To a solution of **Cpd 9** (2.68 g, 6.2 mmol) in CH_3OH (10 mL) was added a solution of tris(hydroxymethyl)aminomethane (1.5 g, 12.4 mmol) in CH_3OH (10 mL). The solution was concentrated, and the resulting white solid was recrystallized from *i*-PrOH to yield 4.0 g of the tromethamine salt of **Cpd 9** as an off-white solid. HPLC: 4.4 min, 94%; MS (ES) m/z (MH^+) = 432; ^1H NMR ($\text{DMSO}-d_6$) δ 3.32 (s, 10H), 4.59 (d, 1H), 7.30 – 7.42 (overlapping m, 3H), 7.56 (d, 1H), 7.71 – 7.80 (overlapping m, 3H), 7.94 – 7.05 (overlapping m, 3H), 8.28 (s, 1H), 11.40 (s, 1H); Anal. Calc'd for $\text{C}_{20}\text{H}_{15}\text{NO}_4\text{PSCl} \cdot 1.6 \text{ C}_4\text{H}_{11}\text{NO}_3 \cdot 1.0 \text{ } i\text{-PrOH} \cdot 0.25 \text{ H}_2\text{O}$: C, 51.16; H, 6.01; N, 5.28; H_2O , 0.66. Found: C, 51.21; H, 5.92; N, 5.22; H_2O , 0.74.



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure for Example 1, the following compounds were prepared without further purification:

Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
30	439	76	476
31	392	82	382
55	436 (MH ⁻)	96	393
57	393	106	430
59	398	129	381
64	398	135	386
67	510 (MH ⁻)	137	393
68	379 (MH ⁻)	138	434
79	393		

5

EXAMPLE 2

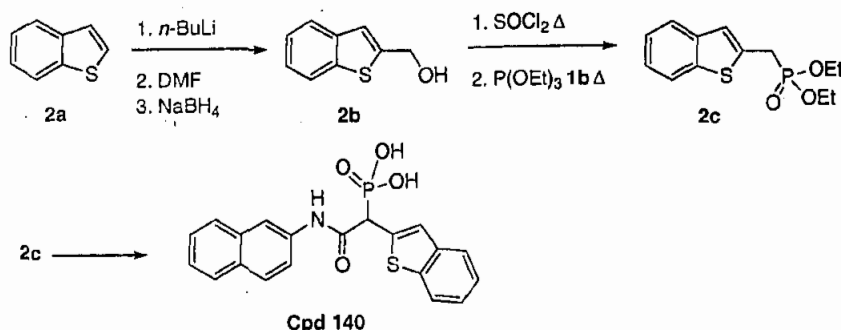
[(Benzo[*b*]thiophen-2-yl)- (naphthalen-2-ylcarbamoyl)-methyl]-
phosphonic acid, Cpd 140

10 To a solution of Compound **2a** (3.5 g, 26.1 mmol) in 25 mL of THF at -78°C was added a solution of 2.5 M *n*-BuLi in hexanes (13 mL, 32.6 mmol). The reaction was warmed to 0°C and stirred for 25 min, then 4 mL of DMF was added slowly. The solution was heated to reflux for 1 h. The reaction was cooled to rt, poured into water and extracted three times with Et₂O. The combined organic extracts were washed with brine, dried
15 (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The crude oil was dissolved in 25 mL of MeOH, cooled to 0°C , and NaBH₄ (1.6 g, 42 mmol) was added and stirred for 2 h. After quenching with excess acetone, the mixture was concentrated, and the residue was partitioned between EtOAc and brine. The brine was extracted twice with EtOAc, and the combined organic extracts were washed twice with brine, dried (Na₂SO₄),
20 filtered and concentrated under reduced pressure at rt. The crude solid was stirred with 6:1 CH₂Cl₂/hexane, then collected to afford Compound **2b** (2.52 g) as an off-white powder: HPLC: 2.85 min.

To Compound **2b** (2.52 g, 16.8 mmol) was added 10 mL of thionyl chloride and refluxed for 1.5 h. The reaction was concentrated under reduced pressure at rt, and the
25 residue was treated with hexanes. After concentration, the residue was treated with excess triethylphosphite Compound **1b** and refluxed for 1.5 h. The reaction was

concentrated under reduced pressure at 90 °C and purified by flash column chromatography (silica, 0 to 40% EtOAc/Hexane) to yield Compound **2c** (2.5 g) as an oil: HPLC: 3.32 min; MS (ES) m/z 285 (MH^+).

From Compound **2c** (0.64 g, 2.25 mmol) was prepared Compound **140** according to
 5 Procedure A: HPLC: 3.87 min; MS (ES) m/z 398 (MH^+).



EXAMPLE 3

10 [(5-Chloro-benzo[*b*]thiophen-3-yl)-(naphthalen-2-ylthiocarbamoyl)-
 methyl]-phosphonic acid, Cpd 45

Using the procedure described in Example 1 and substituting 2-
 naphthylthioisocyanate for 2-naphthylisocyanate, Compound **45** was synthesized as a pale
 15 yellow powder: HPLC: 4.89 min; MS (ES) m/z 448 (MH^+).

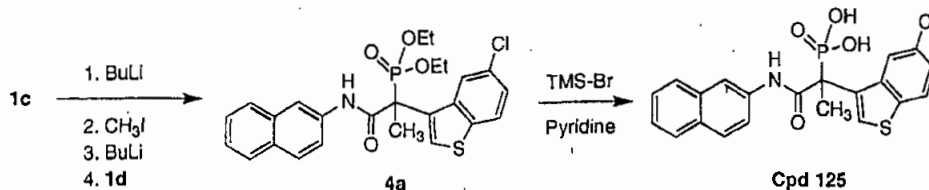
EXAMPLE 4

[1-(5-Chloro-benzo[*b*]thiophen-3-yl)-1-(naphthalen-2-ylcarbamoyl)-
 ethyl]-phosphonic acid, Cpd 125

20 To a solution of 2.5 M *n*-BuLi in hexanes (0.44 mL, 12 mmol) in THF (7 mL) at -78 °C was added dropwise a solution of Compound **1c** (3.77 g, 1.1 mmol) in THF (7 mL). After stirring for 30 min, methyl iodide (0.068 mL, 1.1 mmol) was added dropwise by syringe. The reaction was warmed to 0 °C and then to rt. The solution was returned to
 25 -78°C and a solution of 2.5 M *n*-BuLi in hexanes (0.44 mL, 12 mmol) was added dropwise. After stirring for 30 min, Compound **1d** (0.19, 1.1mmol) in THF (7 mL) was added dropwise to the mixture. After the addition was complete, the solution was allowed to reach rt and stirred overnight. Excess saturated NH_4Cl (aq) was added, and the layers were separated. The aqueous portion was extracted with EtOAc (3 x 5 mL). The combined organic extracts
 30 were dried (Na_2SO_4), filtered, and concentrated under reduced pressure at rt. The residue was dissolved in CH_3CN (5 mL), and filtered. The filtrate was purified by flash column

chromatography (silica, CH₂Cl₂) to yield Compound **4a** (0.036 g) HPLC: 4.62 min; MS (ES) m/z 502 (MH⁺).

Compound **4a** was converted to Compound **125** using Procedure A: HPLC: 4.34 min (94%); MS (ES) m/z 444 (MH⁺).

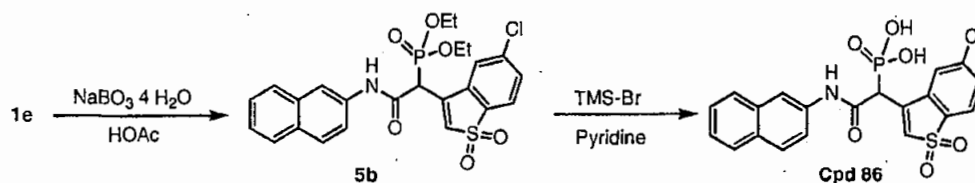


EXAMPLE 5

[(5-Chloro-1,1-dioxo-1H-1λ⁶-benzo[b]thiophen-3-yl)-
(naphthalen-2-ylcarbamoyl)-methyl]-phosphonic acid, Cpd 86

10 Compound **1e** (0.20 g, 0.41 mmol) was suspended in acetic acid (5 mL) and heated to 47.5 °C and sodium perborate tetrahydrate Compound **5a** (0.31 g, 2.0 mmol) was added portionwise over 15 min, and the reaction was stirred at 47.5 °C overnight. The reaction was partitioned between water and EtOAc, and the layers were separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed sequentially with saturated NaHCO₃ (aq), brine, and then dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0 – 40% EtOAc/ hexane) to yield Compound **5b** (0.052 g): HPLC: 3.87 min; MS (ES) m/z 520 (MH⁺).

20 Compound **5b** (0.052 g, 0.10 mmol) was converted Compound **86** (0.0185 g) by Procedure A: HPLC: 3.25 min, 95%; MS (ES) m/z 462 (MH⁺).



EXAMPLE 6

25 {[(5-Chloro-benzo[b]thiophen-3-yl)-
[2-(3,4-difluoro-phenyl)-vinylcarbamoyl]-methyl]-methyl-phosphinic acid, Cpd 17

30 A solution of Compound **1a** (1.96 g, 7.48 mmol) in excess diethylmethylphosphonite was refluxed for 3 h. The solution was concentrated under high vacuum at 90 °C, and the residue was purified by flash column chromatography (silica, 0-100% EtOAc/ hexanes) to yield 1.88 g of Compound **6a** as a slightly cloudy pale yellow viscous oil: HPLC: 3.19 min;

MS (ES) m/z 290 (MH^+).

To a suspension of Compound **6b** (5.0 g, 27.2 mmol) in dry benzene (20 mL) was added triethylamine (3.74 mL, 27.2 mmol). The solution cooled to 0°C, and Compound **6c** (5.86 mL, 27.2 mmol) was added rapidly dropwise, and the cooling was removed. The reaction was stirred 18 h, then poured into H₂O. The mixture was extracted three times with EtOAc, and the combined organic extracts were washed once with brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0-100% EtOAc/hexanes) to yield 4.88 g of Compound **6d** as a white solid: HPLC: 3.65 min.

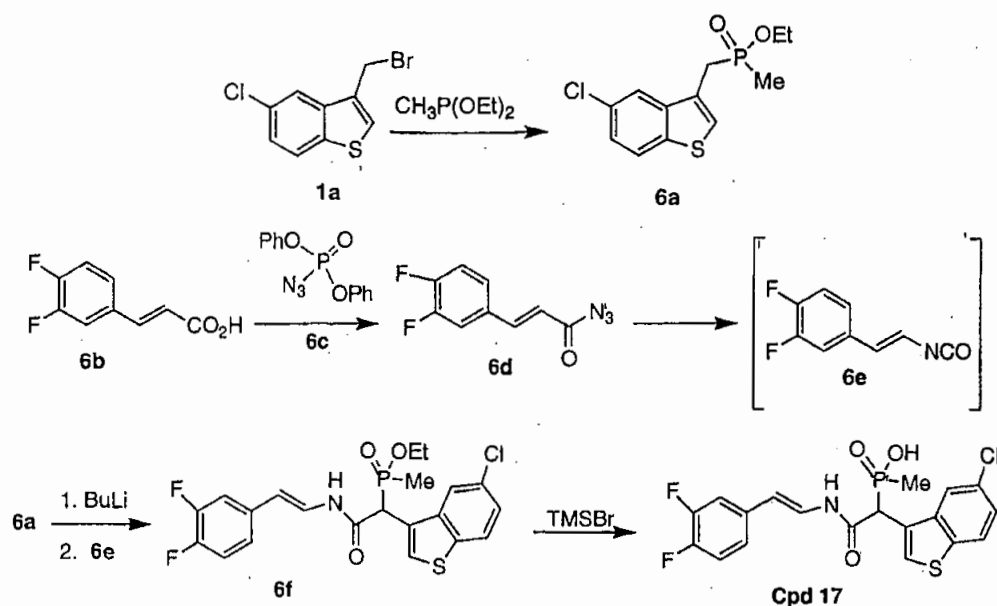
Compound **6d** (3.4 g, 16.3 mmol) was dissolved in benzene (30 mL) and refluxed for 3 h. The solution was concentrated under reduced pressure at rt and the resulting crude Compound **6e** was used without purification in the next reaction.

To a solution of 2.5M *n*-BuLi in hexanes (8.9 mL, 22.3 mmol) in THF (30 mL) at -78°C was added dropwise a solution of Compound **6a** (4.7 g, 16.3 mmol) in THF (30 mL) over 15 min. After stirring for an additional 30 min, a solution of Compound **6d** (3.4 g, 16.3 mmol) in THF (30 mL) was added dropwise to the mixture over 5 min. After the addition was complete, the solution was stirred at -78°C for 30 min, then quenched cold with excess NH₄Cl (saturated, aq.), and stirred overnight at rt. The layers were separated, and the aqueous portion was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed once with brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0-50% EtOAc/hexanes) to yield 4.1 g of a pale yellow solid, which was stirred with 15 mL CH₃CN, collected, and dried under N₂/vacuum to afford 3.5 g of Compound **6f** as a white powder: HPLC: 4.04 min., 97%, broad; MS (ES) m/z 470 (MH^+).

Compound **6f** (3.5 g, 7.46 mmol) was deethylated following Procedure A. The solid was further purified by taking it up in MeOH, followed by collection of the precipitate to afford Compound **17** (2.93 g) as a white powder: HPLC 4.0 min.

To a mixture of Compound **17** (2.93 g, 6.2 mmol) in CH₃OH (10 mL) was added a solution of tris(hydroxymethyl)aminomethane (0.75 g, 6.2 mmol) in CH₃OH (10 mL). The solution was filtered and concentrated under reduced pressure at rt, and the resulting white solid was recrystallized from CH₃CN/EtOAc to yield the tromethamine salt of Compound **17** (3.35 g) as a white solid. HPLC: 4.02 min, 100%; MS (ES) 442 (MH^+); ¹H NMR (DMSO-*d*₆) δ 1.07 (d, 3H), 3.45 (s, 6H), 4.48 (d, 1H), 6.12 (d, 1H), 7.12 – 7.18 (br m, 1H), 7.24 – 7.45 (overlapping m, 4H), 7.92 – 8.00 (overlapping m, 3H), 10.92 (d, 1H); Anal. Calc'd for C₁₉H₁₅NO₃PSCI F₂ · 1.0 C₄H₁₁NO₃ · 0.15 H₂O: C, 48.84; H, 4.69; N, 4.96; H₂O, 0.48.

Found: C, 48.99; H, 4.62; N, 4.97; H₂O, 0.42.



- 5 Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 6, the following compounds were prepared without further purification:

Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
14	406	153	490
15	422 (MH ⁻)	154	436
16	460	155	420
20	430	156	442
21	422 (MH ⁻)	157	431
24	422 (MH ⁻)	160	440
28	444	161	440
29	456	162	442
33	389	163	442
66	422 (MH ⁻)	164	485
144	382	165	466
145	436	166	451
146	420	167	485
147	451	168	464 (MH ⁻)
148	464	169	442
150	407	170	475
152	474	171	442

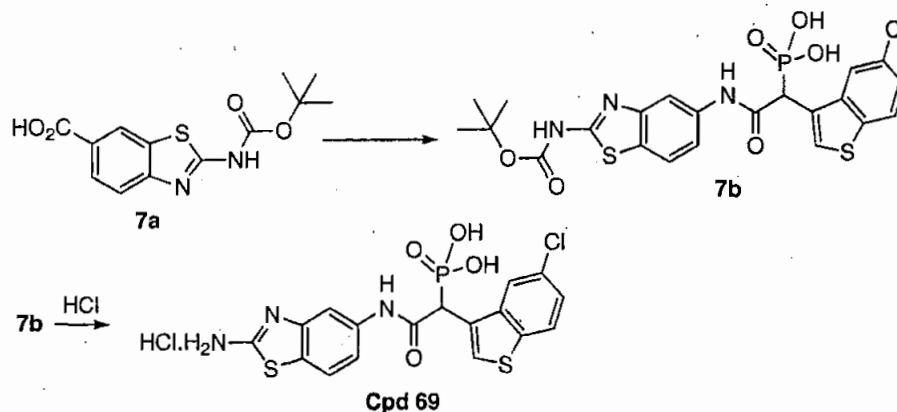
The following compounds can be made by those skilled in the art by using Example 6 and varying the starting materials, reagent(s) and conditions used: compounds 300, 301, 302, 303, 304, 305, 306, and 307.

5

EXAMPLE 7

[(5-Chloro-benzo[*b*]thiophen-3-yl)-(2-amino-4-benzothiazol-6-ylcarbamoyl)-methyl]-phosphonic acid, Cpd 69

Using the procedure described in Example 6 for the conversion of Compound **6b** to
 10 Compound **17**, Compound **7a** was converted to Compound **7b**. Compound **7b** was
 suspended in a small volume of 1,4-dioxane and gaseous HCl was bubbled in to yield a
 clear yellow solution and the solution was stirred for 1 h. The reaction was concentrated
 under reduced pressure at rt, the residue stirred with 1N HCl (aq) for 45 min, and the solid
 was collected to yield Compound **69** as a yellow powder: HPLC: 2.58 min; MS (ES) *m/z*
 15 454(MH⁺).

**EXAMPLE 8**

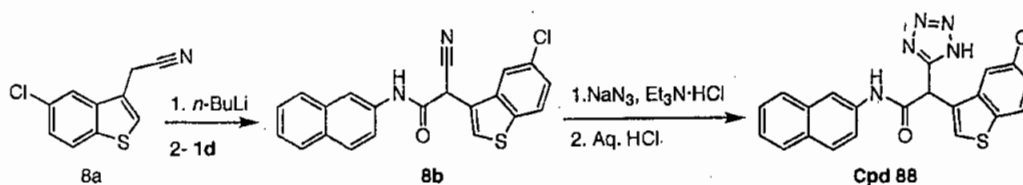
2-(5-Chloro-benzo[*b*]thiophen-3-yl)-*n*-naphthalen-2-yl-2-(1*h*-tetrazol-5-yl)-acetamide,

20

Cpd 88

A solution of Compound **8a** (1.15 g, 5.53 mmol) in THF (10 mL) was added
 dropwise to a solution of 2.5M *n*-BuLi in hexanes (2.40 mL, 6.08 mmol) in THF (10 mL) at
 -78°C. After stirring for 30 min at -78°C, a solution of Compound **1d** (0.94 g, 5.60 mmol) in
 THF (10 mL) was added dropwise. After 1 h, the reaction was quenched at -78°C with
 25 excess NH₄Cl (aq). After warming to rt gradually, the layers were separated, and the
 aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts
 were dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue
 was stirred with MeOH, and the precipitate was collected to yield Compound **8b** (1.5 g) as
 an off-white powder: HPLC: 4.39 min.

A suspension of Compound **8b** (0.28 g, 0.75 mmol), sodium azide (0.15 g, 2.24 mmol), and triethylamine hydrochloride (0.31 g, 2.24 mmol) in toluene (7 mL) was refluxed overnight. Upon cooling to rt, EtOAc (10 mL) and 1 N HCl (10 mL) were added and the mixture was stirred vigorously. The biphasic mixture was filtered and a tan solid was collected. The layers were separated, and the organic layer was concentrated under reduced pressure at rt. The residue was treated with CH₃CN, and a tan solid was collected. The combined solids were treated with hot CH₃CN (100 mL), cooled, and the solid was collected to afford Compound **88**: HPLC: 4.11 min; MS (ES) *m/z* 420 (MH⁺) = 420; ¹H NMR (DMSO-*d*₆) δ 6.15 (s, 1H), 7.41-7.62 (overlapping m, 4H), 7.82-7.93 (overlapping m, 5H), 8.10 (d, 1H, *J* = 8.6 Hz), 8.32 (s, 1H), 10.92 (s, 1H).



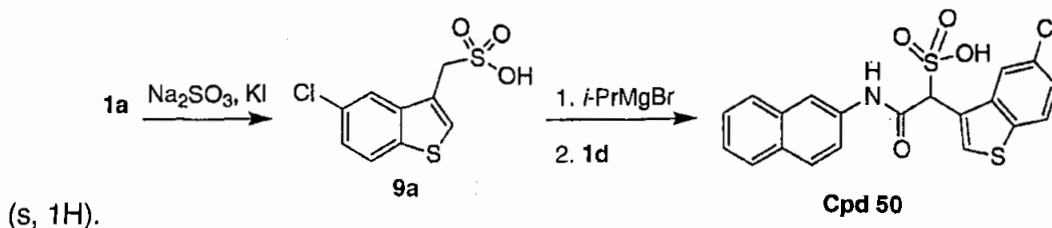
EXAMPLE 9

[(5-Chloro-benzo[*b*]thiophen-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-sulfonic acid, Cpd 50

To a solution of Compound **1a** (1.0 g, 3.85 mmol) in acetone (5 mL) was added a solution of sodium sulfite (0.49 g, 3.85 mmol) and KI (potassium iodide) (0.13 g, 0.77 mmol) in water (10 mL). The solution was refluxed for 3.5 h, then cooled to rt and concentrated under reduced pressure. The residue was treated with 1N HCl (15 mL), filtered, and the filtrate was extracted with EtOAc (3 x 10 mL). The combined organic extracts were filtered, and concentrated under reduced pressure at rt to yield 0.60 g of Compound **9a** as a white powder: HPLC: 3.38 min; MS (ES) *m/z* 261 (MH⁺).

To a suspension of Compound **9a** (0.29 g, 1.11 mmol) in THF (7 mL) at -5°C was added a solution of 2 M *i*-PrMgBr in Et₂O (1.39 mL, 2.77 mmol). The mixture was stirred for 2 h at rt, then cooled to -10°C before treatment with a solution of Compound **1d** (0.20 g, 1.17 mmol) in THF (7 mL). After stirring overnight at rt, the reaction was quenched with 3 mL of 1N HCl (aq), and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The resulting tan foam was dissolved in a minimum volume of CH₃CN and allowed to stand overnight. The solution was filtered, and the filtrate was concentrated under reduced pressure and the residue was purified by reverse phase HPLC (20-90% CH₃CN/H₂O). The resulting white powder was dissolved in CH₃CN, filtered, and concentrated under reduced pressure at rt to yield Compound **50** (0.14 g) as a white solid:

HPLC: 3.14 min; MS (ES) m/z 430 (MH^+); 1H NMR (DMSO- d_6) δ 5.35 (s, 1H), 7.28-7.51 (overlapping m, 4H), 7.72-7.80 (m, 3H), 7.92-8.05 (overlapping m, 3H), 8.24 (s, 1H), 10.40



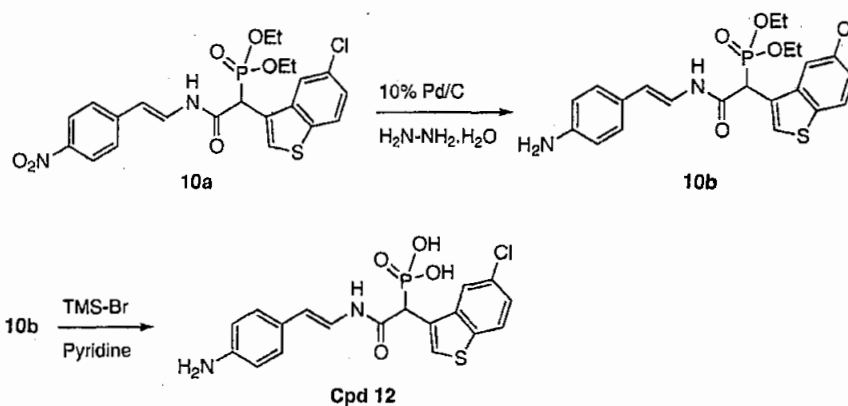
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EXAMPLE 10

[[[(5-Chloro-benzo[*b*]thiophen-3-yl)-[2-(4-amino-phenyl)-vinylcarbamoyl]-methyl]-methyl-phosphonic acid, Cpd 12

Using the procedure described in Example 6, substituting *p*-nitro-cinnamic acid for 3,4-difluorocinnamic acid and substituting Compound **1c** for Compound **6a**, Compound **10a** was prepared. To a solution of Compound **10a** (0.115 g, 0.226 mmol) in 6 mL of 1:1 EtOH /CH₂Cl₂ was added 10% Pd/C (0.060 g) and hydrazine hydrate (0.173 mL, 3.35 mmol). After 2 h, the reaction mixture was filtered, concentrated under reduced pressure at rt, and the resulting yellow solid was taken up in hot acetonitrile and filtered. The filtrate was concentrated under reduced pressure at rt, and the residue was purified by flash column chromatography (silica, 1% CH₃OH/CH₂Cl₂) to yield Compound **10b** (0.064 g) as a bright yellow solid: HPLC: 2.94 min; MS (ES) m/z 479 (MH^+).

Compound **10b** (0.064 g, 0.134 mmol) was deethylated by Procedure A to yield Compound **12** (0.036 g) as an orange solid: HPLC: 2.41 min; MS (ES) m/z 423 (MH^+).



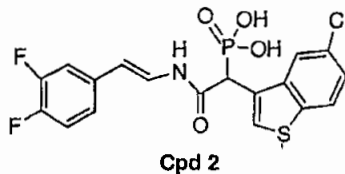
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EXAMPLE 11

[[[(5-Chloro-benzo[*b*]thiophen-3-yl)-[2-(3,4-difluoro-phenyl)-vinylcarbamoyl]-methyl]-methyl-phosphonic acid, Cpd 2

Using the procedure described in Example 6, substituting phosphonate Compound **1c** (0.75 g, 2.34 mmol) for Compound **6a**, followed by deethylation by Procedure A,

Compound **2** (0.116 g) was prepared as a white solid: HPLC: 3.98 min; MS (ES) m/z 444 (MH^+); Anal. Calc'd for $C_{18}H_{13}NO_3PSClF_2 \cdot 1.0 C_4H_{11}NO_3 \cdot 0.10 H_2O C_4H_{11}NO_3 \cdot 0.33 C_2H_6O$: C, 46.34; H, 4.43; N, 4.87; H_2O , 1.04. Found: C, 46.47; H, 4.09; N, 4.65; H_2O , 1.34.



5

Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 11, the following compounds were prepared without further purification:

Cpd	MS (MH^+)	Cpd	MS (MH^+)
18	407 (MH^-)	42	422
19	424 (MH^-)	49	468
25	409	78	440
37	368	81	476
38	437	199	442 (MH^-)

10

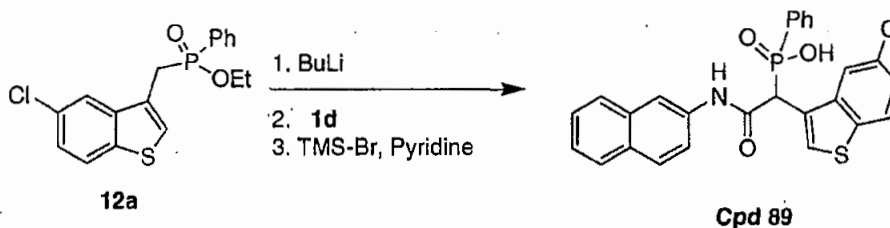
The following compounds can be made by those skilled in the art by using Example 11 and varying the starting materials, reagent(s) and conditions used: compounds 192, 193, 194, 195, 196, 197, 198, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 308, 309, 310, 311, 312, 313, 314, and 315.

15

EXAMPLE 12

[(5-Chloro-benzo[*b*]thiophen-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-phenyl-phosphinic acid, Cpd 89 Compound **12a** (0.35 g, 1.17 mmol) was prepared by the method described in *Aust.J.Chem.* **1983**, 36, 2517-2536. Using the procedure described in Example 1 and Procedure A, substituting Compound **12a** for Compound **1c**, Compound **89** was prepared as a white solid: HPLC: 4.19 min; MS (ES) m/z 490 (MH^+).

20



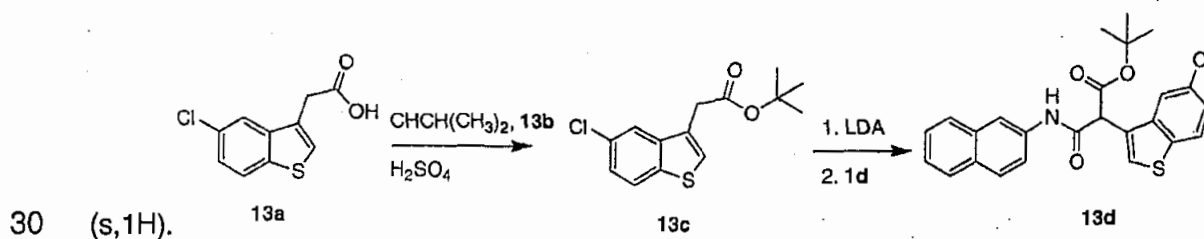
EXAMPLE 13

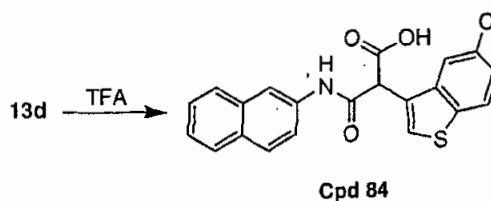
[(5-Chloro-benzo[*b*]thiophen-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-carboxylic acid, Cpd 84

5 A stream of isobutylene (g) Compound **13b** was introduced into a suspension of Compound **13a** (1.07 g, 4.71 mmol) in acetone (15 mL) containing H₂SO₄ (0.026 mL, 0.94 mmol). After 40 min, the cloudy solution was stoppered and stirred overnight. The reaction was poured into 1N NaOH (aq), and the layers were separated. The aqueous portion was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were
 10 washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt to yield Compound **13c** (1.20 g): HPLC: 4.37 min.

To a solution of diisopropylamine (0.26 mL, 1.84 mmol) in THF (7 mL) at -40°C was added a 2.5M solution of *n*-BuLi in hexanes (0.74 mL, 1.84 mmol). The temperature lowered to -70°C, and a solution of Compound **13c** (0.38 g, 1.34 mmol) in THF (7 mL) was added slowly dropwise. The mixture was stirred for 30 min, at which time a solution of
 15 Compound **1d** (0.24 g, 1.41 mmol) in THF (7 mL) was added dropwise. After 45 min the reaction was quenched with 3 mL of NH₄Cl (aq), then extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column
 20 chromatography (silica, 0-10% EtOAc/hexanes) to afford Compound **13d** (0.18 g): HPLC: 4.73 min; MS (ES) *m/z* 452 (MH⁺).

A solution of Compound **13d** (0.10 g, 0.22 mmol) in 1 mL of 1:1 CH₂Cl₂/TFA was allowed to stand for 65 min. The solution was concentrated under reduced pressure at rt and the residue was held under vacuum at rt overnight. The residue was dissolved in
 25 CH₃CN, filtered and concentrated under reduced pressure at rt. The residue was triturated from diethyl ether at rt, and the white solid was collected to yield Compound **84** (0.023 g) as a tan solid: HPLC: 4.16 min; MS (ES) *m/z* 396 (MH⁺); ¹H NMR (DMSO-*d*₆) δ 5.33 (s, 1H), 7.39-7.59 (overlapping m, 4H), 7.82-7.91 (overlapping m, 4H), 8.02-8.08 (overlapping m, 2H), 8.31 (s, 1H), 10.63





EXAMPLE 14

[(5-Chloro-benzo[*b*]thiophen-3-yl)-

5 (naphthalen-2-ylcarbamoyl)-methyl]-carbamate, Cpd 80

Compound **14d** was prepared from Compound **14a** by the methods described in *J. Med. Chem.* **1989**, 32(12), 2548-2554 and *J. Het. Chem.* **1998**, 25, 1271: HPLC: 3.95 min.

Compound **14d** was converted to Compound **14e** using the method described in *Eur. J. Med. Chem.* **2001**, 36(1), 55-62). Compound **14e** was oxidized with selenium dioxide, to yield Compound **14f** using the method described in British patent 1399089 (1971):
 10 HPLC: 3.78 min; MS (ES) *m/z* 239 (*MH*⁺).

To a solution of Compound **14f** (2.0 g, 8.22 mmol), Compound **14g** (1.18 g, 8.22 mmol), and HOBT (1.11 g, 8.22 mmol) in DMF (15 mL) was added DCC (1.69 g, 8.22 mmol) and the reaction was stirred for 48 h. The slurry was filtered, and the filtrate
 15 concentrated under high vacuum at rt. The residue was purified by trituration from boiling CH₃CN to yield Compound **14h** (1.41 g) as a bright yellow powder: HPLC: 4.91 min; MS (ES) *m/z* 364 (*MH*⁺).

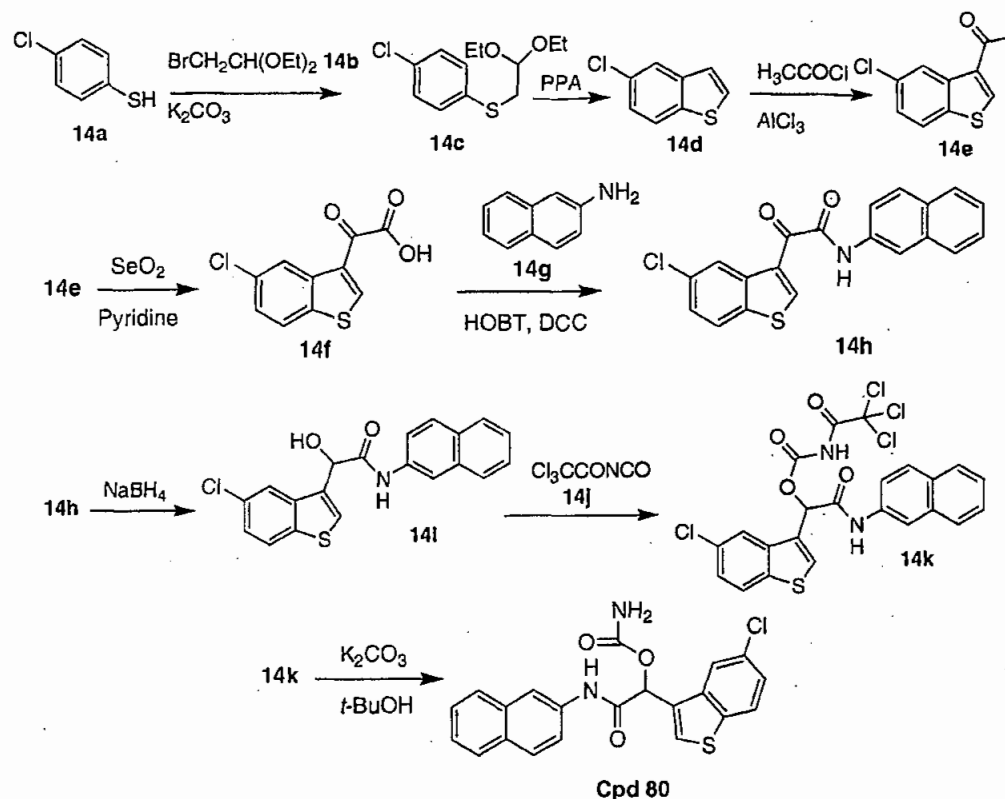
To a suspension of Compound **14h** (1.02 g, 2.79 mmol) in 20 mL of 1:1 THF/MeOH was added NaBH₄ (0.32 g, 8.42 mmol). The reaction was stirred for 1 h, then
 20 quenched with 1N HCl (5 mL). The volume was reduced approximately 50% under reduced pressure at rt and the solution was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by recrystallization from CH₃CN, to yield Compound **14i** (0.70 g): HPLC: 4.18 min; MS (ES) *m/z* 368 (*MH*⁺).

To a suspension of Compound **14i** (0.25 g, 0.68 mmol) in CH₂Cl₂ (10 mL) at 0°C, was added Compound **14j** (0.11 mL, 0.88 mmol). After stirring for 3 h at rt, a white solid was collected and rinsed with a minimal volume of CH₂Cl₂, then dried under N₂/vacuum to
 25 yield 0.36 g of Compound **14k**: HPLC: 4.56 min; MS (ES) *m/z* 554 (*MH*⁺).

A suspension of Compound **14k** (0.36 g, 0.65 mmol) in saturated aqueous K₂CO₃ (6 mL) and *t*-BuOH (3 mL) was refluxed for 2 h, then stirred at rt for 24 h. The reaction was concentrated under reduced pressure at rt, treated with aqueous 1N HCl (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt to yield
 30

Compound **80** (0.105 g): HPLC: 4.29 min; MS (ES) m/z 410 (MH^+); 1H NMR ($DMSO-d_6$) δ 6.16 (s, 1H), 7.38-7.49 (overlapping m, 3H), 7.57-7.61 (m, 1H), 7.77-7.86 (overlapping m, 3H), 7.97 (s, 1H), 8.07 (d, 1H, $J = 8.7$ Hz), 8.13 (s, 1H), 8.22 (d, 1H, $J = 2$ Hz), 10.02 (s, 1H).

5



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EXAMPLE 15

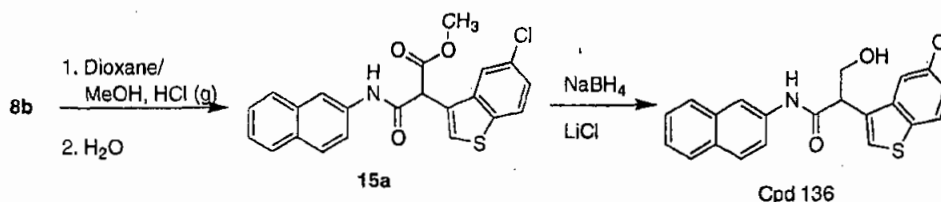
2-(5-Chloro-benzo[b]thiophen-3-yl)-3-hydroxy-N-naphthalen-2-yl-propionamide, Cpd 136

A suspension of Compound **8b** (1.23 g, 3.27 mmol) in 1,4-dioxane/methanol (1:1, 50 mL) at $-78^\circ C$ was saturated with HCl (g). The mixture was maintained at $-20^\circ C$ overnight, then concentrated under vacuum, such that the temperature remained below $20^\circ C$. The residue was partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure at rt, and the resulting residue was recrystallized from CH_3CN to afford Compound **15a** (1.47 g) as a white powder: HPLC: 4.31 min.

20

To a solution of Compound **15a** (0.23 g, 0.56 mmol) in THF (5 mL) was added $NaBH_4$ (0.043 g, 1.12 mmol), LiCl (0.048 g, 1.12 mmol), and EtOH (10 mL). The reaction was stirred for 90 min, then quenched with several drops of 1N HCl (aq). The mixture was cooled to $-10^\circ C$ and treated with 10 mL of 1N HCl. The mixture was extracted with EtOAc (4x) and the combined organic extracts were washed with brine (4x), dried (Na_2SO_4),

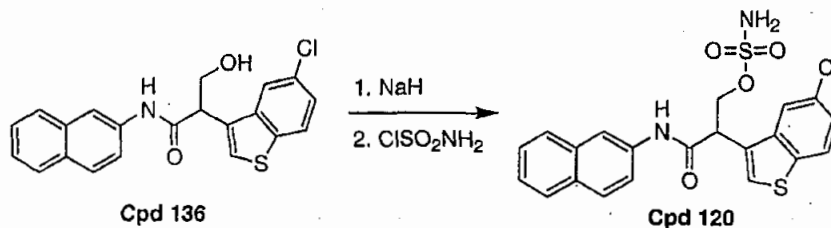
filtered, and concentrated under reduced pressure at rt to yield a white solid. The solid was triturated with CH₃CN to yield Compound **136** (0.14 g) as a snow-white solid: HPLC: 4.11 min; MS (ES) *m/z* 382 (MH⁺); ¹H NMR (DMSO-*d*₆) δ 3.69–3.75 (m, 1H), 4.11–4.19 (m, 1H), 4.33–4.37 (m, 1H), 5.17 (t, 1H, *J* = 5 Hz), 7.37–7.49 (m, 3H), 7.59–7.63 (m, 1H), 7.76 (s, 1H), 7.80–7.88 (m, 3H), 8.05 (d, 1H, *J* = 8 Hz), 8.18 (d, 1H, *J* = 2 Hz), 8.35 (s, 1H), 10.46 (s, 1H).



EXAMPLE 16

Sulfamic acid 2-(5-chloro-benzo[*b*]thiophen-3-yl)-2-(naphthalen-2-ylcarbamoyl)-ethyl ester, Cpd **120**

To a suspension of 95% NaH (0.017 g, 0.68 mmol) in DMF (2 mL) at 0°C was added a solution of Compound **136** (0.10 g, 0.26 mmol) in DMF (2 mL) dropwise. The suspension was stirred at 0°C for 1 h, then sulfamoyl chloride (0.067 g, 0.58 mmol) was added as a solid. After stirring for 1 h at 0°C, the mixture was treated with excess sulfamoyl chloride. After stirring overnight, the reaction was quenched with water and extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0–40% EtOAc/hexanes) to yield Compound **120** (0.10 g) as a white foam: HPLC: 4.12 min; MS (ES) *m/z* 461 (MH⁺); ¹H NMR (DMSO-*d*₆) δ 4.29–4.34 (m, 1H), 4.65–4.75 (m, 2H), 7.39–7.50 (m, 3H), 7.57–7.64 (m, 1H), 7.81–7.90 (m, 4H), 8.09 (d, 1H, *J* = 8.5 Hz), 8.215 (d, 1H, *J* = 2 Hz), 8.34 (s, 1H), 10.55 (s, 1H).



EXAMPLE 17

[(4-[[1-(Naphthalene-2-carbonyl)-piperidine-4-carbonyl]-amino]-naphthalen-2-ylcarbamoyl)-naphthalen-1-yl-methyl]-phosphonic acid, Cpd **8**

A solution of Compound **17a** (10 g, 45.9 mmol) in MeOH (200 mL) was added to 10% Pd/C and hydrogenated for 3.5 h at 40–50 psi. The mixture was filtered (Celite) and concentrated under reduced pressure at rt, and the resulting material was triturated with EtOAc to yield Compound **17b** as a crude black solid. Compound **17b** (1.36 g, approx. 8.61 mmol) was dissolved in DMF (20 mL) and TEA (1.32 mL, 9.46 mmol). To this solution was added 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile, (BOC-ON) (2.33 g, 9.46 mmol), and the reaction was heated at 55 °C overnight. The solution was concentrated under reduced pressure at rt and filtered through a plug of silica gel. The crude product was stirred with CH₂Cl₂ and filtered to yield 0.18 g of Compound **17c**: HPLC: 2.68 min; MS (ES) m/z 259 (MH⁺).

A solution of ethyl isonipecotamate, Compound **17d** (2.04 g, 13.0 mmol), and DIPEA (2.3 mL, 13.0 mmol) in 10 mL of CH₂Cl₂ was treated with 2-naphthoyl chloride, Compound **17e** (2.48 g, 13.0 mmol). After stirring for 1.5 h, the mixture was sequentially washed with 1N HCl (2 x 10 mL), saturated Na₂CO₃ (aq) (2 x 10 mL), and brine (10 mL). The organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was dissolved in 1,4-dioxane (41 mL) and treated with a solution of LiOH·H₂O (1.63 g, 39 mmol) in 5 mL of water. After 2 h, the reaction was concentrated under reduced pressure at rt, and the residue was acidified with 1N HCl (aq), and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt to yield 3.57 g of Compound **17g**: HPLC: 2.77 min; MS (ES) m/z 284 (MH⁺).

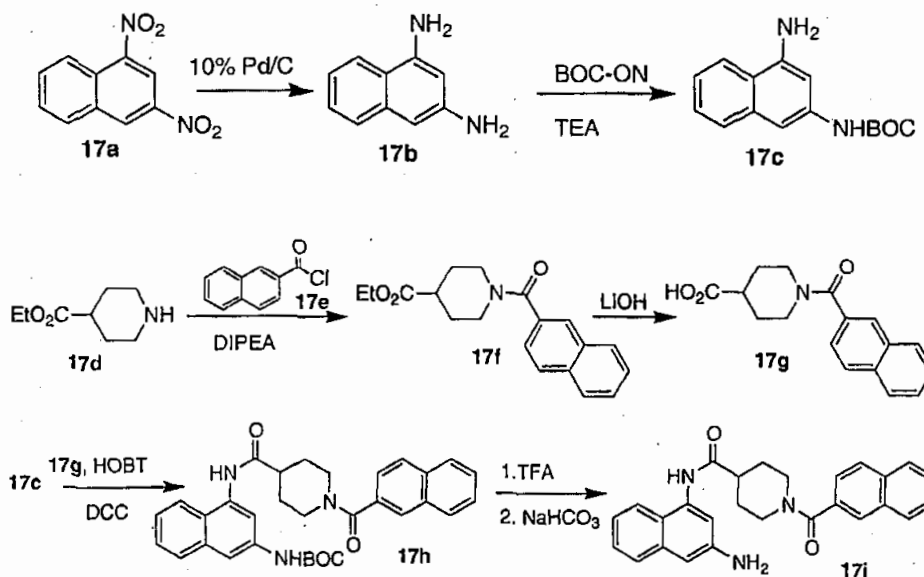
To a solution of Compound **17c** (0.18 g, 0.70 mmol), Compound **17g** (0.20 g, 0.70 mmol), and HOBT (0.094 g, 0.70 mmol) in DMF (8 mL) was added DCC (0.14 g, 0.70 mmol) and the reaction was stirred for 6 d. The mixture was filtered, concentrated under reduced pressure at rt, and the residue suspended in a minimal volume of CH₂Cl₂, and filtered again. The clear solution was washed with 1N KHSO₄ (aq) and the organic phase was filtered and washed sequentially with saturated Na₂CO₃ (aq) and brine. The organic phase was then dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0–3% MeOH/ CH₂Cl₂) to afford Compound **17h** (0.20 g, 0.382 mmol). A solution of **17h** in TFA (3 mL) was stirred for 50 min. The mixture was concentrated under reduced pressure at rt and the residue was suspended in CH₂Cl₂, washed with saturated Na₂CO₃ (2 x 5 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt to yield 0.17 g of Compound **17i**.

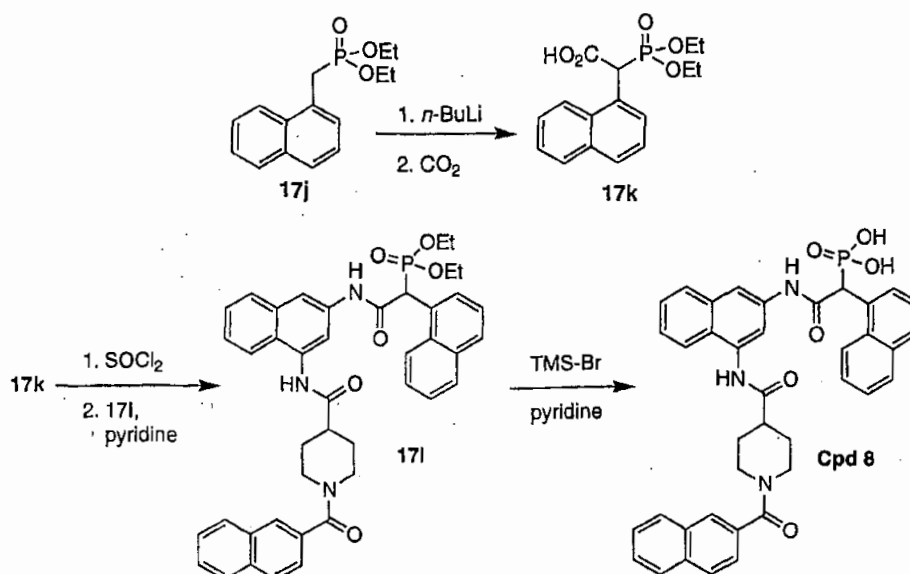
To 100 mL of THF and 2.5 M *n*-BuLi (79.2 mL, 0.198 mol) at –78 °C was added dropwise a solution of Compound **17j** (50 g, 0.18 mol). After 30 min, CO₂ was bubbled through the reaction for 1 h, after which point the mixture was warmed to rt. The ice bath-cooled mixture was quenched with excess saturated Na₂CO₃ (aq), and the volatile solvents

were removed under reduced pressure at rt. The resulting solution was washed with Et₂O (3x), acidified with 3N HCl (aq), and extracted with EtOAc (4x). The combined organic extracts were washed once with water, dried (Na₂SO₄), filtered (Celite), and concentrated under reduced pressure at rt to yield 32.59 g of Compound **17k**: HPLC: 3.06 min, MS (ES) m/z 323 (MH⁺).

Compound **17k** (0.13 g, 0.40 mmol) was stirred with 1 mL of thionyl chloride for 30 min and the mixture was concentrated under reduced pressure at rt. The residue was treated with hexanes and concentrated under reduced pressure at rt again. The residue was dissolved in THF (5 mL), at -78 °C, treated with a solution of Compound **17l** (0.17 g, 0.40 mmol) in pyridine (3.5 mL). The solution was stirred at rt overnight, then concentrated under reduced pressure at rt. The residue was taken up in CH₂Cl₂ (5 mL) and washed sequentially with 1N KHSO₄ (aq), saturated Na₂CO₃ (aq) (3 x 5 mL), and brine (5 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by prep-plate chromatography (75% EtOAc/hexanes) to yield 0.11 g of Compound **17l**: HPLC: 4.02 min; MS (ES) m/z 728 (MH⁺).

Compound **17l** was deethylated by Procedure A to yield Compound **8** (0.063 g): HPLC: 3.91 min; MS (ES) m/z 424 [M - [COCH(1-Naph)P(=O)(OH)₂]; ¹H NMR (DMSO-d₆) δ 1.6–2.2 (br overlapping m, 4H), 2.7–3.3 (br overlapping m, 3H), 3.6–4.0 (br m, 1H), 4.45–4.75 (br m, 1H), 5.32 (d, 1H, J = 24 Hz), 7.39–7.60 (overlapping m, 8H), 7.79–8.0 (overlapping m, 9H), 8.24 (s, 1H), 8.31 (d, 1H, J = 7 Hz), 8.38 (d, 1H, J = 10 Hz), 9.95 (s, 1H), 10.6 (s, 1H).





EXAMPLE 18

- 5 [(4-Chloro-1-methyl-1*H*-indol-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-phosphonic acid,
Cpd 63

To a stirred mixture of 95% sodium hydride (0.35 g, 13.85 mmol) in THF (3 mL) at 0°C was added a solution of 4-chloroindole Compound 18a (0.35 g, 6.59 mmol) in THF (3 mL), and the mixture was stirred for 15 min. Methyl iodide (1.03 g, 7.26 mmol) was added and the reaction was stirred overnight. The reaction was quenched with saturated NaHCO₃ (aq), the volatiles were removed under reduced pressure at rt, and the resulting mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered (Celite), and concentrated under reduced pressure at rt to yield 1.11 g of Compound 18b as an oil: HPLC: 3.37 min, 77%.

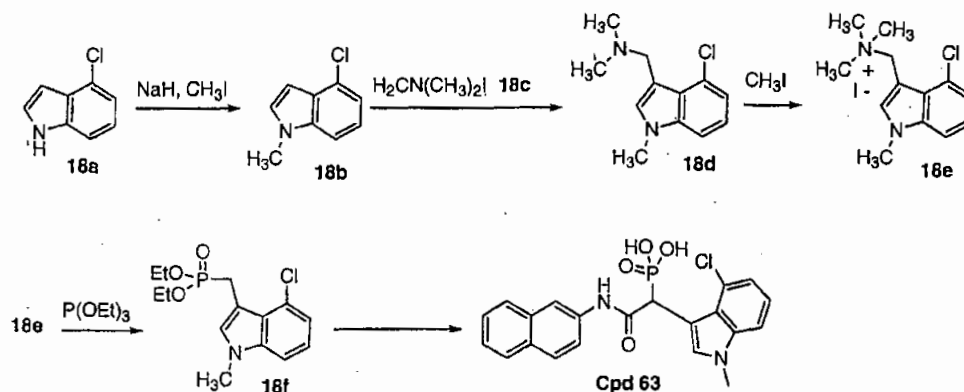
- 15 To a stirred suspension of Compound 18b (1.09 g, 6.59 mmol) in CH₂Cl₂ (10 mL) was added Compound 18c (1.58 g, 8.57 mmol). After stirring overnight, the solid was collected and rinsed sequentially with CH₂Cl₂ and Et₂O. The solid was dissolved in 1N NaOH (aq) and extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered (Celite), and concentrated under reduced pressure at rt to yield 0.95 g Compound 18d as a clear oil: HPLC: 1.18 min, 97%; MS (ES) *m/z* 223 (MH⁺).

To a stirred solution of Compound 18b (0.944 g, 4.24 mmol) in EtOH (10 mL) at 0°C was added methyl iodide (0.66 g, 4.66 mmol). After stirring at room temperature overnight, a solid was collected by filtration and rinsed sequentially with EtOH and Et₂O to yield 1.46 g of Compound 18e as a white solid: HPLC: 1.93 min, 68%.

- 25 A mixture of Compound 18e (1.0 g, 2.74 mmol) in triethyl phosphite (8 mL) was refluxed overnight and concentrated under high vacuum at 90 °C. The residue was dissolved in EtOAc, washed with H₂O, dried (Na₂SO₄), filtered (Celite), and concentrated

under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0 – 1% MeOH/ CH₂Cl₂) to yield 0.82 g of Compound **18f** as an oil: HPLC: 3.39 min; MS (ES) m/z 316 (MH⁺).

- Using the procedure described in Example 1 for the conversion of Compound **1c** to Compound **9**, including deethylation by Procedure A, Compound **18f** was converted to Compound **63**.



- Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 18, the following compounds were prepared without further purification:

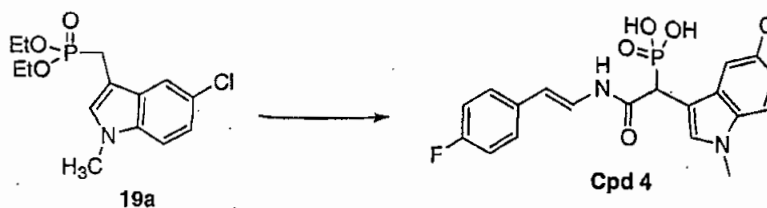
Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
3	429	58	429
11	413	62	433 (MH ⁻)
13	471 (MH ⁻)	65	420
22	395	74	425
27	497	77	423
52	451 (M + Na)	116	396

EXAMPLE 19

- {(5-Chloro-1-methyl-1*H*-indol-3-yl)-[2-(4-fluoro-phenyl)-vinylcarbamoyl]-methyl}-phosphonic acid, Cpd 4

Using the procedure described in Example 18, substituting 5-chloroindole for 4-chloroindole, Compound 19a was prepared.

- Using the procedure described in Example 11, Compound 4 was prepared: HPLC: 3.60 min; MS (ES) m/z 423 (MH⁺).

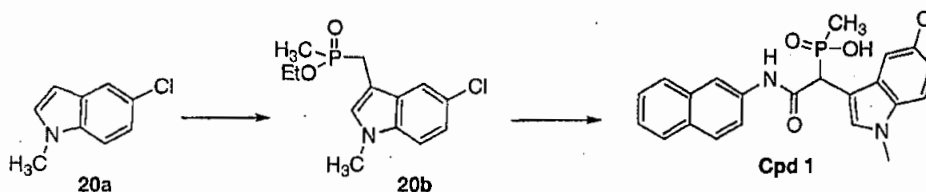
**EXAMPLE 20**

5 [(5-Chloro-1-methyl-1*H*-indol-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-methyl-phosphinic acid, Cpd 1

Using the procedure described in Example 18, substituting 5-chloroindole for 4-chloroindole, Compound **20a** was prepared.

10 Using the procedure described in Example 18, substituting Compound **20a** for Compound **18b**, Compound **20b** was prepared.

Using the procedure described in Example 1 followed by deethylation by Procedure A, Compound **20b** was converted to Compound **1**: HPLC: 3.77 min, 97%; MS (ES) *m/z* 427 (MH⁺).



15 Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 20, the following compounds were prepared without further purification:

Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
6	419 (MH ⁺)	7	439

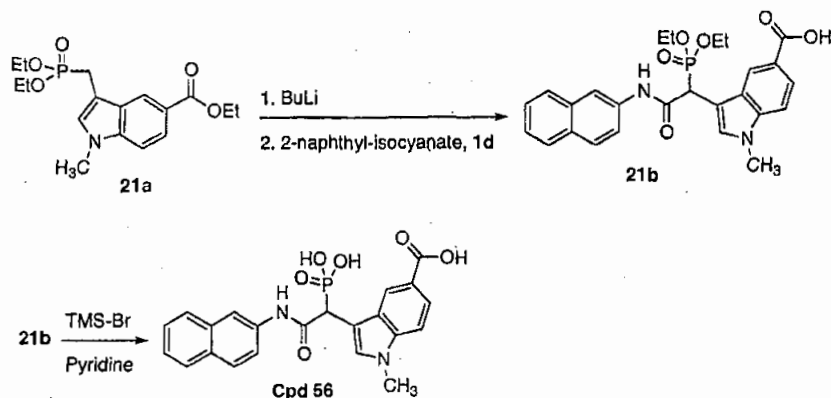
EXAMPLE 21

1-Methyl-3-[(naphthalen-2-ylcarbamoyl)-phosphono-methyl]-1*H*-indole-5-carboxylic acid, Cpd 56

25 Using the procedure described in Example 18, Compound **21a** was prepared. To a solution of 2.5 M *n*-BuLi in hexanes (0.56 mL, 1.40 mmol) in THF (2 mL) at -78°C was added dropwise a solution of Compound **21a** (0.27 g, 0.79 mmol) in THF (1 mL). After stirring for an additional 45 min, Compound **1d** (0.15 g, 0.87 mmol) in THF (1.5 mL) was

added dropwise to the mixture. After the addition was complete, the solution was stirred at -78°C for 2 h. The mixture was warmed to rt, excess saturated NaHCO_3 (aq) was added, and the solid was collected by filtration. The solid was rinsed (THF), and air dried to yield Compound **21b** (0.12 g): HPLC: 3.77 min.

- 5 Compound **21b** (0.060 g, 0.12 mmol) was deethylated by Procedure A to yield Compound **56** (0.042 g): HPLC: 3.19 min; MS (ES) m/z 420 ($M - \text{H}_2\text{O}$).



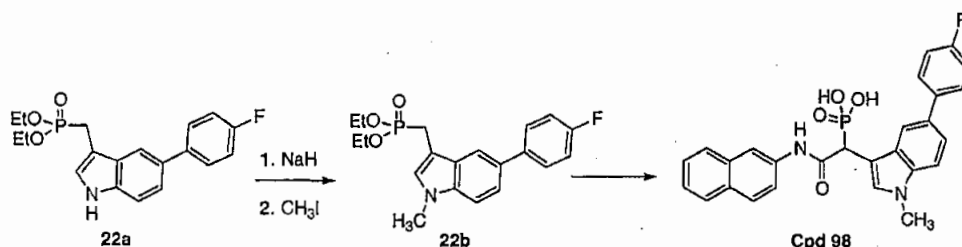
10

EXAMPLE 22

[[5-(4-Fluoro-phenyl)-1-methyl-1H-indol-3-yl]-(naphthalen-2-ylcarbamoyl)-methyl]-phosphonic acid, Cpd 98

- Compound **22a** (0.27 g, 0.75 mmol), prepared by the method of *Synlett Jan. 1994*, 93, was methylated as described in Example 18 to yield 0.27 g of Compound **22b**: HPLC: 3.65 min, 96.5%; MS (ES) m/z 362 (MH^+).

Using the procedure described in Example 1, followed by deethylation Procedure A, Compound **22b** converted to Compound **98**: HPLC: 4.46 min; MS (ES) m/z 487 (MH^+).



20

EXAMPLE 23

[(Naphthalen-2-ylcarbamoyl)-(1-phenyl-1H-indol-3-yl)-methyl]-phosphonic acid, Cpd 128

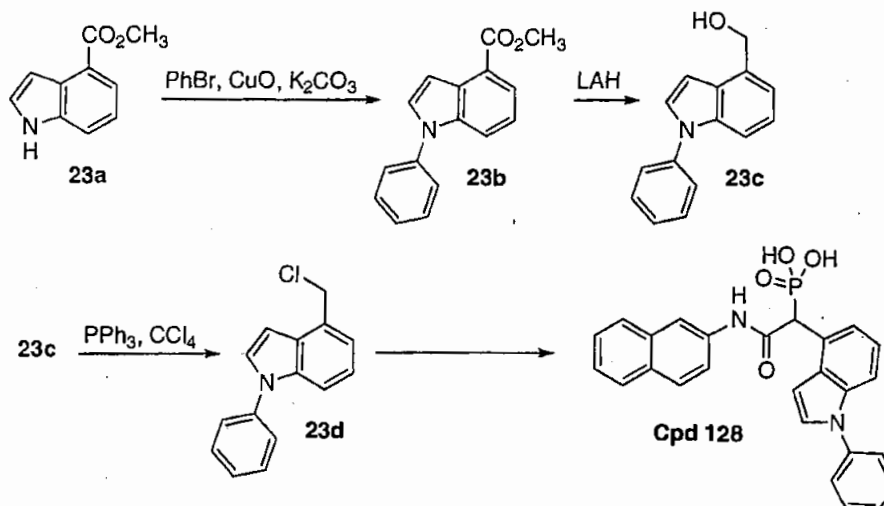
- A mixture of Compound **23a** (5.0 g, 29 mmol), copper(II) oxide (4.9 g, 63 mmol), potassium carbonate (5.0 g, 36 mmol), and bromobenzene (30 mL) was refluxed for 13 h.

After cooling to rt, the mixture was filtered (dicalite) and concentrated under reduced pressure at rt. The residue was triturated with hexanes to yield 5.2 g of Compound **23b** as a brown solid: HPLC: 4.44 min, 93%; MS (ES) m/z 252 (MH^+).

To a suspension of lithium aluminum hydride (1.0 g, 26 mmol) in THF (30 mL) was added Compound **23b** (5.2 g, 20 mmol) in THF (25 mL) at 0°C. The reaction was stirred for 1 h, then quenched at 0°C with moist Na_2SO_4 . The mixture was diluted with THF and filtered (dicalite). The filtrate was concentrated under reduced pressure at rt, and the residue was purified by flash column chromatography (silica, 25% EtOAc/hexanes) to yield 2.7 g of Compound **23c** as a white solid: HPLC: 3.62 min, 99%; MS (ES) m/z 224 (MH^+).

To a solution of Compound **23c** in DMF (15 mL) and CCl_4 (4 mL) at 0°C was added triphenylphosphine (3.4 g, 13 mmol) and the mixture was stirred at rt overnight. The reaction was concentrated under reduced pressure at rt, dissolved in EtOAc and passed through a short plug of silica gel (30% EtOAc/hexanes) to yield 1.3 g of Compound **23d**: HPLC: 4.19 min, 91%; MS (ES) m/z 513 (MH^+).

Using the procedure described in Example 1, substituting Compound **23d** for Compound **1a**, Compound **128** was prepared: HPLC: 4.23 min, 83%; MS (ES) m/z 479 ($M + Na$).



20

EXAMPLE 24

Methyl-((naphthalen-2-ylcarbonyl)-[2-(4-phenyl-piperidine-1-carbonyl)-benzo[b]thiophen-3-yl]-methyl)-phosphinic acid, Cpd 32

Compound **24a** was prepared according to the procedures described in JACS 1963, 6, 711 – 716 and JACS 1971, 93(12), 2897-2904.

To a solution of 2.5 M *n*-BuLi in hexanes (8.5 mL, 21.2 mmol) and THF (33 mL) at -78°C was added dropwise a solution of Compound **24a** (3.52 g, 18.4 mmol) in THF (33

mL). After stirring the resulting yellow slurry for 45 min, di-*tert*-butyldicarbonate (4.14 g, 19.0 mmol) in THF (33 mL) was added dropwise to the mixture. After the addition was complete, the solution was allowed to reach rt then quenched with 50 mL of saturated NH_4Cl (aq). The layers were separated, and the aqueous portion was extracted with
5 EtOAc (2 x 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0 to 75% EtOAc/ hexanes) to yield 3.68 g of Compound **24b**: HPLC: 2.74 min, 90%; MS (ES) m/z (MH^+) = 292.

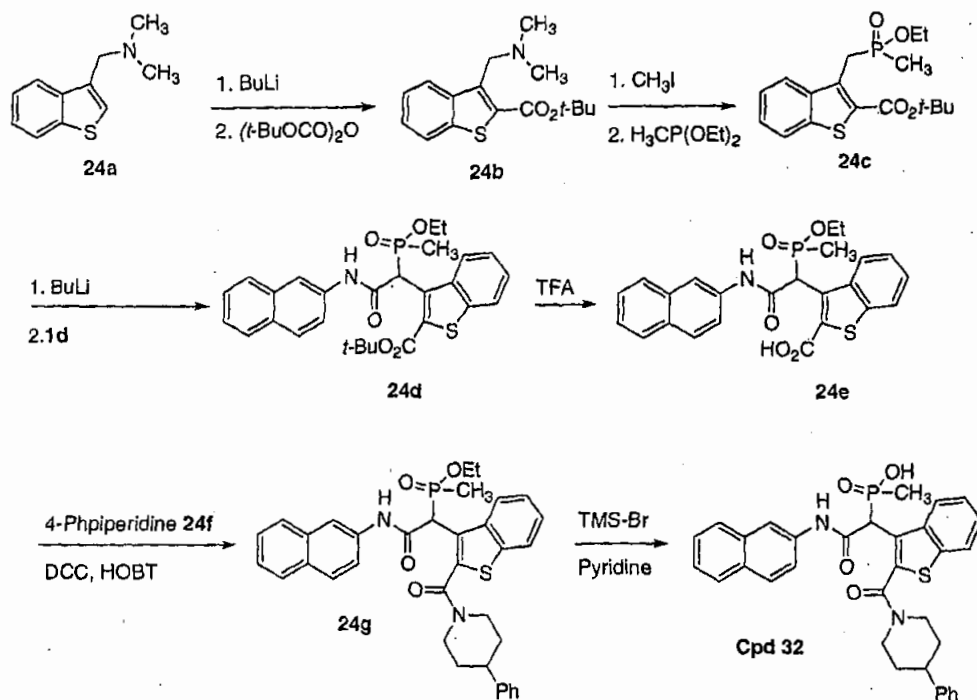
Using the procedure described in Example 18, substituting Compound **24b** (3.68 g, 12.65 mmol) for Compound **18d**, and diethylmethylphosphonite for triethylphosphite,
10 Compound **24c** (3.36 g) was prepared: HPLC: 3.67 min.

Using the procedure described in Example 1, followed by deethylation Procedure A, Compound **24c** (3.36 g, 9.5 mmol) was converted to Compound **24d** (2.18 g): HPLC: 4.24 min; MS (ES) m/z 524 (MH^+).

To Compound **24d** (2.18 g, 4.17 mmol) was added 5 mL of TFA. After 50 min, the
15 mixture was concentrated under reduced pressure at rt and the residue was purified by flash column chromatography (silica, 0 to 20% MeOH/EtOAc) to yield 0.30 g of Compound **24e**: HPLC: 3.63 min, 91%; MS (ES) m/z 468 (MH^+).

To a solution of Compound **24e** (0.20 g, 0.43 mmol), Compound **24f** (0.07 g, 0.45 mmol), and HOBT (0.061 g, 0.45 mmol) in DMF (2 mL) was added DCC (0.093 g, 0.45 mmol). After 1 h, the reaction mixture was filtered, the residue was suspended in a minimal volume of CH_2Cl_2 and filtered. The filtrate was washed sequentially with 1N HCl (2X), 10% aqueous Na_2CO_3 , and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography
20 (silica, 0 – 60% EtOAc/heptane) to yield 0.12 g of Compound **24g**: HPLC: 4.44 min; MS (ES) m/z 611 (MH^+).

Compound **24g** (0.12 g, 0.197 mmol) was deethylated by Procedure A to afford Compound **32** (0.086 g): HPLC: 4.49 min, 92%; MS (ES) m/z 583 (MH^+).



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 24, the following compounds were prepared without further purification:

5

Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
38	611 (MH ⁻)	121	438 (MH ⁻)
44	640 (MH ⁻)	130	529
50	599 (MH ⁻)		

EXAMPLE 25

10

[(5-Chloro-benzo[b]thiophen-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-(3-phenyl-propyl)-phosphinic acid, Cpd 36

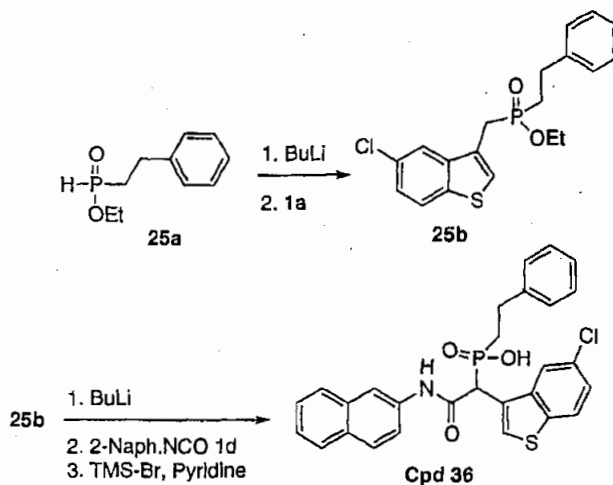
Compound **25a** was prepared according to the procedures described in *JACS* **2002**, 124, 9386-9387 and *J.Organomet.Chem* **2002**, 643-644, 154-163.

15

To a solution of Compound **25a** (0.51 g, 2.58 mmol) in THF (10 mL) at -78°C was added a solution of 2.5 M *n*-BuLi in hexanes (1.29 mL, 3.22 mmol). After stirring for 30 min, a solution of Compound **1a** (0.225 g, 0.86 mmol) in THF (7mL) was added dropwise. After 35 min, the reaction was quenched with excess saturated NH_4Cl (aq), and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the combined

organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0 – 30% EtOAc/hexanes) to yield 0.070 g of Compound **25b**: HPLC: 3.93 min, 88%; MS (ES) m/z 379 (MH^+).

- 5 Using the procedure described in Example 1 with deethylation Procedure A, Compound **25b** was converted to Compound **36**: HPLC: 4.70 min, 90%; MS (ES) m/z 520 (MH^+).



- Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 25, the following compounds were prepared without further purification:

Cpd	MS (MH^+)	Cpd	MS (MH^+)
34	488	48	534
39	578	51	548
40	582	53	562 (MH^-)
43	548 (MH^-)		

EXAMPLE 26

- 15 3-(2-Naphthalen-1-yl-2-phosphono-acetylamino)-naphthalene-2-carboxylic acid methyl ester, Cpd **75**

Using the procedure described in Example 17, Compound **17k** was converted to Compound **75**: HPLC: 4.13 min; MS (ES) m/z 450 (MH^+).

- 20 Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 26, the following compounds were prepared without further purification:

Cpd	MS (MH ⁺)
139	478

EXAMPLE 27

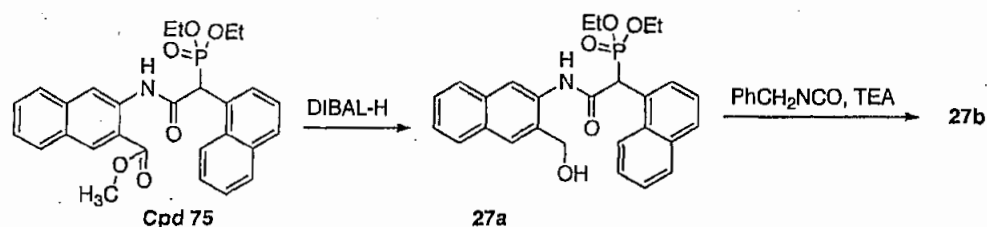
[(3-Benzylcarbamoyloxymethyl)-naphthalen-2-ylcarbamoyl]-
naphthalen-1-yl-methyl]-phosphonic acid, Cpd 72

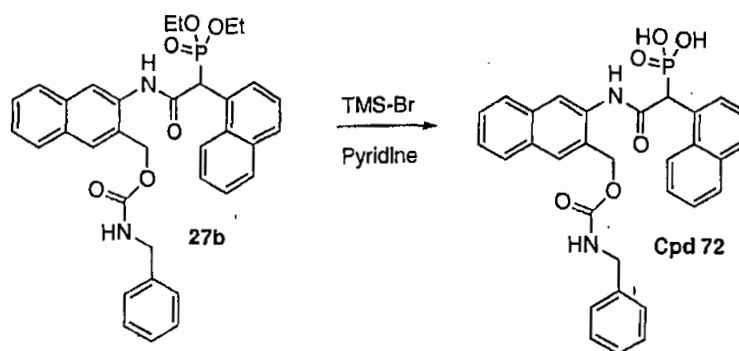
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To a suspension of Compound **75** (7.6 g, 15.03 mmol) in THF (150 mL) at 0°C was added dropwise a 1M solution of diisobutyl aluminum hydride in toluene (90 mL) and stirred at rt overnight. The reaction was cooled to 0°C, quenched with saturated NH₄Cl (aq), and extracted with EtOAc (2x). The combined organic extracts were filtered (Celite), washed with
10 brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (0 – 3% MeOH/CH₂Cl₂). The product was recrystallized from MeOH to yield Compound **27a** (1.85 g) as a crystalline solid: HPLC: 3.66 min; MS (ES) m/z 478 (MH⁺).

To a solution of Compound **27a** (0.30 g, 0.63 mmol) in THF (4 mL) was added
15 triethylamine (28 µL, 0.20 mmol) followed by benzylisocyanate (0.084 g, 0.63 mmol) in THF (2 mL) dropwise. The flask was wrapped with foil and stirred at rt for 96 h. Additional benzylisocyanate (0.042 g, 0.032 mmol) and triethylamine (60 µL, 0.43 mmol) were added and the reaction was stirred for an additional 48 h. The mixture was concentrated under reduced pressure at rt and the residue was taken up in CH₂Cl₂ and washed sequentially with
20 1N KHSO₄ (aq) (2x), brine, dried (Na₂SO₄), then filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0 – 3% MeOH/CH₂Cl₂) to yield 0.22 g of Compound **27b**: HPLC: 4.19 min, 95%; MS (ES) m/z 611 (MH⁺).

Compound **27b** (0.22 g, 0.36 mmol) was deethylated by Procedure A to yield
25 Compound **72** (0.16 g): HPLC: 3.80 min; MS (ES) m/z 555 (MH⁺).





Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 27, the following compounds were prepared without further purification:

Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
97	541	108	591
100	631 (MH ⁻)		

EXAMPLE 28

{[3-(2-Benzylcarbamoyl-vinyl)-naphthalen-2-ylcarbamoyl]-naphthalen-1-yl-methyl}-phosphonic acid, Cpd 109

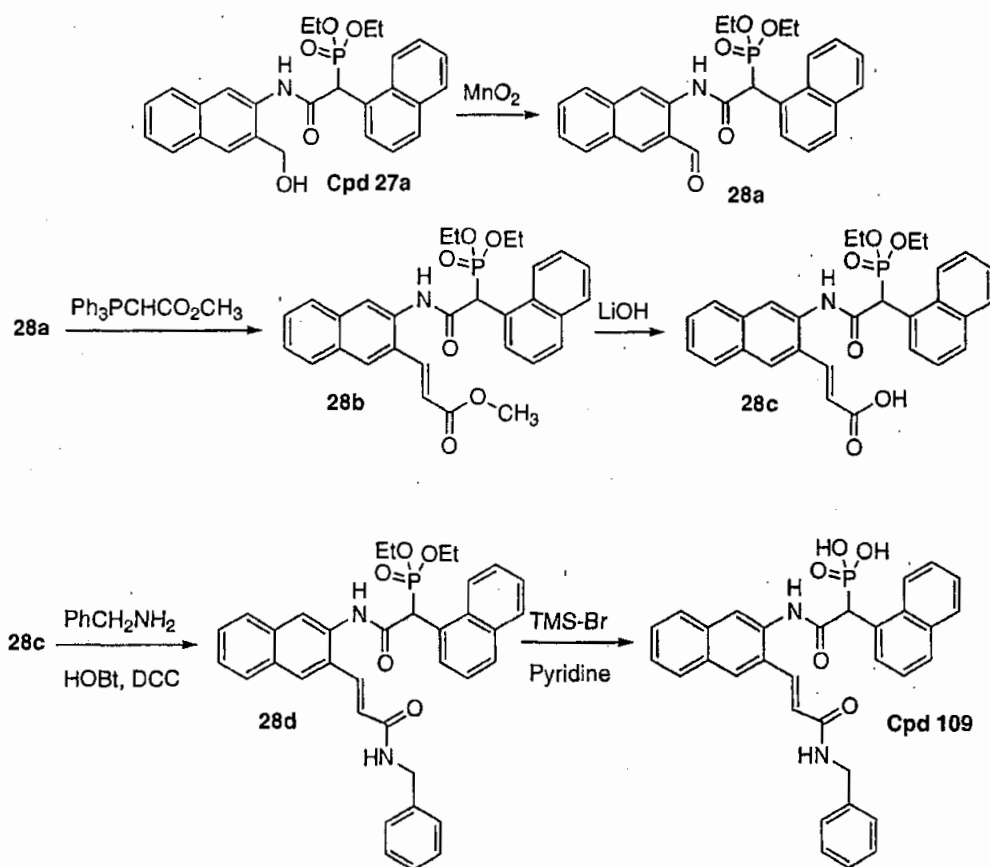
A solution of Compound **27a** (3.9 g, 8.1 mmol) in CHCl₃ (50 mL) was treated with activated MnO₂ (7.0 g, 80 mmol) and stirred for 48 h. The mixture was filtered (Celite), and concentrated under reduced pressure at rt. The residue was triturated with Et₂O to obtain 3 g of Compound **28a** as a yellow powder: HPLC: 4.35 min; MS (ES) m/z 476 (MH⁺).

A solution of Compound **28a** (1.0 g, 2.0 mmol), methyl-triphenylphosphoranylidene acetate (1.5 g, 4.5 mmol), and THF (25 mL) was refluxed for 7 h, then concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 5% MeOH/ CH₂Cl₂) to obtain 1.4 g of Compound **28b**: HPLC: 4.33 min; MS (ES) m/z 531 (MH⁺).

To a solution of Compound **28b** (1.0 g, 1.89 mmol) in 3:1 dioxane-H₂O (20 mL) was added LiOH (0.18 g, 7.50 mmol) and the mixture was stirred for 3 h. The layers were separated, and the aqueous layer was acidified with 3N HCl and extracted repeatedly with EtOAc. The combined organic extracts were dried (Na₂SO₄), and filtered. The filtrate was concentrated under reduced pressure at rt to afford 0.52 g of Compound **28c** as a white foam: HPLC: 3.89 min, 70%; MS (ES) m/z 518 (MH⁺).

A solution of Compound **28c** (0.40 g), benzylamine (0.10 g, 0.93 mmol) and HOBt (0.104 g, 0.77 mmol) in DMF (5 mL) was treated DCC (0.16 g, 0.77 mmol) in DMF (1 mL). The mixture was stirred for 24 h, then filtered (Celite) and concentrated under reduced pressure at rt. The residue was taken up in CH₂Cl₂ and washed sequentially with saturated NaHCO₃ (aq), H₂O, 1 N KHSO₄ (aq) and H₂O, then dried (Na₂SO₄) and filtered. The residue was purified by flash column chromatography (silica, 5% MeOH/ CH₂Cl₂) to yield 0.22 g of Compound **28d**: MS (ES) m/z 607 (MH⁺).

Compound **28d** was deethylated by Procedure A to afford Compound **109**: HPLC: 3.64 min; MS (ES) m/z (MH⁺) = 551.



15

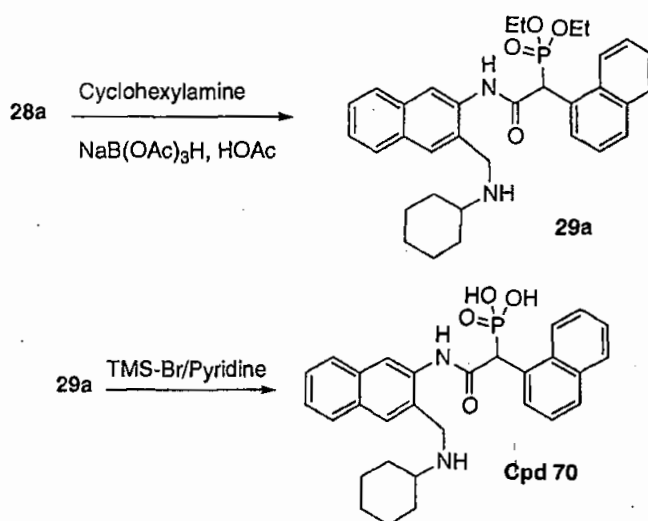
EXAMPLE 29

[(3-Cyclohexylaminomethyl-naphthalen-2-ylcarbonyl)-
naphthalen-1-yl-methyl]-phosphonic acid, Cpd 70

To a stirred solution of Compound **28a** (0.125 g, 0.263 mmol) and cyclohexyl amine (0.031 g, 0.316 mmol) in DCE (4 mL) was added $\text{NaB}(\text{OAc})_3\text{H}$ (0.111 g, 0.526 mmol) and glacial acetic acid (0.017 g, 0.316 mmol) and the mixture was stirred for 48 h. The reaction

was treated with 3N NaOH, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3x) and the combined organic extracts were washed with water, dried (Na₂SO₄), filtered (Celite), and concentrated under reduced pressure at rt. The residue was treated with 1N HCl (aq), and the solid was collected, rinsed with water, and air-dried. The product was dissolved in CH₃CN, precipitated with Et₂O, and the solid was collected and rinsed with Et₂O to yield 0.084 g of Compound **29a**: HPLC: 3.27 min; MS (ES) m/z 559 (MH⁺).

From Compound **29a** (0.079 g) was prepared Compound **70** by deethylation Procedure A. The crude product was dissolved in 1:1 CH₂Cl₂/TFA and concentrated. The residue was stirred with Et₂O, and the solid was collected and rinsed with Et₂O to yield Compound **70** (0.046 g): HPLC: 2.91 min; MS (ES) m/z 503 (MH⁺).



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 29, the following compounds were prepared without further purification:

Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
90	517	117	541
92	549	124	489
107	511	126	539
110	575 (M+Na)	133	507
112	667	142	525

EXAMPLE 30

{[3-({Methyl-[1-(naphthalene-2-carbonyl)-piperidin-4-yl]-amino}-methyl)-naphthalen-2-ylcarbamoyl]-naphthalen-1-yl-methyl}-phosphonic acid, Cpd 102

Using the procedure of Example 29, substituting (4-methylamino-piperidin-1-yl)-

naphthalen-2-yl-methanone for cyclohexylamine, Compound **102** was prepared: HPLC: 3.12 min; MS (ES) m/z 672 (MH^+).

EXAMPLE 31

5 ({3-[(1-Benzoyl-piperidin-4-ylamino)-methyl]-naphthalen-2-ylcarbamoyl}-naphthalen-1-yl-methyl)-phosphonic acid, Cpd 44

Using the procedure of Example 29, substituting (4-amino-piperidin-1-yl)-phenyl-methanone for cyclohexylamine, Compound **44** was prepared: HPLC: 2.84 min; MS (ES) m/z 608 (MH^+).

EXAMPLE 32

15 ({3-[4-(6-Chloro-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-naphthalen-2-ylcarbamoyl}-naphthalen-1-yl-methyl)-phosphonic acid, Cpd 60

Using the procedure of Example 17, Compound **17k** was converted to Compound **32a**.

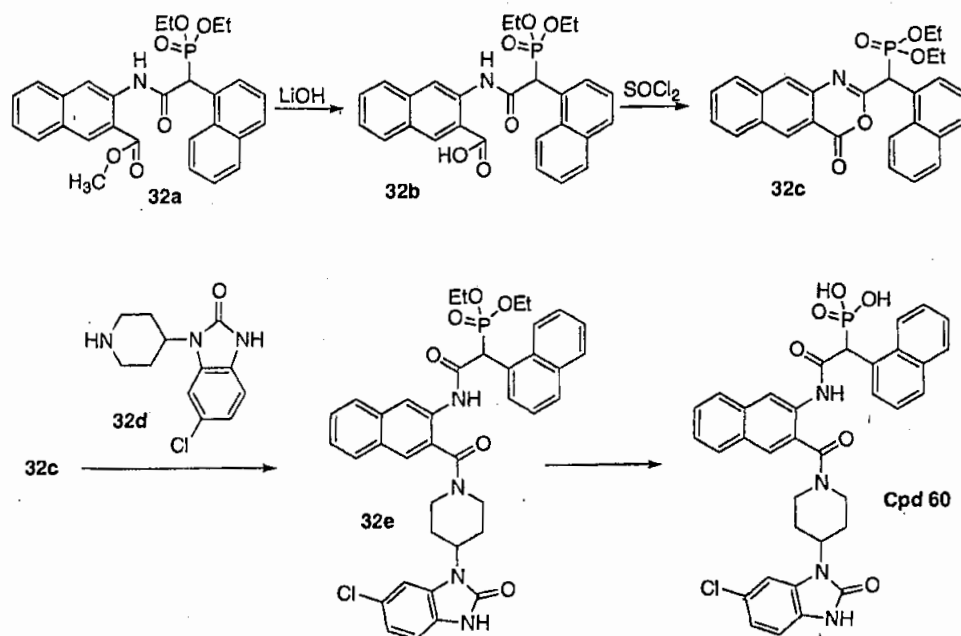
To a suspension of Compound **32a** (9.02 g, 17.9 mmol) in 1,4-dioxane (200 mL) was added a mixture of LiOH·H₂O (2.25 g, 53.6 mmol) in water (25 mL). The mixture was stirred for 4.5 h, then concentrated under reduced pressure at rt. The residue was partitioned between 1N HCl and EtOAc, and the aqueous portion was extracted with EtOAc (5x). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure at rt. The solid was suspended in MeOH, collected, washed with MeOH, and dried under N₂/vacuum to yield 6.87 g of Compound **32b** as a white powder: HPLC: 3.99 min.

A mixture of Compound **32b** (2.85 g, 9.79 mmol) and excess thionyl chloride was stirred until the solution became clear. The solution was concentrated under reduced pressure at rt, and the residue was taken up in hexanes and concentrated under reduced pressure at rt. The residue was stirred with CH₃CN, and the solid was collected and dried under N₂/vacuum to yield 2.45 g of Compound **32c**: HPLC: 4.10 min, 87%.

A mixture of Compound **32c** (0.31 g, 0.66 mmol) Compound **32d** (0.33 g, 1.311 mmol; *J. Med. Chem.* **1987**, 30(5), 814-819) in CH₃CN (15 mL) was refluxed for 1 h. The mixture was cooled to rt, filtered, and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0 – 3% MeOH/CH₂Cl₂) to yield 0.38 g of Compound **32e**: HPLC: 3.98 min.

Compound **32e** (0.18 g, 0.25 mmol) was deethylated by Procedure A to yield

Compound **60** (0.14 g): HPLC: 3.65 min; MS (ES) m/z 669 (MH^+).



5

Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 32, the following compounds were prepared without further purification:

Cpd	MS (MH^+)	Cpd	MS (MH^+)
54	593	101	579
73	566	103	629
83	618	104	649
87	565	111	539
91	517	113	636
93	635	115	613
100	620	131	565

10

EXAMPLE 33

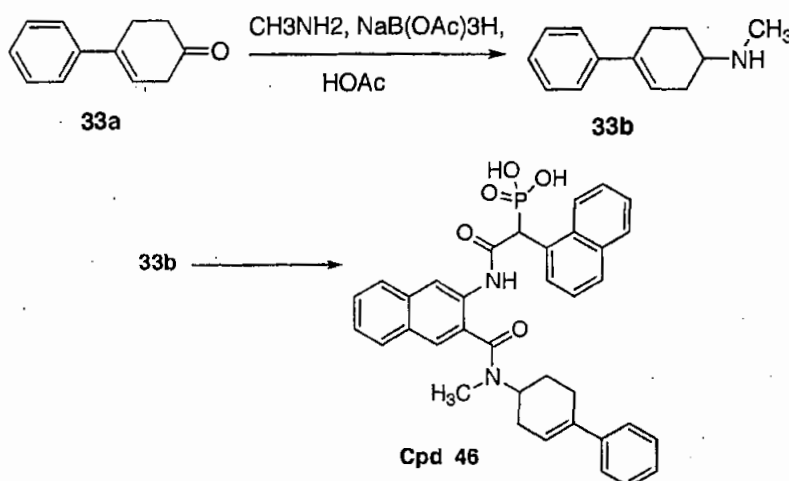
((3-[Methyl-(4-phenyl-cyclohex-3-enyl)-carbamoyl]-naphthalen-2-ylcarbamoyl)-naphthalen-1-yl-methyl)-phosphonic acid, Cpd 46

15

To a stirred solution of Compound **33a** (0.68 g, 3.96 mmol; *Syn.Comm.* **1994**, 24(6), 799-808) and a 2 mL of a 2M solution of methyl amine in THF (6 mL) was added sodium triacetoxymethylborohydride (1.30 g, 5.94 mmol) followed by glacial acetic acid (0.24 g, 3.96 mmol). After stirring for 2.5 h, the mixture was treated with water and extracted with CH₂Cl₂ (3x). The

combined organic extracts were dried (Na_2SO_4), filtered (Celite) and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0 – 10% MeOH/ CH_2Cl_2) to yield 0.25 g of Compound **33b** as a light brown tacky solid: HPLC: 1.91 min; MS (ES) m/z 188 (MH^+).

- 5 Using the procedure described in Example 32, Compound **33b** was converted to Compound **46**: HPLC: 3.97 min; MS (ES) m/z 605 (MH^+).



10

EXAMPLE 34

[(3-Benzylcarbamoyl-naphthalen-2-ylcarbamoyl)-naphthalen-1-yl-methyl]-phosphonic acid, Cpd 119

- Compound **119** was prepared from Compound **32b** via a standard BOP-Cl/TEA coupling and deethylation by Procedure A: HPLC: 3.81 min, 90%; MS (ES) m/z 525 (MH^+).

15

EXAMPLE 35

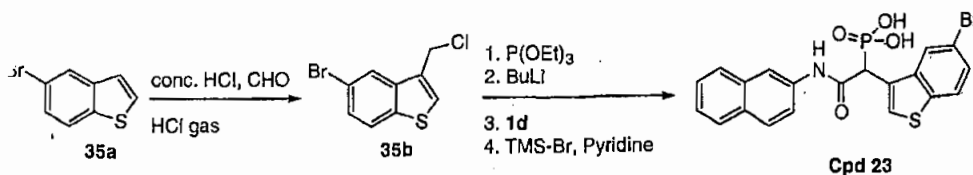
[(5-Bromo-benzo[b]thiophen-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-phosphonic acid, Cpd 23

20

Compound **35a** (6-bromobenzothiophene) was prepared by the method described in *J. Med. Chem* **1998**, 41, 4486-4491. Compound **35a** (3.45 g, 16.2 mmol) was converted to 3.68 g of crude Compound **35b** by the method described in the reference cited supra: HPLC: 4.14 min, 53%.

25

Following the procedure of Example 1 for the conversion of Compound **1c** to Compound **9**, Compound **35b** was converted to Compound **23**: HPLC: 4.53 min; MS (ES) m/z 475 (MH^+).



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 35, the following compounds were prepared without further purification:

5

Cpd	MS (MH ⁺)	Cpd	MS (MH ⁺)
5	412	76	474 (MH ⁻)
10	None (verified by NMR)	99	476/478
29	396 (MH ⁻)		

EXAMPLE 36

[(5-phenyl-benzo[b]thiophen-3-yl)-(naphthalen-2-ylcarbamoyl)-methyl]-phosphonic acid, Cpd 71

10

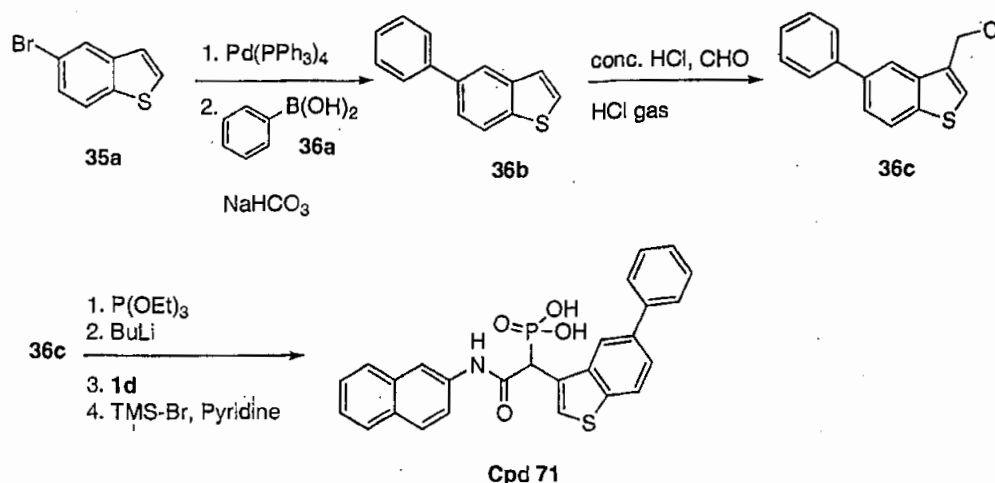
To a heat-gun dried flask under Ar was sequentially added toluene (15 mL), Compound 35a (0.33 g, 0.91 mmol) and then tetrakis triphenylphosphine Pd(0) (0.053 g, 0.046 mmol). After stirring for 30 min, the mixture was treated with a solution of phenyl boronic acid, Compound 36a (0.17 g, 1.36 mmol) in EtOH (5 mL) followed by saturated NaHCO₃ (aq) (7.5 mL). After 4 h at reflux, the mixture was cooled to rt and treated with brine (15 mL). The layers were separated, and the aqueous portion was extracted with EtOAc (3x) and the combined organic extracts were washed sequentially with 0.1 N NaOH (aq) (3x), brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure at rt. The residue was purified by flash column chromatography (silica, 0–3% MeOH/CH₂Cl₂) to yield 0.27 g of Compound 36b: HPLC: 3.91 min, 95%; MS (ES) m/z 361 (MH⁺).

20

Following the procedure of Example 35 for the conversion of Compound 35a to Compound 35b, Compound 36b was converted to Compound 36c.

Following the procedure of Example 1 with Procedure A for the conversion of Compound 1c to Compound 9, Compound 36c was converted to Compound 71: HPLC: 4.84 min; MS (ES) m/z 572 (MH⁺).

25



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 36, the following compounds were prepared without further purification:

5

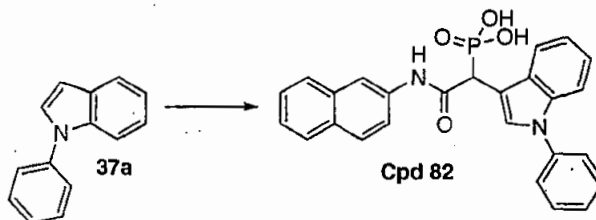
Cpd	MS (MH^+)
143	623 (M+pyr) H^+

EXAMPLE 37

[(Naphthalen-2-ylcarbamoyl)-(1-phenyl-1H-indol-3-yl)-methyl]-phosphonic acid, Cpd 82

10 *N*-phenyl indole Compound **37a** was prepared by the procedure described in *JOC* **2001**, 66(23), 7729-7737.

Using the procedure described in Example 18, substituting Compound **37a** for Compound **18b**, Compound **82** was prepared: HPLC: 4.04 min; MS (ES) m/z 457 (MH^+).



15

EXAMPLE 38

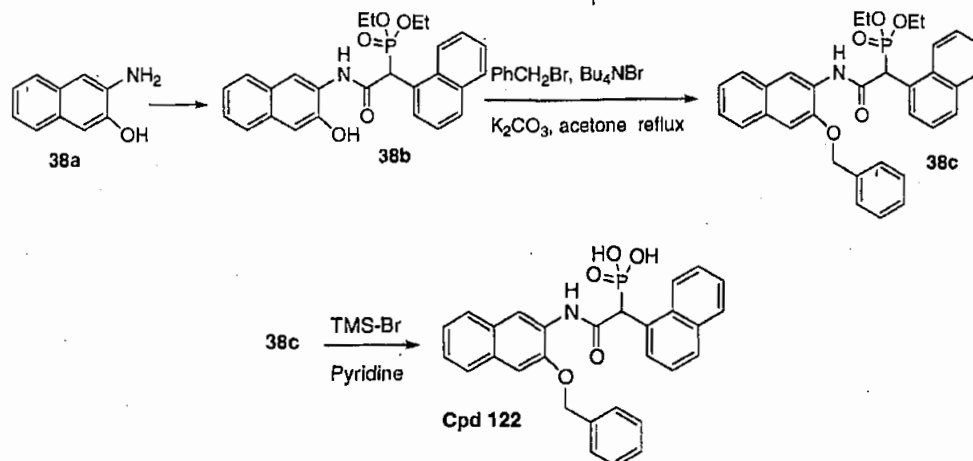
[(3-Benzyloxy-naphthalen-2-ylcarbamoyl)-naphthalen-1-yl-methyl]-phosphonic acid, Cpd 122

20

Using the procedure described in Example 17, substituting Compound **38a** (0.30 g, 1.89 mmol) for Compound **17i**, Compound **38b** (0.38 g) was prepared: HPLC: 3.85 min, 95%; MS (ES) m/z 464 (MH^+).

Using the method described in *JACS* **1998**, *110*(14), 4789, Compound **38b** (0.22 g, 0.48 mmol) was converted to Compound **38c** (0.16 g): HPLC: 4.43 min, 98%.

Compound **38c** (0.14 g, 0.25 mmol) was deethylated by Procedure A to give Compound **122** (0.114 g): HPLC: 4.08 min; MS (ES) m/z 498 (MH^+).



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 38, the following compounds were prepared without further purification:

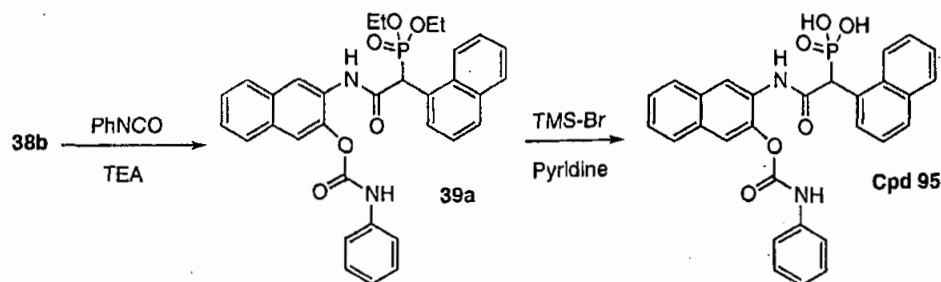
Cpd	MS (MH^+)	Cpd	MS (MH^+)
108	408	123	480
121	524		

EXAMPLE 39

[Naphthalen-1-yl-(3-phenylcarbamoyloxy-naphthalen-2-yl-carbamoyl)-methyl]-phosphonic acid, Cpd 95

Using the procedure described in Example 27, substituting Compound **38b** (0.19 g, 0.41 mmol) for Compound **27a** and phenylisocyanate for benzylisocyanate, Compound **39a** (0.18 g) was prepared: HPLC: 4.30 min, 95%; MS (ES) m/z 583 (MH^+).

Compound **39a** (0.18 g, 0.31 mmol) was deethylated by Procedure A to give Compound **95** (0.12 g): HPLC: 4.16 min; MS (ES) m/z 527 (MH^+).



EXAMPLE 40

5 [(3-[[1-(Naphthalene-2-carbonyl)-piperidine-4-carbonyl]-amino]-naphthalen-2-ylcarbamoyl)-naphthalen-1-yl-methyl]-phosphonic acid, Cpd 141

Compound **40a** was synthesized by the method described in *JACS* **1993**, *115*(4), 1321-1329.

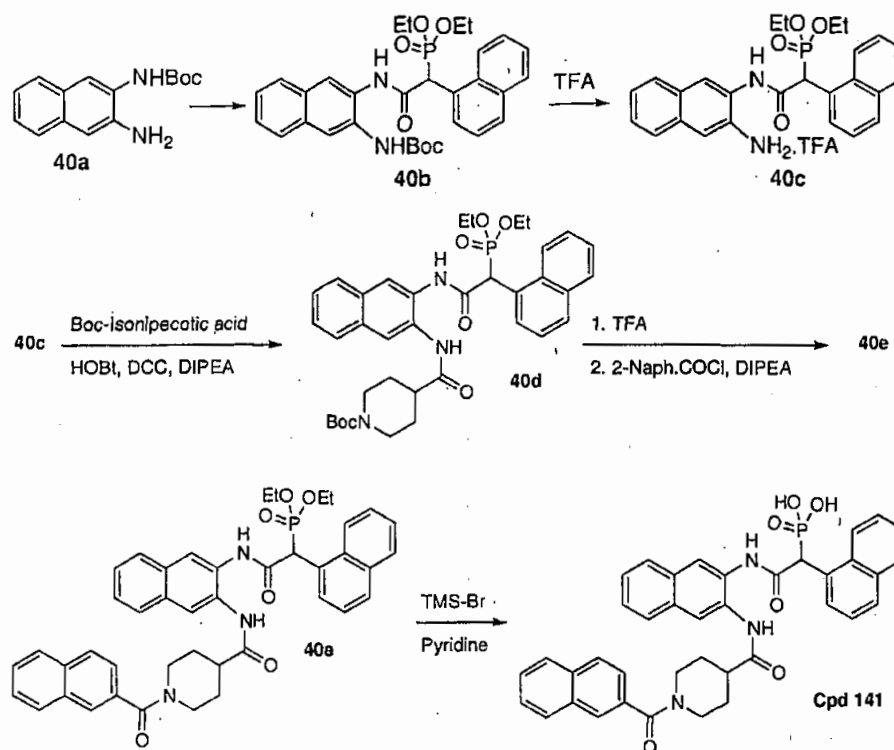
Using the procedure described in Example 17, substituting Compound **40a** (0.80 g, 3.11 mmol) for Compound **17c**, Compound **40b** (0.53 g) was prepared: HPLC: 4.20 min.

Compound **40b** (0.28 g, 0.50 mmol) was dissolved in TFA (1 mL) and allowed to stand for 30 min. The solution was concentrated under reduced pressure at rt to yield 0.47 g of Compound **40c** as a 4.2 TFA solvate: HPLC: 3.40 min; MS (ES) m/z 463 (MH^+).

To a solution of Compound **40c** (0.47 g), diisopropylamine (0.37 mL, 2.1 mmol), HOBT (0.068 g, 0.50 mmol), and Boc-isonipecotic acid (0.115 g, 0.50 mmol) in CH_2Cl_2 (5 mL) was added DCC (0.103 g, 0.50 mmol). After stirring for 72 h, the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was washed sequentially with 1N $KHSO_4$, saturated $NaHCO_3$ (aq), and brine, then dried (Na_2SO_4), filtered and concentrated under reduced pressure at rt. The residue was crystallized from CH_3CN to yield 0.14 g of Compound **40d** as a white solid: HPLC: 4.08 min; MS (ES) m/z 674 (MH^+).

Compound **40d** (0.14 g, 0.21 mmol) was stirred with TFA (1 mL) for 45 min, then concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) containing DIPEA (0.21 mL, 1.2 mmol). To the mixture was added 2-naphthoyl chloride (0.04 g, 0.21 mmol) and the reaction stirred for 20 min. The mixture was washed sequentially with 1N $KHSO_4$ (aq), saturated $NaHCO_3$ (aq), and brine, then dried (Na_2SO_4), filtered and concentrated under reduced pressure at rt to yield 0.15 g of Compound **40e** as a white solid: HPLC: 4.01 min.

Compound **40e** was deethylated by Procedure A to yield Compound **141**: HPLC: 3.75 min; MS (ES) m/z 672 (MH^+).



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 40, the following compounds were prepared without further purification:

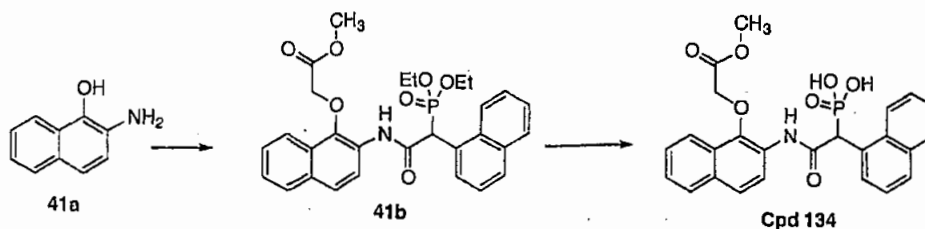
Cpd	MS (MH ⁺)
132	407

EXAMPLE 41

[2-(2-Naphthalen-1-yl-2-phosphonoacetyl)-naphthalen-1-yloxy]-acetic acid methyl ester, Cpd 134

Using the procedure described in Example 38 for the conversion of Compound 38a to 38c, substituting methyl bromoacetate for benzyl bromide, Compound 41a was reacted to give Compound 41b.

Compound 41b was deethylated by Procedure A to yield Compound 134: HPLC: 4.23 min; MS (ES) m/z 498 (MH⁺).

**EXAMPLE 42**

(Naphthalen-1-yl-{1-[2-oxo-2-(4-phenyl-piperidin-1-yl)-ethoxy]-naphthalen-2-ylcarbamoyl}-methyl)-phosphonic acid, Cpd 114

5

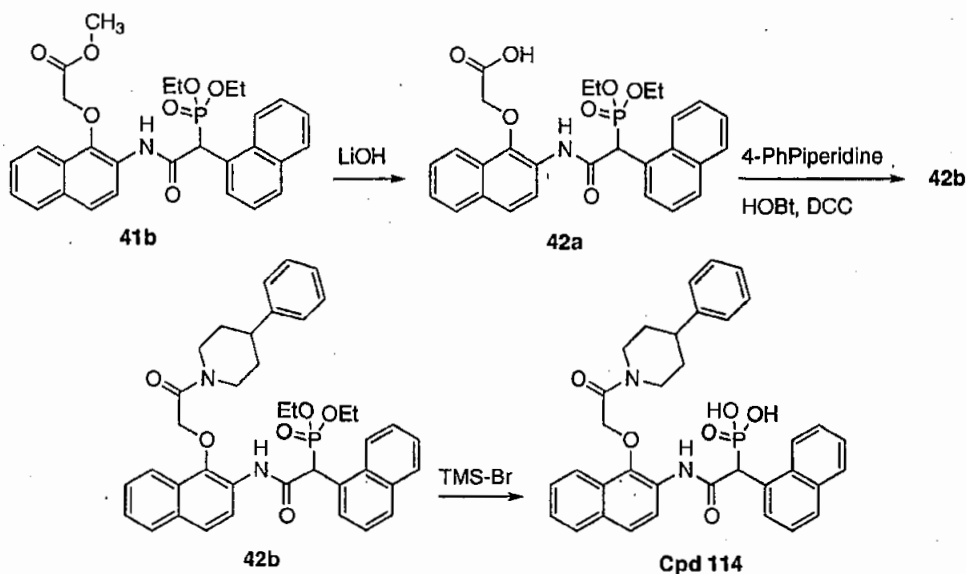
Using the procedure of Example 32 for the saponification of Compound **32a** to **32b**, Compound **41b** (1.01 g, 1.89 mmol) was converted to Compound **42a** (1.12 g): HPLC: 3.78 min; MS (ES) m/z 522 (MH^+).

10

Using the procedure described in Example 24, substituting Compound **42a** (0.25 g, 0.48 mmol) for Compound **24e**, Compound **42b** (0.27 g) was prepared: HPLC: 4.54 min, 97%; MS (ES) m/z 665 (MH^+).

Compound **42b** (0.15 g, 0.23 mmol) was deethylated by Procedure A to give of Compound **114** (0.096 g): HPLC: 4.19 min; MS (ES) m/z 609 (MH^+).

15



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 40, the following compounds were prepared without further purification:

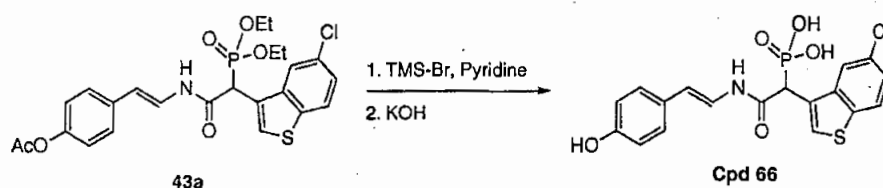
20

Cpd	MS (MH^+)
130	583

EXAMPLE 43

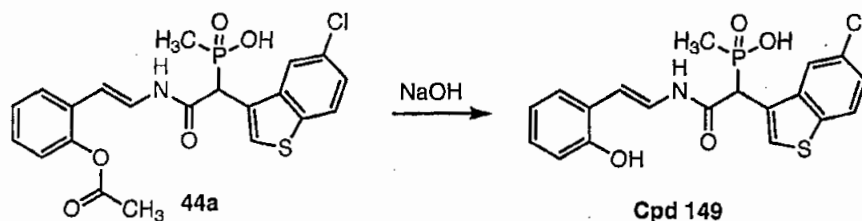
[[[5-Chloro-benzo[*b*]thiophen-3-yl]-[2-(4-hydroxy-phenyl)-vinylcarbamoyl]-methyl]-methyl-phosphonic acid, Cpd 66

- 5 Compound 43a (0.100 g, 0.192 mmol), prepared as in Example 11, was deethylated by Procedure A and the crude product was dissolved in 5 mL of methanol and treated with 0.210 g of KOH. The mixture was stirred for 7.5 h, then acidified with 1N HCl (aq), concentrated under reduced pressure at rt and purified by reverse phase HPLC (12-90% MeCN/H₂O) to yield 0.014 g of Compound 66 as a grey powder: HPLC: 3.04 min;
10 77%; MS (ES) *m/z* 422 (MH⁺).

**EXAMPLE 44**

- 15 {[5-Chloro-benzo[*b*]thiophen-3-yl]-[2-(2-hydroxy-phenyl)-vinylcarbamoyl]-methyl]-methyl-phosphonic acid, Cpd 149

A solution of Compound 44a (0.29 g, 0.63 mmol; prepared according to Example 6) in 15 mL of methanol containing 5 mL of 1N NaOH (aq) was stirred for 25 min. The
20 solution was concentrated under reduced pressure, and the residue was suspended in 1N HCl (aq) and stirred for 1 h. The solid was collected, rinsed sequentially with 1N HCl and water, then dried under a stream of N₂ to yield 0.23 g of Compound 149 as a pale yellow powder: HPLC: 3.71 min; MS (ES) *m/z* 422 (MH⁺).



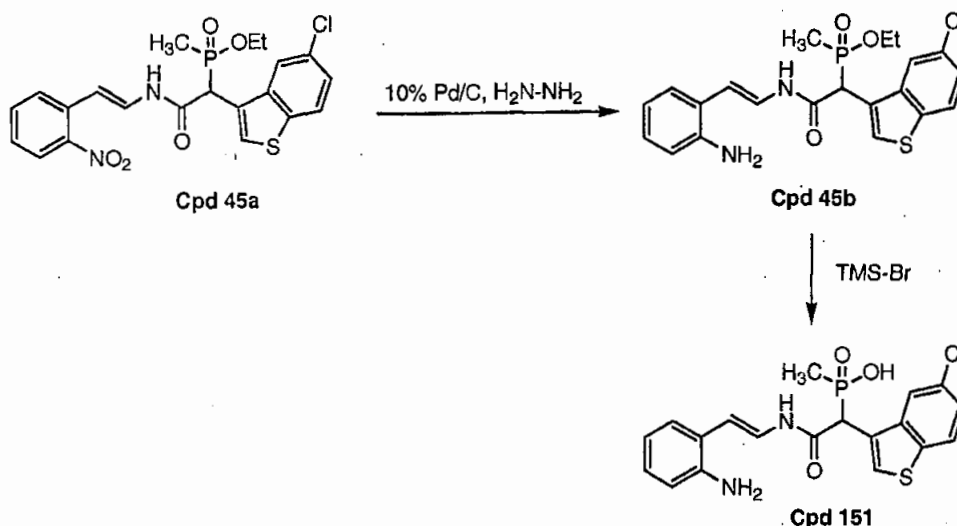
25

EXAMPLE 45

[[2-(2-Amino-phenyl)-vinylcarbamoyl]-(5-chloro-benzo[*b*]thiophen-3-yl)-methyl]-methyl-phosphonic acid, Cpd 151

Compound **45a** (prepared according to Example 6) was converted to compound **45b** by the method of Example 10. Compound **45b** was deethylated according to Procedure A and purified by trituration with 1N HCl (aq) to yield Compound **151**: HPLC: 2.78 min; MS (ES) m/z 421 (MH^+).

5



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 45, the following compounds were prepared without further purification:

10

Cpd	MS (MH^+)
172	421.

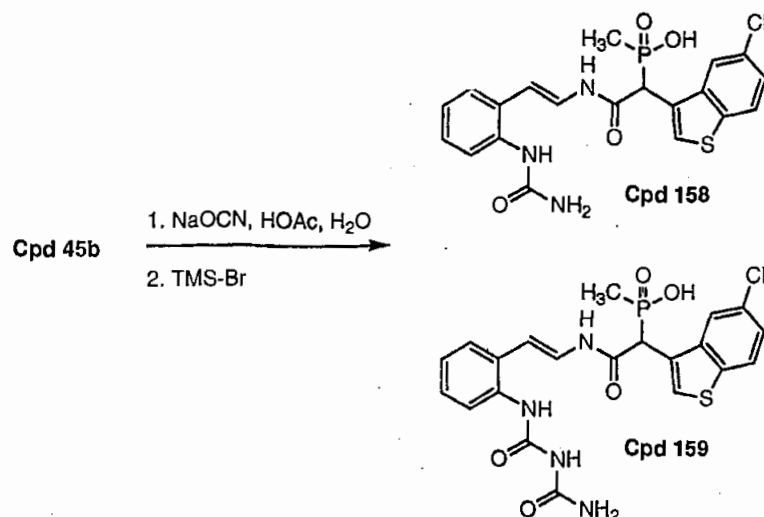
EXAMPLE 46

{(5-Chloro-benzo[b]thiophen-3-yl)-[2-(2-ureido-phenyl)-vinylcarbonyl]-methyl}-methyl-phosphinic acid, Cpd 158

15

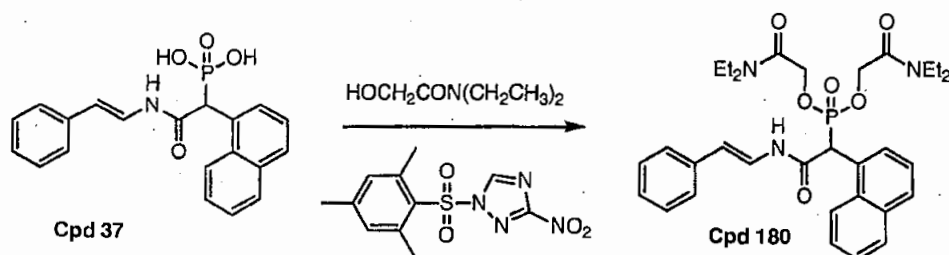
To a suspension of Compound **45b** (0.14 g, 0.31 mmol), acetic acid (0.4 mL) and water (1.6 mL) was added a five-fold excess of sodium cyanate. The reaction was stirred at 60°C for 1 h, and the crude product was collected, washed with water, dried under a stream of N_2 and deethylated by Procedure A. The product was subjected to reverse phase HPLC (25-90% MeCN/ H_2O) to yield 0.026 g of Compound **158** as a white powder: HPLC: 3.22 min; MS (ES) m/z 464 (MH^+), and 0.037 g of Compound **159** as a white powder: HPLC: 3.46 min; MS (ES) m/z 507 (MH^+).

20

**EXAMPLE 47**

(Naphthalen-1-yl-styrylcarbamoyl-methyl)-phosphonic acid di-diethylcarbamoylmethyl ester,
Cpd 180

To a solution of Compound **37** (0.21 g, 0.53 mmol) and *N,N*-diethyl-2-hydroxyacetamide (0.15 g, 1.17 mmol) in pyridine (5 mL) was added 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT; 0.47 g, 1.59 mmol) and the mixture was stirred at rt for 3.5 h. The reaction was concentrated under reduced pressure, and the residue taken up in EtOAc. The solution was washed sequentially with 1N KHSO₄ (aq); saturated NaHCO₃ (aq), and brine, then dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica, 0 – 30% acetone/heptane) to yield 0.07 g of Compound **180** as a yellow solid: HPLC: 3.88 min; MS (ES) *m/z* 594 (MH⁺).



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 47, the following compounds were prepared:

Cpd	MS (MH ⁺)
179	510
181	656

EXAMPLE 48

2-Naphthalen-1-yl-2-(2-oxo-2λ5-[1,3,2]dioxaphosphinan-2-yl)-
N-styryl-acetamide, Cpd 178

5

Using the procedure described in Example 47, Compound **37** (0.10 g, 0.27 mmol), 1,3-propanediol (0.02 g, 0.27 mmol), and MSNT (0.48 g, 1.62 mmol) in pyridine (5 ml) afforded 0.01 g of Compound **178**, as a white powder: HPLC: 3.52 min; MS (ES) m/z 408 (MH⁺).

10

Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 48, the following compound was prepared:

Cpd	MS (MH ⁺)
173	436

EXAMPLE 49

15

{{(5-Chloro-benzo[b]thiophen-3-yl)-[2-(3,4-difluoro-phenyl)-vinylcarbamoyl]-methyl}-methyl-phosphinic acid diethylcarbamoylmethyl ester, Cpd 185

Using the procedure described in Example 47, Compound **17** (0.25 g, 0.57 mmol), *N,N*-diethyl-2-hydroxyacetamide (0.37 g, 2.86 mmol), and MSNT (0.25 g, 0.86 mmol) in pyridine (5 ml) yielded 0.14 g of Compound **185**, as a white powder (~3:1 mixture of diastereomers). HPLC: 4.03 min (24%), 4.11 min (76%); MS (ES) m/z 555 (MH⁺).

20

Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 49, the following compound was prepared:

25

Cpd	MS (MH ⁺)	Diastereomer ratio
183	513	1:1

EXAMPLE 50

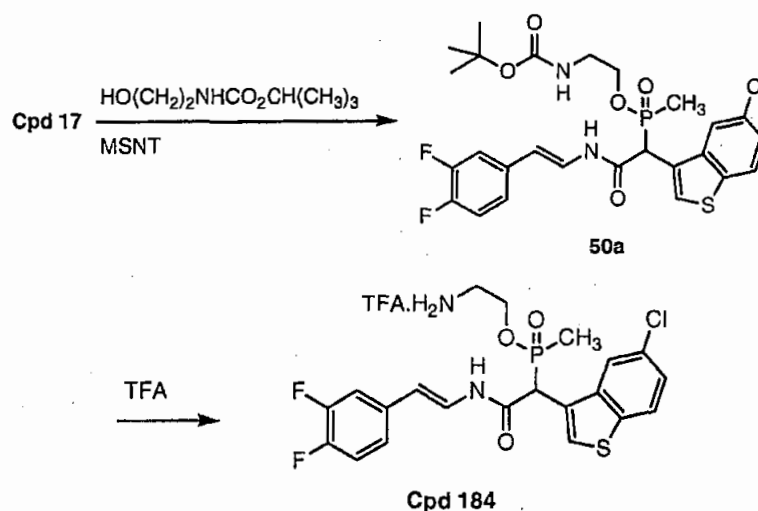
{{(5-Chloro-benzo[b]thiophen-3-yl)-[2-(3,4-difluoro-phenyl)-vinylcarbamoyl]-methyl}-methyl-phosphinic acid 2-amino-ethyl ester, Cpd 184

30

Using the procedure described in Example 47, Compound **17** (0.27 g, 0.61 mmol), *N*-Boc-ethanolamine (0.11 g, 0.67 mmol), and MSNT (0.54 g, 1.83 mmol) in pyridine (5 mL)

yielded 0.27 g of Compound **50a**, as a white powder: (~2:1 mixture of diastereomers).
HPLC: 4.17 min (22%), 4.20 min (46%); MS (ES) m/z 585 (MH^+).

A solution of Compound **50a** (0.27 g, 0.46 mmol) in 3 mL of TFA was stirred for 30 min, then concentrated under reduced pressure. The residue was purified by reverse
5 phase HPLC (30-90% MeCN/ H_2O) to afford 0.12 g of Compound **184** as a white powder (TFA salt; ~1:1 mixture of diastereomers by 1H NMR); HPLC: 3.17 min; MS (ES) m/z 485 (MH^+).



10

EXAMPLE 51

2,2-Dimethyl-propionic acid {(5-chloro-benzo[b]thiophen-3-yl)-[2-(3,4-difluoro-phenyl)-vinylcarbamoyl]-methyl}-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester,

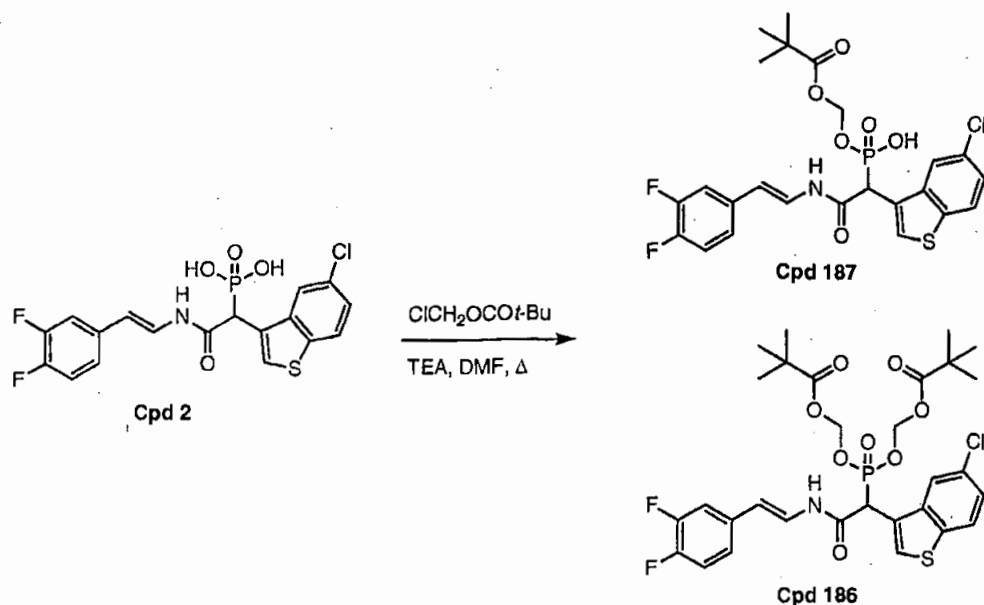
Compound **186**

15

and

2,2-Dimethyl-propionic acid {(5-chloro-benzo[b]thiophen-3-yl)-[2-(3,4-difluoro-phenyl)-vinylcarbamoyl]-methyl}-hydroxy-phosphinoyloxymethyl ester, Compound **187**

A solution of Compound **2** (0.25 g, 0.56 mmol), triethylamine (0.31 mL, 2.24 mmol),
20 and chloromethylpivaloate (0.32 mL, 2.24 g) in DMF (2 mL) was heated at 60°C for 2.5 h. The mixture was cooled to rt and concentrated under reduced pressure. The crude product mixture was subjected to reverse phase HPLC (37.5 – 90% MeCN/ H_2O) to yield 0.035 g of Compound **186** as a white powder; HPLC: 4.77 min; MS (ES) m/z 672 (MH^+), and 0.16 g of Compound **187** which was converted to its tromethamine salt by treatment of
25 a methanol solution of Compound **186** with 1 eq of tris-(hydroxymethyl) methylamine. The mixture was concentrated under reduced pressure to afford the tromethamine salt of Compound **187** as a white powder: HPLC: 5.13 min; MS (ES) m/z 558 (MH^+).



Other compounds of the present invention may be prepared by those skilled in the art by varying the starting materials, reagent(s) and conditions used. Using the procedure of Example 51, the following compounds were prepared:

Cpd	MS (MH ⁺)
188	670
190	514 (MH ⁺)
191	670

5

Using the procedure of Example 51, and substituting Compound **37** for Compound **2**, the following compounds were prepared:

Cpd	MS (MH ⁺)
174	438 (MH ⁺)
175	512
176	466 (MH ⁺)
177	482

10

Using the procedure of Example 51, and substituting Compound **17** for Compound **2**, the following compound was prepared:

Cpd	MS (MH ⁺)	Diastereomer ratio
182	556	3:2

The following compounds can be made by those skilled in the art by using Example 6 followed by Example 51, and varying the starting materials, reagent(s) and conditions used: compounds 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 316, 317, 318, 319, 320, 321, 322, and 323.

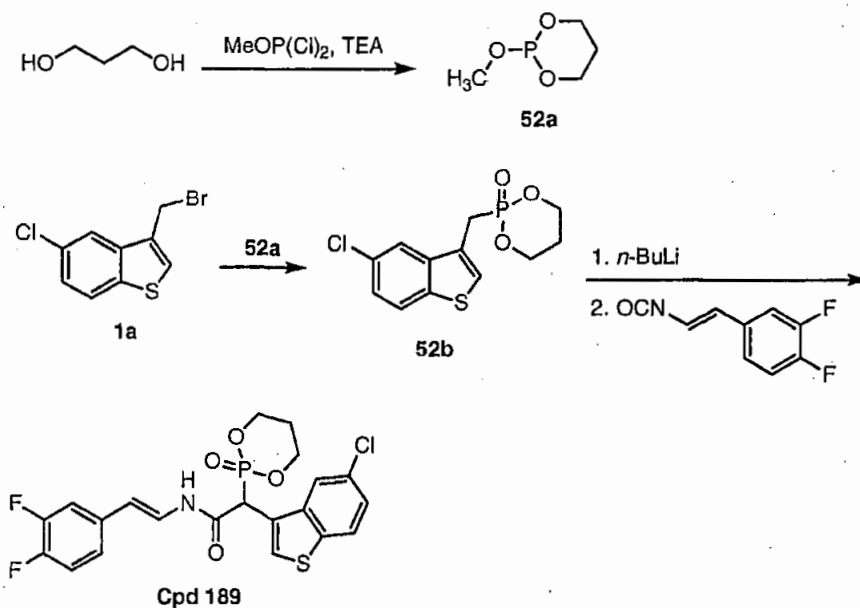
5 The following compounds can be made by those skilled in the art by using Example 11 followed by Example 51, and varying the starting materials, reagent(s) and conditions used: compounds 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 10 296, 297, 298, 299, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 348, 349, 350, 351, 352, 353, 354, and 355.

EXAMPLE 52

2-(5-Chloro-benzo[b]thiophen-3-yl)-N-[2-(3,4-difluoro-phenyl)-vinyl]-
15 2-(2-oxo-2 λ^5 -[1,3,2]dioxaphosphinan-2-yl)-acetamide, Cpd 189

A solution of Compound **1a** (1.75 g, 6.69 mmol) and Compound **52a** (prepared according to *JACS* **1969**, 91(24), 6838-6841; 1.36 g, 10.04 mmol) in toluene (15 mL) was refluxed for 24 h. After cooling to rt, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica; 0-30%
20 acetone/heptane) to afford 1.0 g of Compound **52b** as a viscous oil: HPLC: 3.03 min; MS (ES) m/z 303 (MH^+).

From Compound **52b** (0.51 g, 1.69 mmol) was prepared 0.28 g of Compound **189** by the procedure of Example 1: HPLC: 3.96 min; MS (ES) m/z 484 (MH^+).



The following compounds can be made by those skilled in the art by using Example 52 and varying the starting materials, reagent(s) and conditions used: compounds 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 340, 341, 342, 343, 344, 345, 346, and 347.

5

Biological Experimental Examples

The utility of the compounds of the present invention as a serine protease inhibitor and, particularly, as a chymase inhibitor useful for the treatment of inflammatory or serine
10 protease mediated disorders can be determined according to the procedures described herein.

Example 1

Enzyme-Catalyzed Hydrolysis Assays

Enzyme-catalyzed hydrolysis rates were measured spectro-photometrically using
15 human skin chymase (Cortex Biochem), a chromogenic substrate (Suc-Ala-Ala-Pro-Phe-pNa) (Bachem) in aqueous buffer (450 mM Tris, 1800 mM NaCl, pH 8.0), and a microplate reader (Molecular Devices). IC₅₀ experiments were conducted by fixing the enzyme and substrate concentrations (10 nM enzyme, 0.7 mM substrate) and varying the inhibitor concentration. Changes in absorbance at 405 nM were monitored using the software
20 program Softmax (Molecular Devices), upon addition of enzyme, with and without inhibitor present at 37°C for 30 minutes. Percent inhibition was calculated by comparing the initial reaction slopes of the samples without inhibitor to those with inhibitor. IC₅₀ values were determined using a four parameter fit logistics model. The term "NT" indicates a compound that was not tested.

25 Table VI summarizes the assay results for chymase inhibition for compounds of the present invention:

Table VI

Cpd	IC ₅₀ (μM) Chymase	N	Cpd	IC ₅₀ (μM) Chymase	N
1	0.010 ± 0	2	84	1.750 ± 0.285	2
2	0.011 ± 0	2	85	1.800 ± 1.200	2
3	0.013 ± 0.007	2	86	1.900 ± 0.400	2
4	0.016 ± 0.005	2	87	2.036	1

Cpd	IC ₅₀ (μM) Chymase	N	Cpd	IC ₅₀ (μM) Chymase	N
5	0.019 ± 0.005	2	88	2.040 ± 0.190	3
6	0.020 ± 0	2	89	2.100 ± 0.200	2
7	0.021 ± 0.004	2	90	2.153	1
8	0.021 ± 0.010	4	91	2.320	1
9	0.029 ± 0.009	2	92	2.400	1
10	0.029 ± 0.010	3	93	2.703	1
11	0.037 ± 0.010	2	94	2.755	1
12	0.038 ± 0.013	6	95	2.800	1
13	0.040 ± 0.020	3	96	2.800	1
14	0.050 ± 0.010	2	97	2.882 ± 0.899	2
15	0.052 ± 0.015	3	98	2.900	1
16	0.055 ± 0.005	2	99	2.963 ± 1.180	2
17	0.058 ± 0.012	7	100	3.001 ± 1.431	3
18	0.060 ± 0.020	3	101	3.115	1
19	0.066 ± 0.010	6	102	3.450	1
20	0.080 ± 0.004	2	103	3.627	1
21	0.080 ± 0.020	2	104	3.879 ± 2.414	3
22	0.090 ± 0.028	4	105	4.100	1
23	0.100 ± 0.030	3	106	4.300	1
24	0.100 ± 0.033	3	107	4.300 ± 0.030	2
25	0.109 ± 0.030	3	108	4.338	1
26	0.120 ± 0.030	4	109	4.400	1
27	0.130 ± 0.020	2	110	4.451	1
28	0.160 ± 0.004	2	111	4.617	1
29	0.166 ± 0.012	2	112	4.735 ± 1.655	5
30	0.170 ± 0.010	2	113	4.803 ± 1.688	2
31	0.190	1	114	4.899 ± 1.339	2
32	0.210 ± 0.010	2	115	5.362	1
33	0.210 ± 0.690	2	116	5.400	1

Cpd	IC ₅₀ (μM) Chymase	N	Cpd	IC ₅₀ (μM) Chymase	N
34	0.220 ± 0.010	2	117	5.624 ± 1.074	2
35	0.235 ± 0.045	2	118	5.720 ± 0.013	2
36	0.240 ± 0.010	2	119	5.800	1
37	0.250 ± 0.120	7	120	5.860 ± 1.080	5
38	0.284 ± 0.108	2	121	5.900	1
39	0.310 ± 0.040	2	122	5.944 ± 1.688	2
40	0.320 ± 0.140	2	123	6.600	1
41	0.330 ± 0.020	2	124	6.700	1
42	0.340 ± 0.130	4	125	6.700	1
43	0.350 ± 0.070	2	126	7.000	1
44	0.350 ± 0.220	2	127	7.000 ± 1.100	2
45	0.371 ± 0.110	2	128	7.300	1
46	0.388 ± 0.116	2	129	7.400	1
47	0.410 ± 0.100	2	130	7.436 ± 3.734	2
48	0.421 ± 0.151	2	131	7.681	1
49	0.430 ± 0.090	2	132	7.900	1
50	0.430 ± 0.150	4	133	8.083 ± 3.153	4
51	0.460 ± 0.060	2	134	8.110 ± 4.753	2
52	0.480 ± 0.180	2	135	8.300	1
53	0.490 ± 0.160	2	136	8.630 ± 0.810	2
54	0.510 ± 0.124	3	137	8.665	1
55	0.520 ± 0.510	2	138	8.700	1
56	0.606 ± 0.130	2	139	8.800	1
57	0.609	1	140	9.200 ± 0.730	6
58	0.630 ± 0.130	4	141	9.500	1
59	0.635	1	142	9.538 ± 4.204	2
60	0.663	1	143	9.800	1
61	0.710	1	144	1.26 ± 0.29	2
62	0.820 ± 0.500	3	145	0.035 ± 0.02	2

Cpd	IC ₅₀ (μM) Chymase	N	Cpd	IC ₅₀ (μM) Chymase	N
63	0.830 ± 0.180	4	146	0.11 ± 0	2
64	0.830 ± 0.080	2	147	1.44 ± 0.48	2
65	0.840 ± 0.190	3	148	0.23 ± 0.04	2
66	0.868 ± 0.130	6	149	0.043 ± 0	2
67	0.920 ± 0.250	4	150	0.091 ± 0.02	2
68	0.920 ± 0.530	2	151	0.40 ± 0.12	2
69	0.930 ± 0.0950	2	152	0.13 ± 0.03	2
70	0.930 ± 0.070	2	153	0.06 ± 0.01	2
71	1.000 ± 0.300	5	154	0.036 ± 0.05	2
72	1.300 ± 0.610	2	155	0.34 ± 0.04	2
73	1.352 ± 0.168	3	156	0.036 ± 0.01	2
74	1.390 ± 0.554	2	157	11.0 ± 1.2	2
75	1.400 ± 0.600	3	158	6.0 ± 1.9	2
76	1.430 ± 0.451	2	159	3.0 ± 0.19	2
77	1.480 ± 0.450	2	160	0.065 ± 0.02	2
78	1.500 ± 0.430	2	161	0.0035 ± 0	2
79	1.600	1	162	0.0090 ± 0	2
80	1.650 ± 0.680	2	163	0.017 ± 0	2
81	1.700 ± 0.210	6	164	0.10 ± 0.02	2
82	1.700 ± 0.410	2	165	0.078 ± 0.03	2
83	1.723	1	166	0.0387 ± 0.02	2
			167	0.017 ± 0.04	2
			168	0.0059 ± 0.01	2
			169	0.042 ± 0	2
			170	0.0031 ± 0	2
			171	0.025 ± 0.01	2
			172	0.041 ± 0.02	2
			199	0.0018 ± 0	2

Example 2

Anti-Asthmatic Effects in a Sheep Model of Asthma

5 The efficacy of Compound 17 for the treatment of asthma was evaluated in a validated model of *Ascaris suum* antigen-induced asthmatic response in conscious sheep (Abraham, W.M., Pharmacology of allergen-induced early and late airway responses and antigen-induced airway hyperresponsiveness in allergic sheep, *Pulmonary Pharmacology*, 1989, 2, 33-40).

10

Experimental Protocol

Baseline (BSL) dose response curves to aerosol carbachol were obtained from historical control responses prior to antigen challenge. Baseline values of specific lung resistance (SR_L) were obtained and the sheep were then given a specified amount (mg) of
15 the test compound as an inhaled aerosol or as a oral dose at a specified time before antigen challenge. Post-drug measurements of SR_L were obtained and the sheep were then challenged with *Ascaris suum* antigen. Measurements of SR_L were obtained immediately after challenge, hourly from 1-6 h after challenge and on the half-hour from 6½-8 h after challenge. Measurements of SR_L were obtained 24 h after challenge followed
20 by a 24 h post-challenge with carbachol to measure airway hyperreactivity.

Compound 17 was administered as an aerosol at 4.5 mg/dose (ca. 0.1 mg/Kg/dose, based on a 45 Kg sheep), twice-a-day (*BID*) for three consecutive days, followed by a dose on day 4, 0.5 h prior to antigen challenge. *Ascaris suum* antigen challenge was given at the zero time point.

25 Compound 17 was administered as an oral solution at 15 mg/Kg/dose, twice-a-day (*BID*) for three consecutive days, followed by a dose on day 4, 2 h prior to antigen challenge. *Ascaris suum* antigen challenge was given at the zero time point.

Figure 1 shows that after aerosol administration the early airway response (0-2 h after antigen challenge) was unchanged and that the late airway response (6-8 h after
30 antigen challenge) was completely blocked ($n = 2$ sheep/group).

Figure 2 shows that the delayed airway hyperreactivity measured at 24 h post antigen challenge as measured using carbachol challenge was also completely blocked by compound following aerosol administration.

Figure 3 shows that after oral administration the early airway response (0-2 h after
35 antigen challenge) was unchanged and that the late airway response (6-8 h after antigen challenge) was completely blocked ($n = 2$ sheep/group).

Figure 4 shows that the delayed airway hyperreactivity measured at 24 h post antigen challenge as measured using carbachol challenge was also completely blocked by compound following oral administration.

5

Example 3*Pharmacokinetic Assay for Evaluation of Oral Absorption Potential**Procedural Overview*

Male Sprague Dawley rats, weighing 250-300 g, were fasted overnight then dosed by oral gavage at a level of 15 mg/kg with a compound. Compounds were formulated in
10 20% hydroxy-beta-cyclo dextran.

Blood samples (0.5 mL) were collected into lithium heparinized tubes at 0.5, 1.0 and 2.0 h post dose via orbital sinus puncture. Blood samples were centrifuged at 2000 rpm for ~3 min for cell removal, approximately 200 μ L of plasma supernatant was then transferred to a clean vial, frozen then placed on dry ice and delivered to SFBC Analytical Labs, Inc. for
15 analysis.

Plasma samples were prepared as follows. Two hundred microliters of acetonitrile containing 1 μ M internal standard was added to 100 μ L of plasma to precipitate proteins. Samples were centrifuged at 5000 g for 5 min and supernatant removed for analysis by LC-MS. Two hundred microliters of water was added to adjust sample solvent strength
20 and prevent peak splitting. Calibration standards were prepared by adding appropriate volumes of stock solution directly into plasma and treated identically to collected plasma samples. Calibration standards were prepared in the range of 0.1 to 10 μ M for quantitation. LC-MS analysis was performed using MRM (Multiple Reaction Monitoring) detection of characteristic ions for each drug candidate and internal standard.

25

PK Data (N = 2)

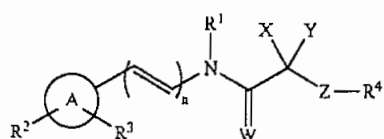
Cpd	C _{Max} (μ M) @ 2 h	Cpd	C _{Max} (μ M) @ 2 h
173	0.1 $\pm$ 0.02	183	0.1 $\pm$ 0.01
174	0.56 $\pm$ 0.36	184	0.1 $\pm$ 0.05
175	0.2 $\pm$ 0.03	185	2.1 $\pm$ 0.23
176	0.3 $\pm$ 0.04	186	20.1 $\pm$ 3.5
177	2.0 $\pm$ 1.1	187	21.4 $\pm$ 11
178	4.1 $\pm$ 0.28	188	0.1 $\pm$ 0.05
179	< 0.1 $\pm$ 0.0	189	21.1 $\pm$ 2.3
180	< 0.1 $\pm$ 0.0	190	2.3 $\pm$ 0.55

Cpd	C _{Max} (μM) @ 2 h	Cpd	C _{Max} (μM) @ 2 h
181	0.2 ± 0.05 (C _{max} at 30 min)	191	19 (N = 1)
182	11.8 ± 3.26		

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come
5 within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



Formula (I)

wherein,

R^1 is selected from the group consisting of hydrogen and C_{1-4} alkyl;



is selected from the group consisting of aryl, heteroaryl, benzo fused heterocyclyl, cyclopropyl when n is 0 and one of R^2 or R^3 is phenyl, and benzo fused cycloalkyl, and ring A is optionally substituted with R^2 and R^3 ;

R^2 is one to two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, methoxy, C_{2-6} alkoxy, C_{1-6} alkylthio, $—OCF_3$, $—NH_2$, $—NH(C_{1-6})$ alkyl, $—N(C_{1-6})$ dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, and nitro; furthermore, R^2 is optionally oxo when ring A is heteroaryl or benzo fused heterocyclyl; and, wherein any aryl-containing substituent of R^2 is optionally substituted with a substituent independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{1-6} alkylthio, $—NH_2$, $—NH(C_{1-6})$ alkyl, $—N(C_{1-6})$ dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, and nitro; and, wherein any of the foregoing C_{1-6} alkyl or C_{2-6} alkoxy containing substituents of R^2 are optionally substituted with a substituent independently selected from the group consisting of $—NR^{11}R^{12}$, aryl, heteroaryl, one to three halogens and hydroxy; wherein R^{11} and R^{12} are independently hydrogen; C_{1-6} alkyl optionally substituted with hydroxy, aryl, $—C(=O)C_{1-4}$ alkoxy, or $—NR^{15}R^{16}$; or aryl;

R^{15} and R^{16} are substituents independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and aryl, and said R^{15} and R^{16} are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

R^3 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkylthio, $—OCF_3$, $—$

OCH₂(C₂₋₆)alkenyl, —NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, —NHC(=O)Cy, —N(C₁₋₆alkyl)C(=O)Cy, —(NC(=O))₂NH₂, —C(=O)C₁₋₄alkoxy, —C(=O)NR¹⁷R¹⁸, —C(=O)NHcycloalkyl, —C(=O)N(C₁₋₆alkyl)cycloalkyl, —C(=O)NHCy, —C(=O)N(C₁₋₆alkyl)Cy, —C(=O)Cy, —OC(=O)C₁₋₆alkyl, —OC(=O)NR¹⁹R²⁰, —C(=O)Oaryl, —C(=O)Oheteroaryl, —CO₂H, ureido, halogen, hydroxy, nitro, cyano, aryl, heteroaryl, heteroaryloxy, and aryloxy; wherein any of the foregoing C₁₋₆alkyl or C₁₋₆alkoxy containing substituents of R³ are optionally substituted with one to three substituents independently selected from the group consisting of —NR²¹R²², —NH(cycloalkyl), —N(C₁₋₆alkyl)(cycloalkyl), —NHCy, —N(C₁₋₆alkyl)Cy, aryl, heteroaryl, hydroxy, halogen, —C(=O)NR²³R²⁴, —OC(=O)NR²⁵R²⁶, —C(=O)C₁₋₄alkoxy, and —C(=O)Cy;

wherein said R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶ are substituents independently selected from the group consisting of hydrogen, C₁₋₆alkyl, and aryl, wherein C₁₋₆alkyl is optionally substituted with hydroxy, aryl, —C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or —N(C₁₋₆)dialkyl; and R¹⁷ and R¹⁸, R¹⁹ and R²⁰, R²¹ and R²², R²³ and R²⁴, and R²⁵ and R²⁶ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

Cy is a heterocyclyl optionally substituted with a substituent selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, —C₁₋₆alkylC(=O)C₁₋₆alkoxy, C₁₋₆alkylC(—O)aryl, —C(—O)(C₁₋₆)alkyl, —C(=O)(C₁₋₆)alkoxy, —C(=O)aryl, —SO₂aryl, aryl, heteroaryl, and heterocyclyl; wherein the aryl portion of any aryl-containing substituent of Cy is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylthio, halogen, hydroxy, NH₂, NH(C₁₋₆alkyl), and —N(C₁₋₆)dialkyl; and wherein heterocyclyl is optionally substituted with aryl, one to three halogen atoms, or one to three oxo substituents; and heterocyclyl is optionally spiro-fused to said Cy;

and wherein the C₁₋₆alkenyl and C₁₋₆alkynyl substituents of R³ are optionally substituted with aryl or —C(=O)NR²⁷R²⁸; wherein said R²⁷ and R²⁸ are independently hydrogen; C₁₋₆alkyl optionally substituted with hydroxy, aryl, —C(—O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or —N(C₁₋₆)dialkyl; or aryl; and R²⁷ and

R²⁸ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

wherein the aryl, heteroaryl, and cycloalkyl substituents of R³ are optionally substituted with one to three substituents independently selected from R¹⁴; wherein R¹⁴ is independently hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₁₋₆alkylthio, —NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, or nitro;

and any one of the foregoing C₁₋₆alkyl- or C₁₋₆alkoxy-containing substituents of R¹⁴ is optionally substituted on a terminal carbon atom with a substituent selected from —NR²⁹R³⁰, aryl, heteroaryl, one to three halogen atoms, or hydroxy; wherein R²⁹ and R³⁰ are independently hydrogen; C₁₋₆alkyl optionally substituted with hydroxy, aryl, —C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or —N(C₁₋₆)dialkyl; or aryl; and R²⁹ and R³⁰ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

n is 0 or 1;

W is O or S;

X is hydrogen or C₁₋₃alkyl;

Y is independently selected from SO₃H and P(=O)OR⁵R⁶;

R⁵ is selected from the group consisting of hydrogen; C₁₋₆alkyl optionally substituted with NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, 1,3-dioxolan-2-yl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylcarbonylthio, (C₁₋₆)alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, one to three halogens, or hydroxy; and aryl optionally substituted with C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylthio, C₂₋₆alkenyl, —NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, or nitro; alternatively, when R⁶ is C₁₋₈alkoxy, R⁵ and R⁶ are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring; provided that R⁵ is other than C₁₋₆alkyl substituted with di(C₁₋₆)alkylamino-carbonyl when ring system A is 3,4-

difluoro-phenyl, n is 1, R⁶ is OH, and Z-R⁴ is 5-chloro-benzothiophen-3-yl; and provided that R⁵ is other than C₁₋₆alkyl substituted with C₁₋₆alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R⁶ is CH₃, and Z-R⁴ is 5-chloro-benzothiophen-3-yl;

R⁶ is selected from the group consisting of C₁₋₈alkyl, C₁₋₈alkoxy, C₂₋₈alkenyl, heteroaryl, aryl, and hydroxy; wherein C₁₋₈alkyl, C₁₋₈alkoxy, and C₂₋₈alkenyl are optionally substituted with a substituent selected from the group consisting of C₁₋₆alkoxy, aryl, heterocyclyl, heteroaryl, NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, C₁₋₆alkyl-carbonyloxy, C₁₋₆alkylcarbonylthio, C₁₋₆alkoxycarbonyloxy, (C₁₋₆)alkylamino-carbonyl, di(C₁₋₆)alkylaminocarbonyl, one to three halogen atoms, and hydroxy; and when R⁶ is C₁₋₈alkyl, said C₁₋₈alkyl is optionally substituted with one to four additional halogen atoms such that one to three halogen atoms are optionally chlorine and one to seven of the halogen atoms are optionally fluorine;

wherein the heteroaryl and aryl substituents of R⁶ are optionally substituted with a substituent independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₁₋₆alkylthio, —NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, and nitro;

Z is a seven to fifteen membered monocyclic or polycyclic ring system selected from the group consisting aryl, heteroaryl, benzo fused heterocyclyl, or benzo fused cycloalkyl;

R⁴ is one to three substituents selected from the group consisting of:

H, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆alkylthio, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkenyl, halogen, —C(=O)Cy, —C(=O)NR³¹R³², aryl, —CO₂H, oxo, and cyano; wherein C₁₋₆alkyl, C₁₋₆alkenyl and C₁₋₆alkoxy are optionally substituted with —NR³³R³⁴, aryl, heteroaryl, cycloalkyl, one to three halogen atoms, or hydroxy; and aryl and heteroaryl are each optionally substituted with a substituent independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₁₋₆alkylthio, —NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, one to three halogen atoms, hydroxy, and nitro;

wherein said R³¹, R³², R³³, and R³⁴ are substituents independently selected

from the group consisting of hydrogen, C₁₋₆ alkyl, and aryl, wherein alkyl is optionally substituted with hydroxy, aryl, —C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or —N(C₁₋₆)dialkyl; and R³¹ with R³², and R³³ with R³⁴ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein R¹ is hydrogen.

3. The compound of claim 1 wherein

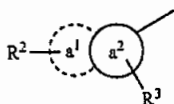


is independently selected from the group consisting of aryl, heteroaryl, and benzo fused heterocyclyl, optionally substituted with R² and R³.

4. The compound of claim 1 wherein



is a bicyclic ring system of the formula:



wherein the a¹ portion of said a¹a² is optionally substituted with R²; and the a² portion is optionally substituted with R³.

5. The compound of claim 4 wherein a² is aromatic.

6. The compound of claim 1 wherein



is selected from group consisting of naphthyl, benzothiazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, dihydronaphthyl, indanyl, tetralinyl, and benzodioxolyl when n is equal to zero; and A is selected from phenyl, pyridin-2-yl, and pyridin-3-yl when n is equal to one.

7. The compound of claim 1 wherein



is selected from naphthyl and benzothiazolyl when n is equal to zero; and A is selected from phenyl, pyridin-2-yl, and pyridin-3-yl when n is equal to one.

8. The compound of claim 1 wherein R^2 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, methoxy, C_{2-6} alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6})dialkyl$, aryl, heteroaryl, halogen, hydroxy, and nitro; wherein C_{1-6} alkyl and C_{2-6} alkoxy are optionally substituted with a substituent selected from the group consisting of $-NR^{11}R^{12}$, aryl, heteroaryl, one to three halogens, and hydroxy.

9. The compound of claim 1 wherein R^2 is a substituent independently selected from the group consisting of C_{1-4} alkyl, methoxy, C_{2-4} alkoxy, hydroxy, halogen, and $-NH_2$.

10. The compound of claim 1 wherein R^2 is C_{1-4} alkyl, halogen, or $-NH_2$.

11. The compound of claim 1 wherein R^3 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, $-OCH_2(C_{2-6}alkenyl)$, NH_2 , $-NH(C_{1-6}alkyl)$, $-N(C_{1-6})dialkyl$, $-NHC(=O)Cy$, $-N(C_{1-6}alkyl)C(=O)Cy$, $-C(=O)C_{1-4}alkoxy$, $-C(=O)NR^{17}R^{18}$, $-C(=O)NHcycloalkyl$, $-C(=O)N(C_{1-6}alkyl)cycloalkyl$, $-C(=O)NHCy$, $-C(=O)N(C_{1-6}alkyl)Cy$, $-C(=O)Cy$, $-OC(=O)NR^{19}R^{20}$, halogen, hydroxy, nitro, cyano, aryl, and aryloxy; wherein alkyl and alkoxy are optionally substituted with one to three substituents independently selected from the group consisting of $-NR^{21}R^{22}$, $-NHcycloalkyl$, $-N(C_{1-6}alkyl)cycloalkyl$, $-NHCy$, $-N(C_{1-6}alkyl)Cy$, aryl, heteroaryl, halogen, $-C(=O)NR^{23}R^{24}$, $-OC(=O)NR^{25}R^{26}$, $-C(=O)(C_{1-4}alkoxy)$, and $-C(=O)Cy$; wherein alkenyl is optionally substituted on a terminal carbon with aryl and $-C(=)NR^{27}R^{28}$; and, wherein aryl and cycloalkyl are optionally substituted with one to three substituents independently selected from R^{14} .

12. The compound of claim 1 wherein R^3 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{19}R^{20}$, $-NHC(=O)Cy$,

$\text{—C(=O)NR}^{17}\text{R}^{18}$, $\text{—C(=O)NHcycloalkyl}$, $\text{—C(=O)N(C}_{1-6}\text{alkyl)cycloalkyl}$, halogen, and aryl; wherein alkyl and alkoxy are optionally substituted on a terminal carbon atom with one to three fluorine atoms, —NH_2 , —NHCy , or $\text{—N(C}_{1-4}\text{alkyl)Cy}$; and wherein aryl and cycloalkyl are optionally substituted with a group independently selected from R^{14} .

13. The compound of claim 1 wherein R^3 is one to two substituents independently selected from trifluoromethyl; $\text{C}_{1-4}\text{alkoxy}$ optionally substituted with one to three fluorine atoms; —NH_2 ; —NHC(=O)Cy ; or halogen.

14. The compound of claim 1 wherein R^3 is NHC(—O)Cy , and Cy is piperadiny; wherein said piperadiny is substituted with a substituent selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkylC(=O)C}_{1-4}\text{alkyl}$, $\text{—C}_{1-4}\text{alkylC(=O)C}_{1-4}\text{alkoxy}$, $\text{C}_{1-4}\text{alkylC(=O)aryl}$, $\text{—C(=O)(C}_{1-4}\text{)alkyl}$, $\text{—C(=O)(C}_{1-4}\text{)alkoxy}$, —C(=O)aryl , $\text{—SO}_2\text{aryl}$, aryl, heteroaryl, and heterocyclyl; wherein aryl and the aryl portion of the $\text{C}_{1-4}\text{alkylC(=O)aryl}$, —C(=O)aryl and $\text{—SO}_2\text{aryl}$ is optionally substituted with one to three substituents independently selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkoxy}$, halogen, hydroxy, NH_2 , $\text{NH(C}_{1-6}\text{alkyl)}$, or $\text{—N(C}_{1-4}\text{dialkyl)}$; and wherein heterocyclyl is optionally substituted with aryl, one to three halogen atoms, or one oxo substituents.

15. The compound of claim 1 wherein R^3 is trifluoromethyl, one to two fluorine atoms, chloro, methoxy, trifluoromethoxy, or NH_2 ; furthermore, when A is naphthyl and n is equal to zero, R^3 is (4-{[1-(naphthalen-2-yl-carbonyl)-piperadin-4-yl-carbonyl]-amino}naphthalen-2-yl).

16. The compound of claim 1 wherein X is $\text{C}_{1-3}\text{alkyl}$.

17. The compound of claim 1 wherein X is hydrogen.

18. The compound of claim 1 wherein Y is $\text{P(=O)OR}^5\text{R}^6$.

19. The compound of claim 1 wherein R^5 is selected from the group consisting of

hydrogen; C₁₋₃alkyl optionally substituted with NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylcarbonylthio, (C₁₋₆)alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, one to three halogens, or hydroxy; and aryl optionally substituted with C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylthio, C₂₋₆ alkenyl, —NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, or nitro; alternatively, when R⁶ is C₁₋₈alkoxy, R⁵ and R⁶ are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring; and provided that R⁵ is other than C₁₋₃alkyl substituted with di(C₁₋₆)alkylaminocarbonyl when ring system A is 3,4-difluoro-phenyl, n is 1, R⁶ is OH, and Z-R⁴ is 5-chloro-benzothiophen-3-yl; and provided that R⁵ is other than C₁₋₃alkyl substituted with C₁₋₆alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R⁶ is CH₃, and Z-R⁴ is 5-chloro-benzothiophen-3-yl.

20. The compound of claim 1 wherein R⁵ is selected from the group consisting of hydrogen, C₁₋₃alkyl optionally substituted with C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylcarbonylthio, (C₁₋₆)alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, one to three halogens, or hydroxyl; and aryl; alternatively, when R⁶ is C₁₋₈alkoxy, R⁵ and R⁶ are taken together with the atoms to which they are attached to form a 6-7 membered monocyclic ring; and provided that when R⁵ is C₁₋₃alkyl substituted with either di(C₁₋₆)alkylaminocarbonyl or C₁₋₆alkylcarbonylthio, ring system A is other than 3,4-difluoro-phenyl when n is 1 and Z-R⁴ is 5-chloro-benzothiophen-3-yl.

21. The compound of claim 1 wherein R⁵ is hydrogen or C₁₋₃alkyl optionally substituted with C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylcarbonylthio, (C₁₋₆)alkylaminocarbonyl, or di(C₁₋₆)alkylaminocarbonyl; and alternatively, when R⁶ is C₁₋₈alkoxy, R⁵ and R⁶ are taken together with the atoms to which they are attached to form a 6-membered monocyclic ring; and provided that R⁵ is other than C₁₋₃alkyl substituted with di(C₁₋₆)alkylaminocarbonyl when ring system A is 3,4-difluoro-phenyl, n is 1, R⁶ is OH, and Z-R⁴ is 5-chloro-benzothiophen-3-yl; and provided that R⁵ is other than C₁₋₃alkyl substituted with C₁₋₆alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R⁶ is CH₃, and Z-R⁴ is 5-chloro-benzothiophen-3-yl.

22. The compound of claim 1 wherein R⁶ is selected from the group consisting of C₁₋₈alkyl, C₁₋₈alkoxy, C₂₋₈alkenyl, heteroaryl, aryl, and hydroxy; wherein alkyl, alkoxy, and alkenyl are optionally substituted on a terminal carbon atom with a substituent independently selected from the group consisting of C₁₋₄alkoxy, aryl, heteroaryl, heterocyclyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylthio, C₁₋₆alkoxycarbonyloxy, (C₁₋₆)alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, and hydroxy; and wherein heteroaryl and aryl are optionally substituted with one to three substituents independently selected from the group consisting of aryl, hydroxy, C₁₋₆alkoxy, and halogen.

23. The compound of claim 1 wherein R⁶ is selected from the group consisting of C₁₋₆alkyl, C₁₋₈alkoxy, heteroaryl, aryl, and hydroxy; wherein alkyl and is optionally substituted on a terminal carbon atom with a substituent selected from C₁₋₃alkoxy, aryl, or hydroxy; and alkoxy is optionally substituted on a terminal carbon with a substituent independently selected from the group consisting of C₁₋₆alkylcarbonyloxy, and di(C₁₋₆)alkylaminocarbonyl; and wherein heteroaryl and aryl are optionally substituted with one to three substituents independently selected from the group consisting of aryl, hydroxy, C₁₋₆alkoxy, and halogen.

24. The compound of claim 1 wherein R⁶ is selected from the group consisting of methyl, ethyl, methoxypropyl, phenethyl, benzo[1,3]dioxol-5-yl-propyl, hydroxy, and C₁₋₃alkoxy optionally substituted with C₁₋₆alkylcarbonyloxy, and di(C₁₋₆)alkylaminocarbonyl.

25. The compound of claim 1 wherein Z is a bicyclic aryl or bicyclic heteroaryl.

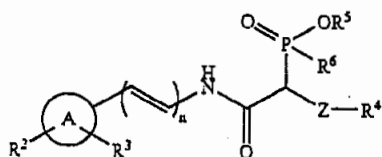
26. The compound of claim 1 wherein Z is independently selected from the group consisting of indolyl, benzothiophenyl, naphthalenyl, quinoliny, isoquinoliny and benzothiazolone.

27. The compound of claim 1 wherein Z is indolyl, benzothiophenyl, or naphthalenyl.

28. The compound of claim 1 wherein R^4 is one to three substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy, aryl(C_{2-6})alkenyl, halogen, $—C(=O)Cy$, $—C(=O)NR^{31}R^{32}$, aryl, $—CO_2H$, oxo, and cyano; wherein the alkyl and alkoxy are optionally substituted with a substituent independently selected from the group consisting of $—NR^{33}R^{34}$, aryl, one to three halogen atoms, and hydroxy; wherein the aryl is optionally substituted with a substituent independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, halogen, hydroxy, and nitro.

29. The compound of claim 1 wherein R^4 is one to two substituents selected from the group consisting of fluorine, chlorine, bromine, methyl, phenyl(C_{2-6})alkenyl, and $—C(—O)(2-(4\text{-phenyl-piperidin-1-carbonyl}))$.

30. A compound of Formula (Ia)



wherein n is 0 or 1;



is independently selected from the group consisting of aryl, heteroaryl, and benzo fused heterocyclyl, optionally substituted with R^2 and R^3 ;

R^2 is one to three substituents independently selected from the group consisting of C_{1-4} alkyl, methoxy, C_{2-6} alkoxy, NH_2 , $NH(C_{1-6}alkyl)$, $—N(C_{1-6})dialkyl$, aryl, heteroaryl, halogen, hydroxy, and nitro; wherein $C_{1-6}alkyl$ and $C_{2-6}alkoxy$ are optionally substituted with a substituent selected from the group consisting of $—NR^{11}R^{12}$, aryl, heteroaryl, one to three halogens and hydroxyl; wherein $C_{1-4}alkyl$ and $C_{2-6}alkoxy$ substituents of R^2 are optionally substituted with a substituent independently selected from the group consisting of $—NR^{11}R^{12}$, aryl, heteroaryl, one to three halogens and hydroxy; wherein R^{11} and R^{12} are substituents independently selected from the group consisting of hydrogen, $C_{1-6}alkyl$, and aryl;

wherein C₁₋₆alkyl substituent of R¹¹ or R¹² is optionally substituted with substituent selected from the group consisting of hydroxy, aryl, —C(=O)C₁₋₄alkoxy, and —NR¹⁵R¹⁶;

wherein said R¹⁵ and R¹⁶ are substituents independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and aryl, and said R¹⁵ and R¹⁶ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

R³ is one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, —OCH₂(C₂₋₆)alkenyl, NH₂, —NH(C₁₋₆alkyl), —N(C₁₋₆) dialkyl, —NHC(=O)Cy, —N(C₁₋₆alkyl)C(=O)Cy, —C(=O)C₁₋₄alkoxy, —C(=O)NR¹⁷R¹⁸, —C(=O)NHcycloalkyl, —C(=O)N(C₁₋₆alkyl)cycloalkyl, —C(=O)NHCy, —C(=O)N(C₁₋₆alkyl)Cy, —C(=O)Cy, —OC(=O)NR¹⁹R²⁰, halogen, hydroxy, nitro, cyano, aryl, and aryloxy; wherein alkyl and alkoxy are optionally substituted with one to three substituents independently selected from the group consisting of —NR²¹R²², —NHcycloalkyl, —N(C₁₋₆alkyl)cycloalkyl, —NHCy, —N(C₁₋₆alkyl)Cy, aryl, heteroaryl, halogen, —C(=O)NR²³R²⁴, —OC(=O)NR²⁵R²⁶, —C(=O)(C₁₋₄)alkoxy, and —C(=O)Cy; wherein alkenyl is optionally substituted on a terminal carbon with aryl and —C(=O)NR²⁷R²⁸; and, wherein aryl and cycloalkyl are optionally substituted with one to three substituents independently selected from R¹⁴;

Cy is a heterocyclyl optionally substituted with a substituent selected from the group consisting of C₁₋₆ alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, —C₁₋₆alkylC(=O)C₁₋₆alkoxy, C₁₋₆alkylC(=O)aryl, —C(=O)(C₁₋₆)alkyl, —C(=O)(C₁₋₆)alkoxy, —C(=O)aryl, —SO₂aryl, aryl, heteroaryl, and heterocyclyl; wherein aryl and the aryl portion of the C₁₋₆alkylC(=O)aryl, —C(=O)aryl and —SO₂aryl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, halogen, hydroxy, NH₂, NH(C₁₋₆alkyl), or —N(C₁₋₆)dialkyl; and wherein heterocyclyl is optionally substituted with aryl, one to three halogen atoms, or one to three oxo substituents; and, wherein heterocyclyl is optionally spiro-fused to said Cy;

R⁵ is selected from the group consisting of hydrogen; C₁₋₃alkyl optionally substituted with NH₂, —NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylcarbonylthio, (C₁₋₆)alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, one to three halogens, or hydroxy; and aryl optionally substituted with C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylthio, C₂₋₆ alkenyl, —NH₂, —

NH(C₁₋₆)alkyl, —N(C₁₋₆)dialkyl, aryl, heteroaryl, aryloxy, heteroaryloxy, halogen, hydroxy, or nitro; alternatively, when R⁶ C₁₋₈alkoxy are C₁₋₈alkoxy, R⁵ and R⁶ are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring; and provided that R⁵ is other than C₁₋₃alkyl substituted with di(C₁₋₆)alkylamino-carbonyl when ring system A is 3,4-difluorophenyl, n is 1, R⁶ is OH, and Z-R⁴ is 5-chloro-benzothiophen-3-yl; and provided that R⁵ is other than C₁₋₃alkyl substituted with C₁₋₆alkylcarbonylthio when ring system A is 3,4-difluorophenyl, n is 1, R⁶ is CH₃, and Z-R⁴ is 5-chlorobenzothiophen-3-yl;

R⁶ is selected from the group consisting of C₁₋₆alkyl, C₁₋₈alkoxy, heteroaryl, aryl, and hydroxy; wherein alkyl and C₁₋₈alkoxy are optionally substituted on a terminal carbon atom with a substituent selected from C₁₋₃alkoxy, aryl, or hydroxy; and alkoxy is optionally substituted on a terminal carbon with a substituent independently selected from the group consisting of C₁₋₆alkylcarbonyloxy, and di(C₁₋₆)alkylaminocarbonyl; and wherein heteroaryl and aryl are optionally substituted with one to three substituents independently selected from the group consisting of aryl, hydroxy, C₁₋₆alkoxy, and halogen;

Z is a bicyclic aryl or bicyclic heteroaryl;

R⁴ is one to three substituents selected from the group consisting of H, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkoxy, aryl(C₂₋₆)alkenyl, halogen, —C(=O)Cy, —C(=O)NR³¹R³², aryl, —CO₂H, oxo, and cyano; wherein the alkyl and alkoxy are optionally substituted with a substituent independently selected from the group consisting of —NR³³R³⁴, aryl, one to three halogen atoms, and hydroxy; wherein the aryl is optionally substituted with a substituent independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, aryl, halogen, hydroxy, and nitro;

wherein said R³¹, R³², R³³, and R³⁴ are substituents independently selected from the group consisting of hydrogen, C₁₋₆alkyl, and aryl, wherein alkyl is optionally substituted with hydroxy, aryl, —C(=O)C₁₋₄alkoxy, NH₂, NH(C₁₋₆alkyl), or —N(C₁₋₆)dialkyl; and R³¹ with R³², and R³³ with R³⁴ are optionally taken together with the atoms to which they are attached to form a ring of five to seven members;

and pharmaceutically acceptable salts thereof.

31. The compound of claim 30 wherein



is selected from group consisting of naphthyl, benzothiazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, dihydronaphthyl, indanyl, tetralinyl and benzodioxolyl when n is equal to zero; and A is selected from phenyl, pyridin-2-yl, or pyridin-3-yl when n is equal to one.

32. The compound of claim 30 wherein



is selected from phenyl, pyridin-2-yl, or pyridin-3-yl when n is equal to one.

33. The compound of claim 32 wherein R^2 is a substituent independently selected from the group consisting of C_{1-4} alkyl, methoxy, C_{2-4} alkoxy, hydroxy, halogen, and $-NH_2$.

34. The compound of claim 33 wherein R^3 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{19}R^{20}$, $-NHC(=O)Cy$, $-C(=O)NR^{17}R^{18}$, $-C(=O)NHcycloalkyl$, $-C(=O)N(C_{1-6}alkyl)cycloalkyl$, halogen, and aryl; wherein alkyl and alkoxy are optionally substituted on a terminal carbon atom with one to three fluorine atoms, $-NH_2$, $-NHCy$, or $-N(C_{1-4}alkyl)Cy$; and wherein aryl and cycloalkyl are optionally substituted with a group independently selected from R^{14} .

35. The compound of claim 34 wherein R^5 is hydrogen or C_{1-3} alkyl optionally substituted with C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyloxy, C_{1-6} alkylcarbonylthio, (C_{1-6}) alkylaminocarbonyl, or $di(C_{1-6})$ alkylaminocarbonyl; and alternatively, when R^6 is C_{1-8} alkoxy, R^5 and R^6 are taken together with the atoms to which they are attached to form a 6-membered monocyclic ring; and provided that R^5 is other than C_{1-3} alkyl substituted with $di(C_{1-6})$ alkylamino-carbonyl when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is OH, and $Z-R^4$ is 5-chloro-benzothiophen-3-yl; and provided that R^5 is other than C_{1-3} alkyl substituted with C_{1-6} alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is CH_3 , and $Z-R^4$ is 5-chloro-benzothiophen-3-yl.

36. The compound of claim 35 wherein R^6 is selected from the group consisting of methyl, ethyl, methoxypropyl, phenethyl, benzo[1,3]dioxol-5-yl-propyl, hydroxy, and C_{1-3} alkoxy optionally substituted with C_{1-6} alkylcarbonyloxy, and di(C_{1-6})alkylamino-carbonyl.

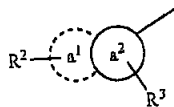
37. The compound of claim 36 wherein Z is independently selected from the group consisting of indolyl, benzothiophenyl, naphthalenyl, quinoliny, isoquinoliny and benzothiazolonyl.

38. The compound of claim 37 wherein R^4 is one to three substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkenyl, aryl(C_{2-6})alkenyl, halogen, and $—C(=O)Cy$; wherein aryl is optionally substituted with a substituent selected from halogen or C_{1-4} alkoxy.

39. The compound of claim 30 wherein

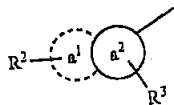


is a ring system of the formula:



wherein the a^1 portion of said a^1a^2 is optionally substituted with R^2 ; and the a^2 portion is optionally substituted with R^3 and n is 0.

40. The compound of claim 39 wherein a^2 portion is aromatic and



is selected from group consisting of naphthyl, benzothiazolyl, benzothiophenyl, quinoliny, isoquinoliny, dihydronaphthyl, indanyl, tetraliny and benzodioxolyl.

41. The compound of claim 40 wherein R^2 is a substituent independently selected from the group consisting of C_{1-4} alkyl, methoxy, C_{2-4} alkoxy, hydroxy, halogen, and $—NH_2$.

42. The compound of claim 41 wherein R^3 is one to three substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{19}R^{20}$, $-NHC(=O)Cy$, $-C(=O)NR^{17}R^{18}$, $-C(=O)NHcycloalkyl$, $-C(=O)N(C_{1-6}alkyl)cycloalkyl$, halogen, and aryl; wherein alkyl and alkoxy are optionally substituted on a terminal carbon atom with one to three fluorine atoms, $-NH_2$, $-NHCy$, or $-N(C_{1-4}alkyl)Cy$; and wherein aryl and cycloalkyl are optionally substituted with a group independently selected from R^{14} .

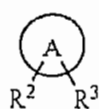
43. The compound of claim 42 wherein R^5 is hydrogen or C_{1-3} alkyl optionally substituted with C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyloxy, C_{1-6} alkylcarbonylthio, (C_{1-6}) alkylaminocarbonyl, or $di(C_{1-6}alkylaminocarbonyl)$; and alternatively, when R^6 is C_{1-8} alkoxy, R^5 and R^6 are taken together with the atoms to which they are attached to form a 6-membered monocyclic ring; provided that R^5 is other than C_{1-3} alkyl substituted with $di(C_{1-6}alkylaminocarbonyl)$ when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is OH, and $Z-R^4$ is 5-chloro-benzothiophen-3-yl; and provided that R^5 is other than C_{1-3} alkyl substituted with C_{1-6} alkylcarbonylthio when ring system A is 3,4-difluoro-phenyl, n is 1, R^6 is CH_3 , and $Z-R^4$ is 5-chloro-benzothiophen-3-yl.

44. The compound of claim 43 wherein R^6 is selected from the group consisting of methyl, ethyl, methoxypropyl, phenethyl, benzo[1,3]dioxol-5-yl-propyl, hydroxy, and C_{1-3} alkoxy optionally substituted with C_{1-6} alkylcarbonyloxy, and $di(C_{1-6}alkylamino-carbonyl)$.

45. The compound of claim 44 wherein Z is independently selected from the group consisting of indolyl, benzothiophenyl, naphthalenyl, quinoliny, isoquinoliny, and benzothiazolone.

46. The compound of claim 45 wherein R^4 is one to three substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkenyl, aryl(C_{2-6})alkenyl, halogen, and $-C(=O)Cy$; wherein aryl is optionally substituted with a substituent selected from halogen or C_{1-4} alkoxy.

47. The compound of claim 30 wherein R^1 , ring A, R^2R^3 , R^5 , R^6 , Z, and R^4 are dependently selected from the group consisting of



	R ⁵	R ⁶	n	W	Z—R ⁴
naphthalen-2-yl	H	CH ₃	0	O	5-Cl—N-methyl-indol-3-yl
3,4-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	5-Cl—N-methyl-indol-3-yl
4-fluoro-phenyl	H	OH	1	O	5-Cl—N-methyl-indol-3-yl
naphthalen-2-yl	H	OH	0	O	5-Me-benzothiophen-2-yl
3-fluoro-phenyl	H	CH ₃	1	O	5-Cl—N-methyl-indol-3-yl
3,4-difluoro-phenyl	H	CH ₃	1	O	5-Cl—N-methyl-indol-3-yl
4-[[1-(naphthalen-2-ylcarbonyl)-piperidin-4-ylcarbonyl]-amino]naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	OH	0	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	5-F-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	5-F—N-methyl-indol-3-yl
4-amino-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	5-Br—N-methyl-indol-3-yl
Phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,4-trifluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
phenyl	H	OH	1	O	5-Cl-benzothiophen-2-yl
4-fluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	CH ₃	0	O	5-Cl-benzothiophen-3-yl
2-fluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	N-methyl-indol-3-yl
naphthalen-2-yl	H	OH	0	O	5-Br-benzothiophen-3-yl
4-fluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
pyridin-3-yl	H	OH	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	N-(3-phenyl-allyl)-indol-3-yl
naphthalen-2-yl	H	CH ₂ CH ₃	0	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	H	CH ₂ CH ₃	1	O	5-Cl-benzothiophen-3-yl
benzothiazol-6-yl	H	OH	0	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	CH ₃	0	O	2-(4-phenyl-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
naphthalen-2-yl	H	CH ₃	0	O	naphthalen-1-yl
naphthalen-2-yl	H	3-methoxy-propyl	0	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	CH ₃	0	O	2-(4-(4-methoxyphenyl)-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
naphthalen-2-yl	H	Phenethyl	0	O	5-Cl-benzothiophen-3-yl
phenyl	H	OH	1	O	naphthalen-1-yl
4-methoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	3-(Benzo[1,3]dioxol-5-yl)-propyl	0	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl	H	3-(naphthyl-en-1-yl)propyl	0	O	5-Cl-benzothiophen-3-yl



R ¹	R ²	R ³	R ⁵	R ⁶	n	W	Z—R ⁴
naphthalen-2-yl			H	CH ₃	0	O	2-(4-Benzoyloxycarbonyl)-piperazin-1-ylcarbonyl)-benzothiophen-3-yl
4-methyl-phenyl			H	OH	1	O	5-Cl-benzothiophen-2-yl
naphthalen-2-yl			H	3-(4-hydroxyphenyl)propyl	0	O	5-Cl-benzothiophen-3-yl
3-((N-Benzoyl-piperidin-4-ylamino)-methyl)-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	S	5-Cl-benzothiophen-3-yl
3-[(1-phenyl)-cyclohex-1-enyl-N-methylaminocarbonyl]-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	CH ₃	0	O	2-((4-F-phenyl)-piperidin-1-ylcarbonyl)-benzothiophen-3-yl
naphthalen-2-yl			H	(3-phenyl)propyl	0	O	5-Cl-benzothiophen-3-yl
3,4-dimethoxy-phenyl			H	OH	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl			H	(4-phenyl)butyl	0	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl			H	OH	0	O	6-Cl-N-methyl-indol-3-yl
naphthalen-2-yl			H	3-(4-methoxyphenyl)propyl	0	O	5-Cl-benzothiophen-3-yl
3-[4-((3-Phenethyl)-pyrrolidin-1-ylcarbonyl)]-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
benzothiophen-5-yl			H	OH	0	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl			H	OH	0	O	5-carboxy-N-Me-indol-3-yl
quinolin-3-yl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	O	7-Cl-N-methyl-indol-3-yl
benzo[b]thiophen-6-yl			H	OH	0	O	naphthalen-1-yl
3-[4-(6-Chloro-2-oxo-2,3-dihydro-benzimidazol-1-yl)-piperidin-1-ylcarbonyl]-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
4-biphenyl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	O	N-cyclopropylmethyl-indol-3-yl
naphthalen-2-yl			H	OH	0	O	4-Cl-N-methyl-indol-3-yl
benzothiophen-2-yl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	O	5-cyano-N-methyl-indol-3-yl
4-hydroxy-phenyl			H	OH	1	O	5-Cl-benzothiophen-3-yl
(6-Br)-naphthalen-2-yl			H	OH	0	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl			H	OH	0	O	Indol-3-yl
2-Amino-benzothiazol-6-yl			H	OH	0	O	5-Cl-benzothiophen-3-yl
3-(Cyclohexylamino)methyl-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	O	5-Ph-benzothiophen-3-yl
3-(N-benzylaminocarbonyloxy-methyl)-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
3-(pyridin-4-yl-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	O	5-methoxy-N-methyl-indol-3-yl
3-(methoxycarbonyl)-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	O	6-Br-benzothiophen-3-yl
naphthalen-2-yl			H	OH	0	O	N-isopropyl-indol-3-yl
4-chloro-phenyl			H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
quinolin-6-yl			H	OH	0	O	naphthalen-1-yl
4-trifluoromethyl-phenyl			H	OH	1	O	5-Cl-benzothiophen-3-yl
naphthalen-2-yl			H	OH	0	O	N-phenyl-indol-3-yl
(4-(1H-indol-3-yl)-piperidin-1-ylcarbonyl)-naphthalen-2-yl			H	OH	0	O	naphthalen-1-yl
Indanyl			H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl			H	OH	0	O	5-Cl-1,1-dioxo-benzothiophen-3-yl



	R ⁵	R ⁶	n	W	Z—R ⁴
((3-phenyl)pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	Ph	0	O	5-Cl-benzothiophen-3-yl
((3-Methyl)-cyclohexylamino)methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(cyclopentyl-N-methylamino-carbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-((5-methoxy carbonyl)aminomethyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(4-(2-oxo-2,3-dihydro-benzimidazol-1-yl)piperidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(phenyl-aminocarbonyloxy)-methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(phenyl-aminocarbonyl)-methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
quinolin-2-yl	H	OH	0	O	naphthalen-1-yl
3-((4-Phenoxy-phenyl)-aminocarbonyloxy methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	OH	0	O	5-(4-F-phenyl)-N-methyl-indol-3-yl
naphthalen-2-yl	H	OH	0	O	4-Br-benzothiophen-3-yl
3-[(4-Benzotriazol-1-yl piperidin-1-ylcarbonyl)]-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(4-phenyl)-piperidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-((naphthalen-2-ylcarbonyl)-piperidin-4-ylmethylamino-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-((3-Benzosulfuryl)-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(N-[3-(4-Oxo-1-phenyl 1,3,8-triaza-spiro[4.5]decane-8-carbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(naphthalen-2-ylaminocarbonyloxy-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
2-fluorenyl	H	OH	0	O	naphthalen-1-yl
3-(Benzylaminomethyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
(3-OH)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(N-Benzyl-3-acrylamide)naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-((5-Phenyl)-pentylamino)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(N-Benzyl-N-methyl-aminocarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-[(5H-Dibenzo[a,d]cyclohepten-5-yl)-propyl]-methyl-amino-methyl-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(4-(Benzothiazol-2-yl)piperidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
1-(2-Oxo-2-(4-phenyl-piperidin-1-yl)-ethoxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-[(2-(3,4-dimethoxy-phenyl)-ethyl)-N-methyl-aminocarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl

	R ⁵	R ⁶	n	W	Z—R ⁴
naphthalen-2-yl	H	OH	0	O	1-Me-1H-pyrrolo[2,3-b]pyridine
3-((4-OH-cyclohexylamino)-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	CH ₃	0	O	2-carboxy-benzothiophen-3-yl
3-(Benzylaminocarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(3-Phenyl-allyloxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(Benzyloxy)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(methoxycarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(Cyclopentylamino-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	OH	0	O	5-Cl-benzothiophen-2-yl
3-(Phenethylmethylaminomethyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	CH ₃	0	O	2-(benzylaminocarbonyl)-benzothiophen-3-yl
naphthalen-2-yl	H	OH	0	O	N-phenyl-indol-4-yl
Indol-5-yl	H	OH	0	O	naphthalen-1-yl
3-(3-Phenylpropylcarbamoyl)-methoxy-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(2-phenyl-pyrrolidin-1-ylcarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-amino-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-((5-hydroxypentylamino)-methyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
1-(methoxycarbonyl)-methoxy-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
benzo[1,3]dioxolyl	H	OH	0	O	naphthalen-1-yl
isoquinolin-3-yl	H	OH	0	O	naphthalen-1-yl
3-phenoxy-phenyl	H	OH	0	O	naphthalen-1-yl
3-(isopropylloxycarbonyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	OH	0	O	benzothiophen-2-yl
3-([1-(naphthalen-2-ylcarbonyl)-piperidin-4-ylcarbonyl]-amino)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
3-(benzylmethylaminomethyl)-naphthalen-2-yl	H	OH	0	O	naphthalen-1-yl
naphthalen-2-yl	H	OH	0	O	6-(4-butylphenyl)-benzothiophen-3-yl
trans 2-phenylcycloprop-1-yl	H	CH ₃	0	O	5-Cl-benzothiophen-3-yl
2-methoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
benzofuran-2-yl	H	CH ₃	0	O	5-Cl-benzothiophen-3-yl
2-nitro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-methylcarbonyloxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-hydroxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
pyridin-2-yl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-amino-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethyl-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-methoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-methyl-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,6-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
4-cyano-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-ureido-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-(NHO(=O)) ₂ NH ₂ -phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-chloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,5-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,3-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-bromo-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,3-dimethoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-nitro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-bromo-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl



	R ⁵	R ⁶	n	W	Z—R ⁴
3,5-dimethoxy-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,5-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,5-dichloro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,4-difluoro-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-amino-phenyl	H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
phenyl	—CH ₂ C(Me) ₂ CH ₂ O—		1	O	naphthalen-1-yl
phenyl	3-methoxy-prop-1-yl	OH	1	O	naphthalen-1-yl
phenyl	3-methoxy-prop-1-yl	3-methoxy-prop-1-yl-oxy	1	O	naphthalen-1-yl
phenyl	2-(1,3-dioxolan-2-yl)-eth-1-yl	OH	1	O	naphthalen-1-yl
phenyl	—CH ₂ OC(=O)t-butyl	OH	1	O	naphthalen-1-yl
phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	naphthalen-1-yl
phenyl	(2-dimethylamino)-eth-1-yl	2-dimethylamino-ethoxy	1	O	naphthalen-1-yl
phenyl	—CH ₂ C(=O)NEt ₂	—OCH ₂ C(=O)NEt ₂	1	O	naphthalen-1-yl
phenyl	—(CH ₂) ₂ S C(=O)t-butyl	—O(CH ₂) ₂ S C(=O)1-butyl	1	O	naphthalen-1-yl
3,4-difluoro-phenyl	—CH ₂ OC(=O)t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	(2-dimethylamino)-eth-1-yl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	(2-amino)-eth-1-yl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	—CH ₂ C(=O)NEt ₂	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	—CH ₂ OC(=O)t-butyl	—OCH ₂ OC(=O)t-butyl	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	—CH ₂ OC(=O)t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	—CH ₂ OC(=O)NEt ₂	—OCH ₂ C(=O)NEt ₂	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	—CH ₂ OC(=O)methyl	OH	1	O	5-Cl-benzothiophen-3-yl
3,4-difluoro-phenyl	—CH ₂ OC(=O)isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2-methoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
pyridin-2-yl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3-methoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2,6-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3-chloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2,3-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2-bromo-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2,3-dimethoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3-nitro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3-bromo-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dimethoxy-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2,5-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dichloro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2,4-difluoro-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
3-amino-phenyl	H	OH	1	O	5-Cl-benzothiophen-3-yl
2-methoxy-phenyl	—CH ₂ OC(=O)t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
pyridin-2-yl	—CH ₂ OC(=O)t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
t-butyl	—CH ₂ OC(=O)t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethoxy-phenyl	—CH ₂ OC(=O)t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-methoxy-phenyl	—CH ₂ OC(=O)t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl



	R ⁵	R ⁶	n	W	Z—R ⁴
2,6-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-chloro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-chloro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,5-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,3-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-bromo-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,3-dimethoxy-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-nitro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-bromo-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,5-dimethoxy-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,5-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,5-dichloro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2,4-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-amino-phenyl	—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-methoxy-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
pyridin-2-yl	CH ₂ OC(=O) t-butyl	OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethoxy-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-methoxy-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2,6-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2-chloro-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-chloro-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3,5-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2,3-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2-bromo-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2,3-dimethoxy-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-nitro-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-bromo-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3,5-dimethoxy-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2,5-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3,5-dichloro-phenyl	—CH ₂ OC(=O)	—OCH ₂	1	O	5-Cl-benzothiophen-3-yl



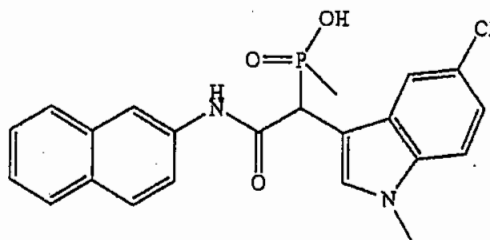
	R ⁵	R ⁶	n	W	Z—R ⁴
	t-butyl	OC(=O)			
2,4-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	t-butyl —OCH ₂ OC(=O)	1	O	5-Cl-benzothiophen-3-yl
3-amino-phenyl	—CH ₂ OC(=O) t-butyl	1-butyl —OCH ₂ OC(=O)	1	O	5-Cl-benzothiophen-3-yl
2-methoxy-phenyl	—CH ₂ OC(=O) t-butyl	t-butyl —OCH ₂	1	O	5-Cl-benzothiophen-3-yl
pyridin-2-yl	—CH ₂ OC(=O) t-butyl	—OCH ₂	1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethoxy-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-methoxy-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2,6-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2-chloro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-chloro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2,3-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2-bromo-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2,3-dimethoxy-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-nitro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-bromo-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dimethoxy-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2,5-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dichloro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2,4-difluoro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-amino-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2-methoxy-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
pyridin-2-yl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethoxy-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-methoxy-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2,6-difluoro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2-chloro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-chloro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3,5-difluoro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2,3-difluoro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2-bromo-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2,3-dimethoxy-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-nitro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-bromo-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3,5-dimethoxy-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2,5-difluoro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3,5-dichloro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2,4-difluoro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-amino-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2-methoxy-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
pyridin-2-yl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-trifluoromethoxy-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-methoxy-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2,6-difluoro-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2-chloro-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl

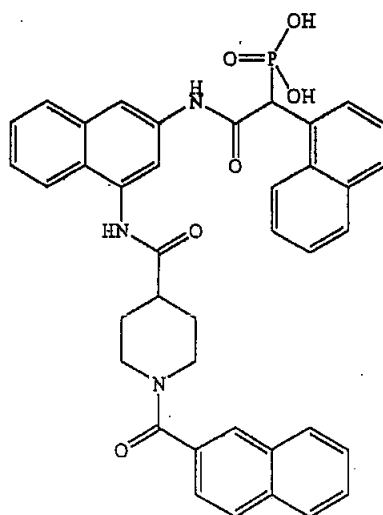
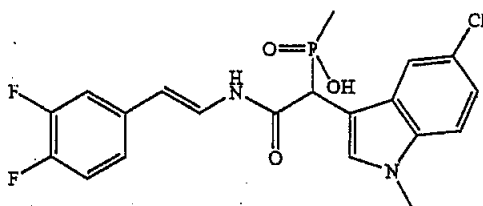
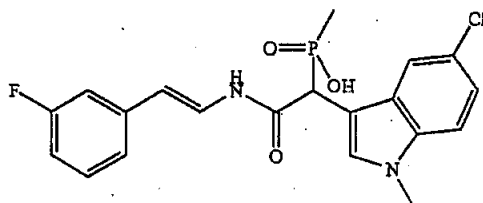
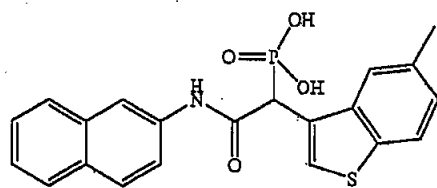
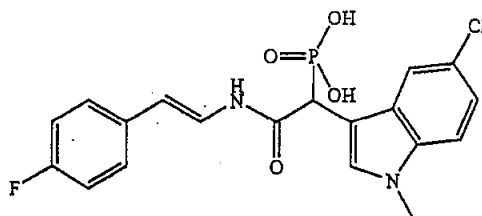
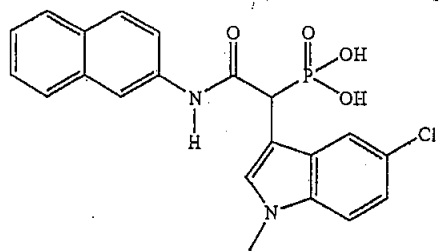
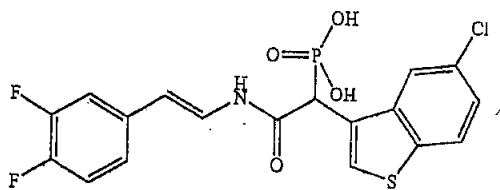


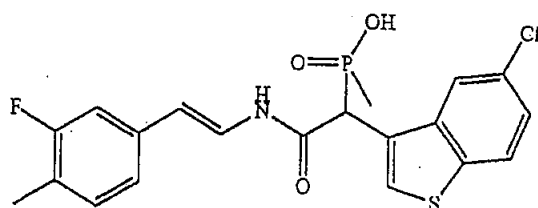
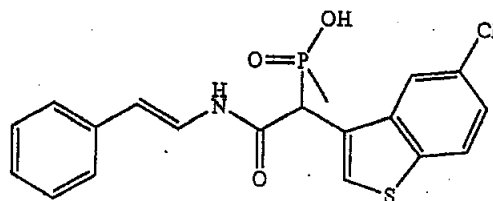
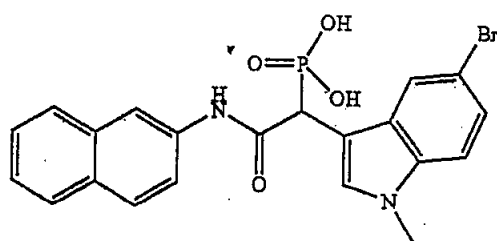
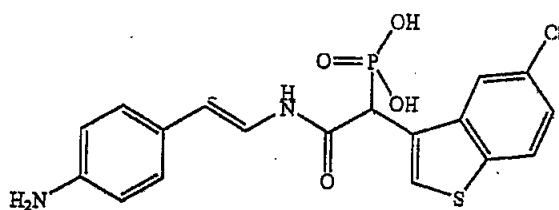
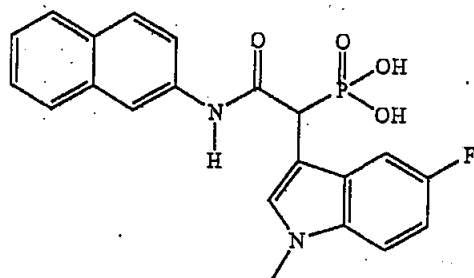
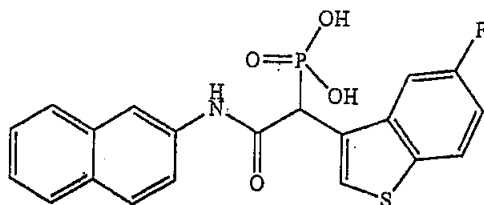
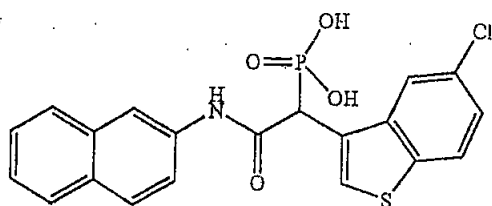
R^2	R^3	R^5	R^6	n	W	Z— R^4
3-chloro-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-difluoro-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2,3-difluoro-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2-bromo-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2,3-dimethoxy-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-nitro-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-bromo-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dimethoxy-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2,5-difluoro-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dichloro-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2,4-difluoro-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-amino-phenyl		—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-chloro-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-3-chloro-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
4-fluoro-3-chloro-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-5-chloro-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,5-dibromo-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-cyano-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-cyano-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-trifluoromethyl-phenyl		H	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-chloro-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-3-chloro-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
4-fluoro-3-chloro-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-5-chloro-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dibromo-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
3-cyano-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
2-cyano-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-trifluoromethyl-phenyl		H	OH	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-chloro-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-3-chloro-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
4-fluoro-3-chloro-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-5-chloro-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3,5-dibromo-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-cyano-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
2-cyano-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-trifluoromethyl-phenyl		—CH ₂ OC(=O) t-butyl	CH ₃	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-chloro-phenyl		—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-3-chloro-phenyl		—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
4-fluoro-3-chloro-phenyl		—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-5-chloro-phenyl		—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3,5-dibromo-phenyl		—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-cyano-phenyl		—CH ₂ OC(=O)	—OCH ₂	1	O	5-Cl-benzothiophen-3-yl

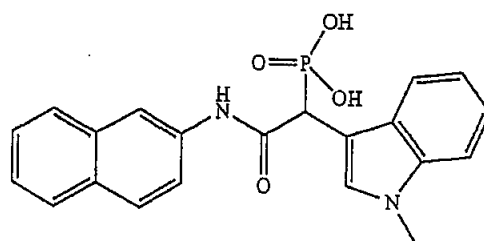
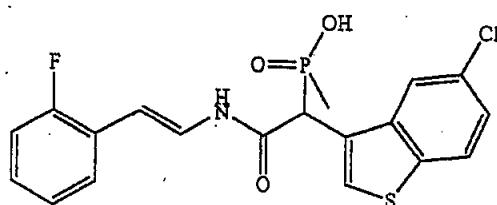
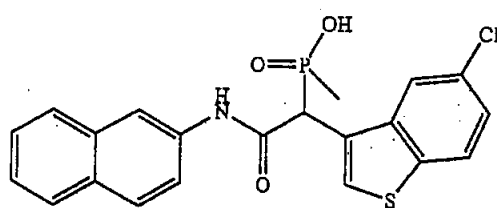
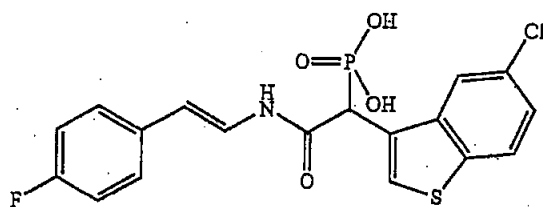
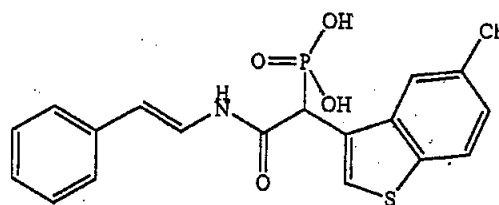
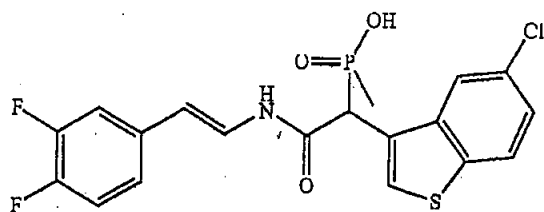
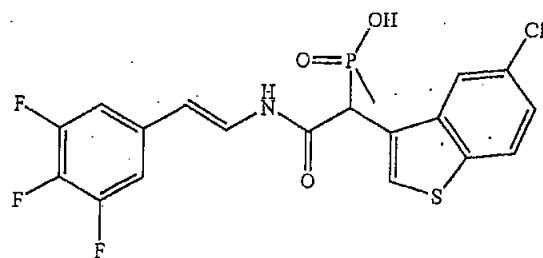
	R ⁵	R ⁶	n	W	Z—R ⁴
	t-butyl	OC(=O) t-butyl			
2-cyano-phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-trifluoromethyl phenyl	—CH ₂ OC(=O) t-butyl	—OCH ₂ OC(=O) t-butyl	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-chloro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-3-chloro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
4-fluoro-3-chloro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-5-chloro-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dibromo-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-cyano-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
2-cyano-phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-trifluoromethyl- phenyl	—CH ₂ OC(=O) t-butyl	OH	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-chloro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2-fluoro-3-chloro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
4-fluoro-3-chloro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2-fluoro-5-chloro-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3,5-dibromo-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-cyano-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
2-cyano-phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-trifluoromethyl- phenyl	—CH ₂ CH ₂ CH ₂ O—		1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-chloro-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-3-chloro-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
4-fluoro-3-chloro-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2-fluoro-5-chloro-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3,5-dibromo-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-cyano-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
2-cyano-phenyl	—CH ₂ OC(=O) isopropoxy	OH	1	O	5-Cl-benzothiophen-3-yl
3-fluoro-5-trifluoromethyl phenyl	—CH ₂ OC(=O) isopropoxy	and OH	1	O	5-Cl-benzothiophen-3-yl,

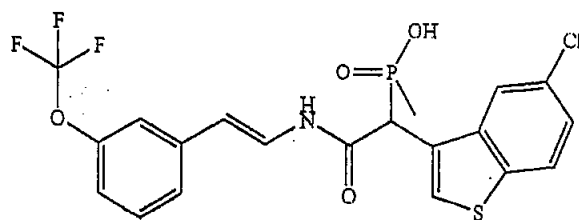
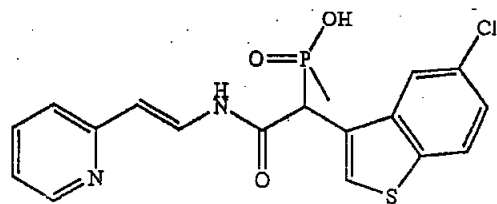
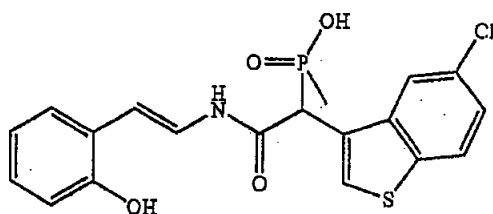
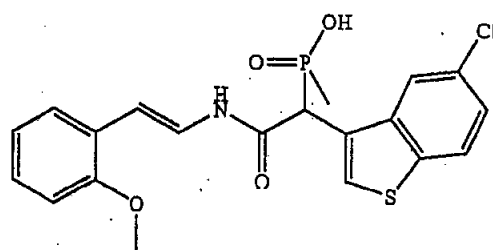
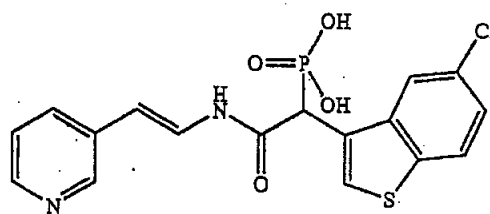
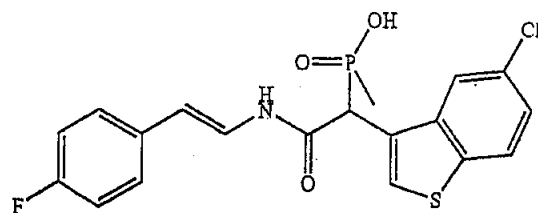
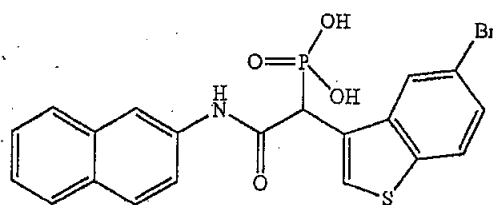
48. The compounds of claim 30 wherein the compounds have a formula selected from the group consisting of:

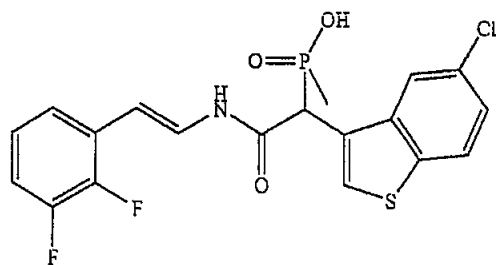
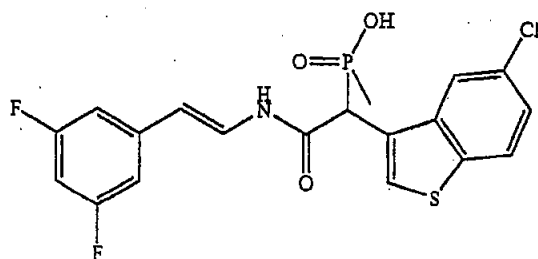
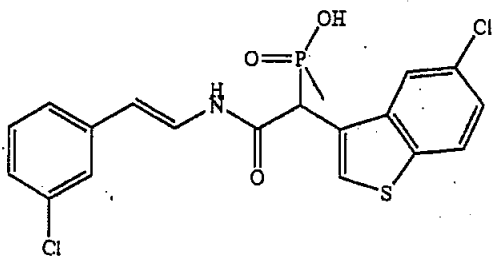
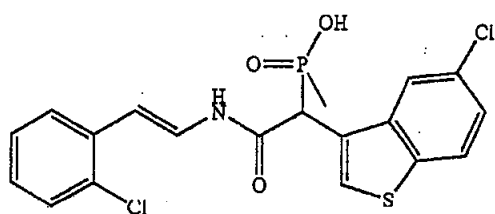
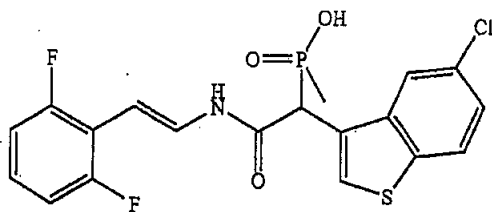
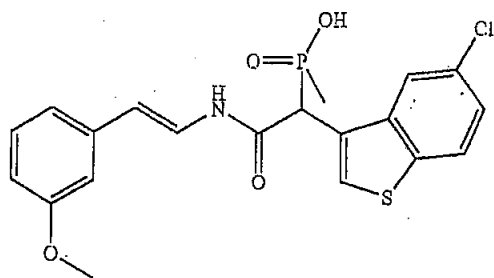


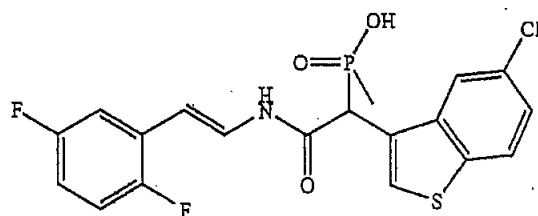
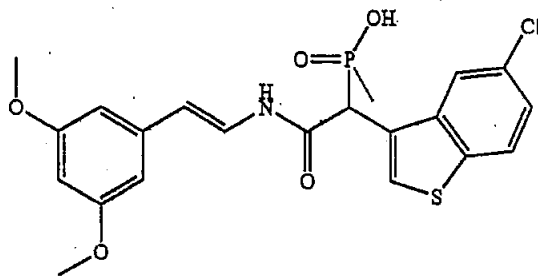
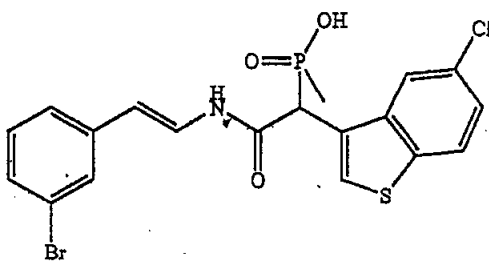
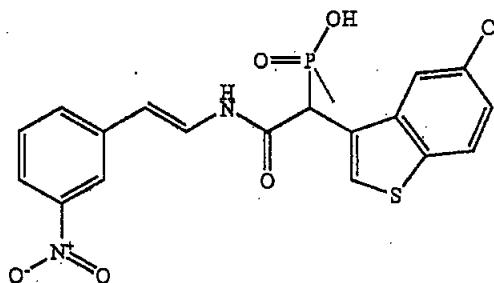
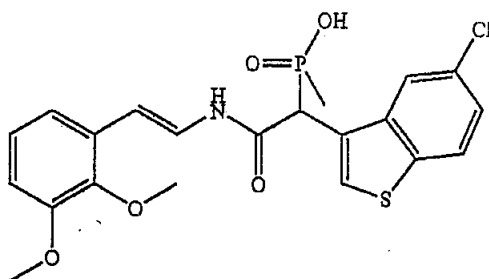
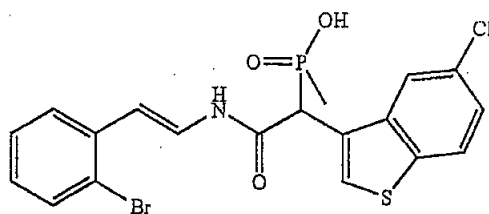


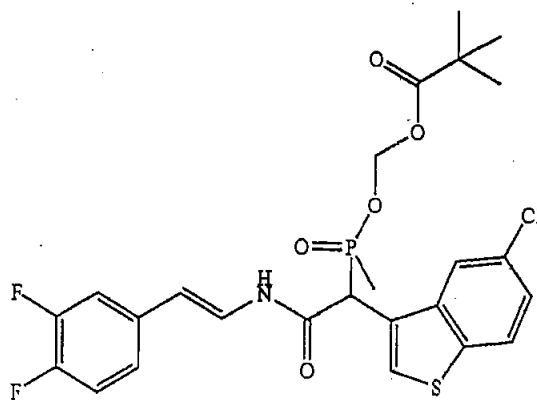
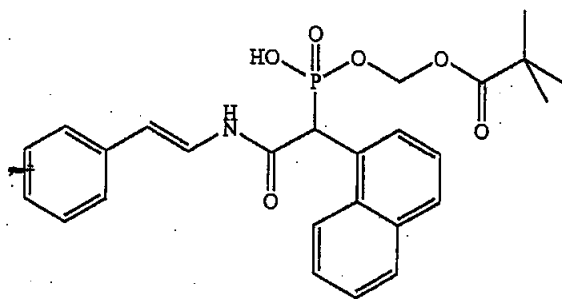
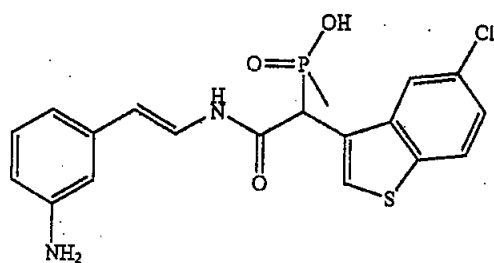
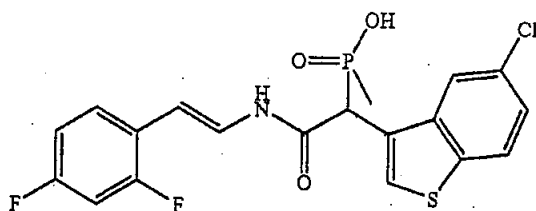
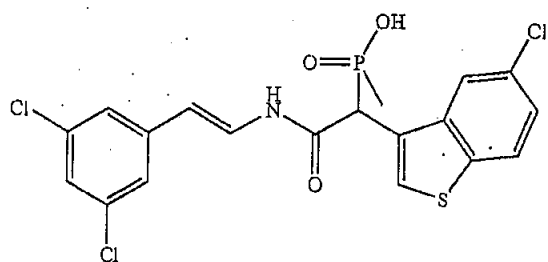


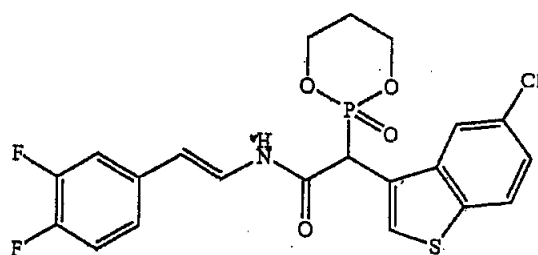
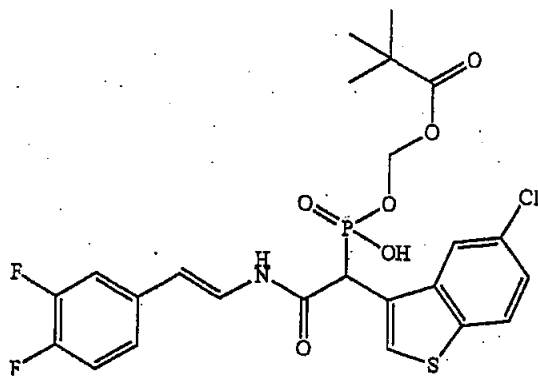
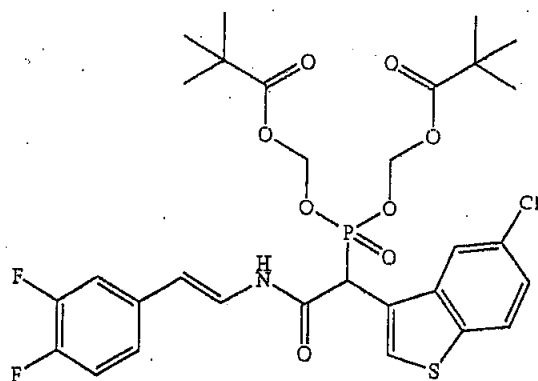




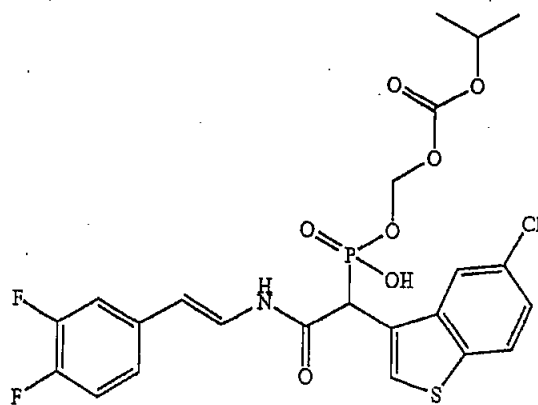




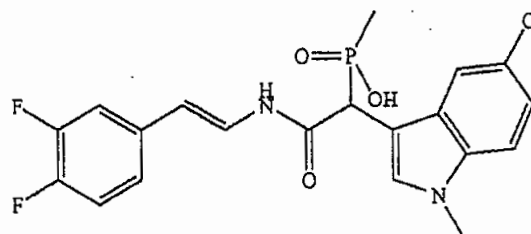
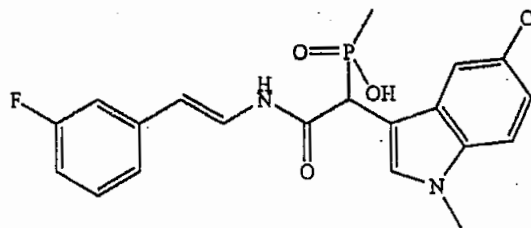
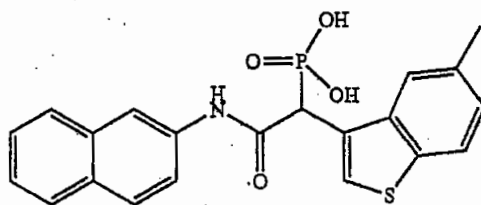
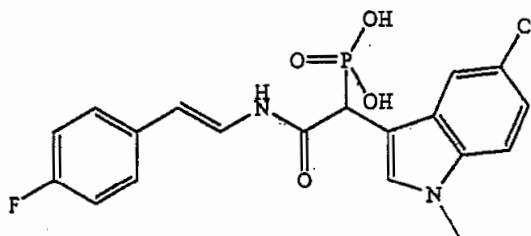
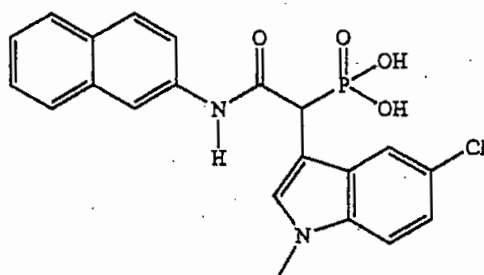
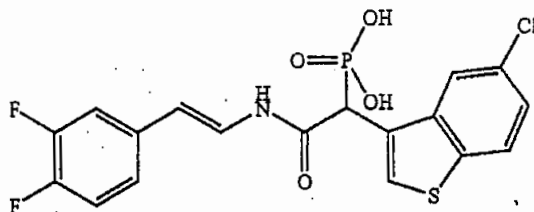
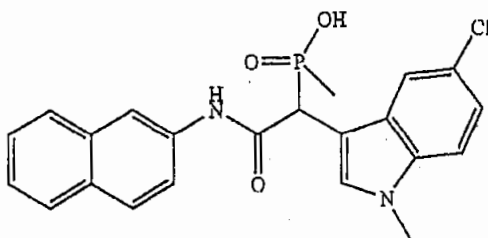


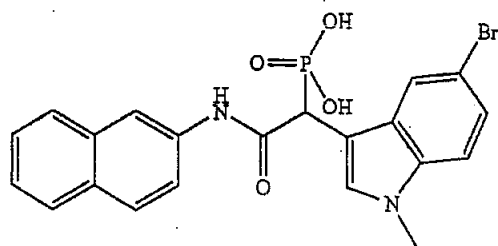
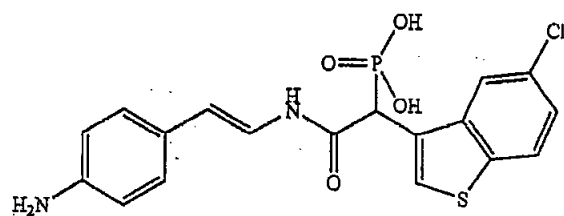
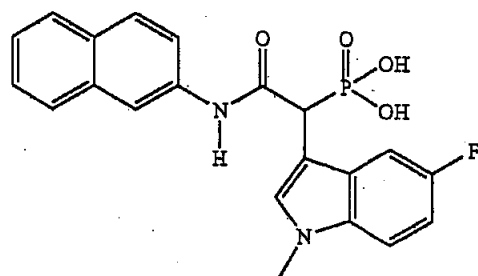
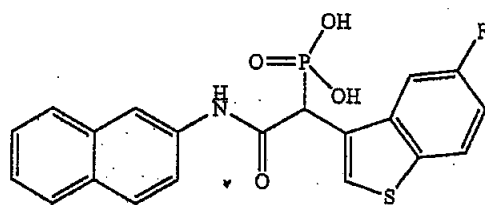
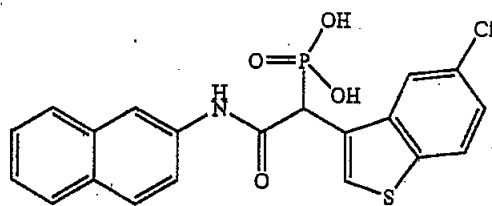
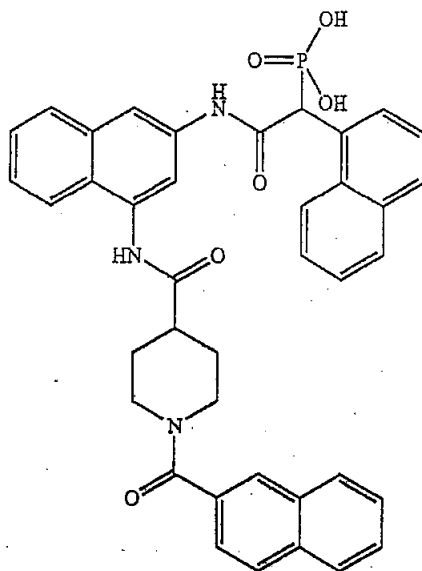


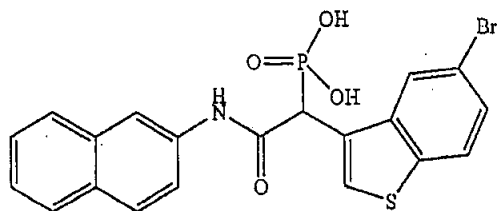
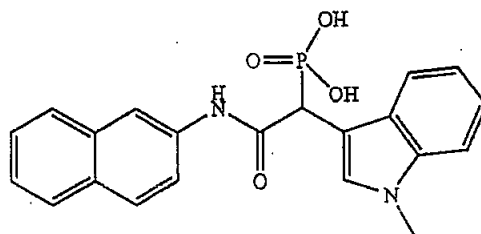
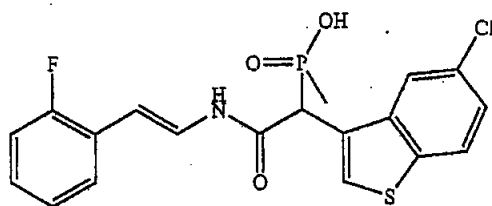
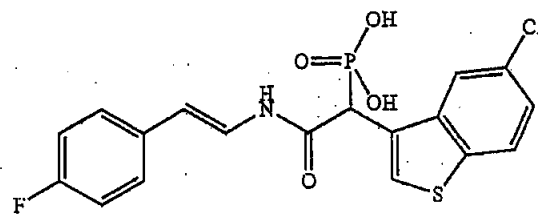
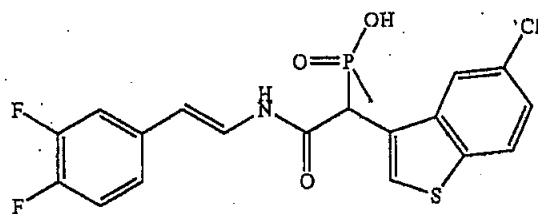
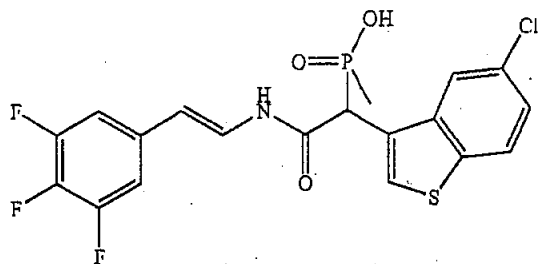
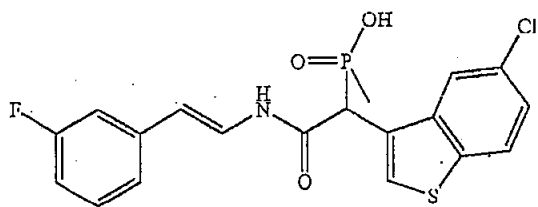
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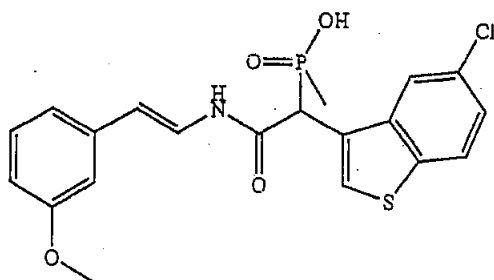
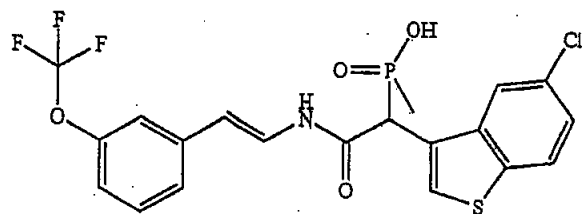
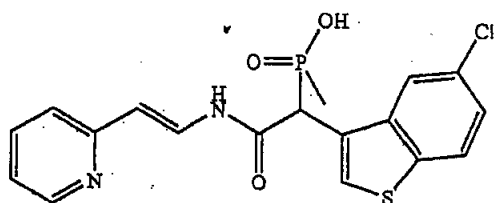
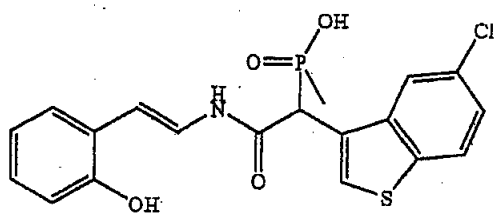
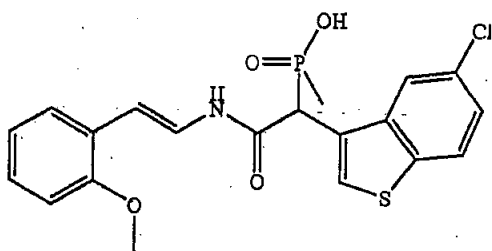
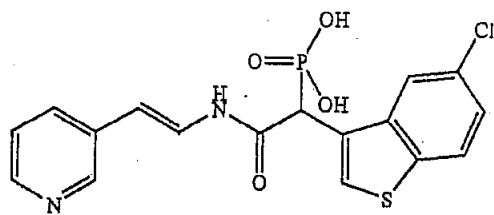
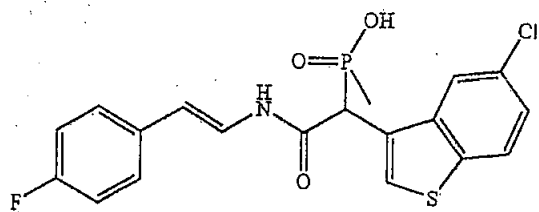


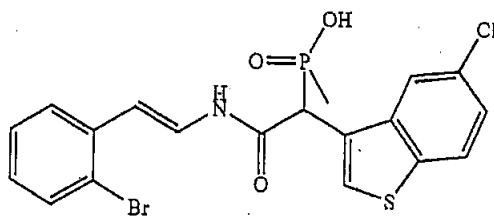
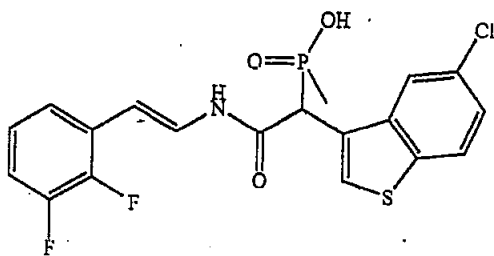
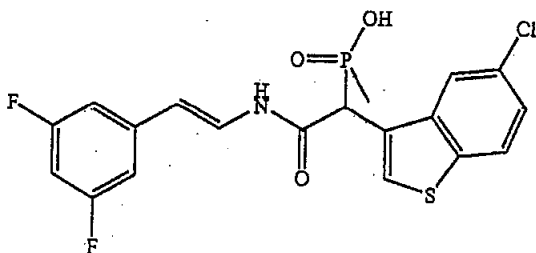
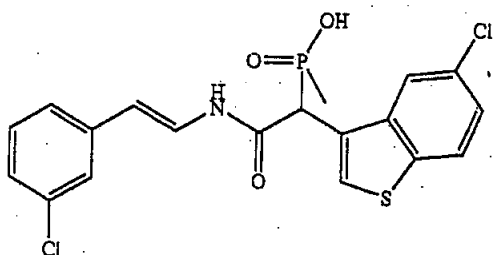
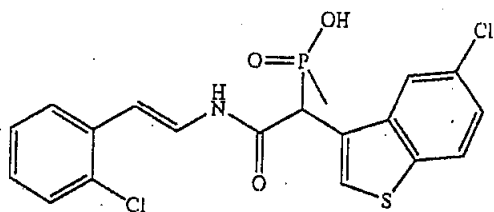
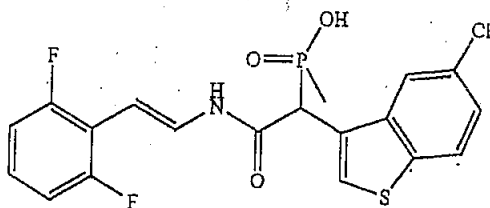
49. The compounds of claim 30 wherein the compounds have a formula of:

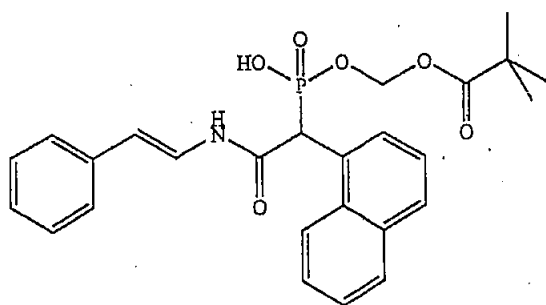
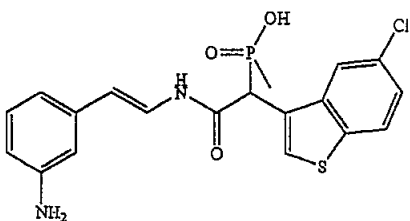
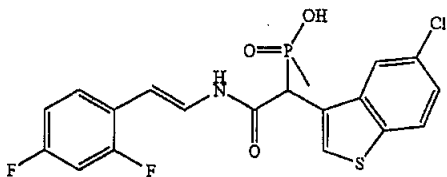
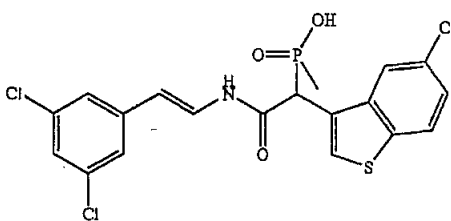
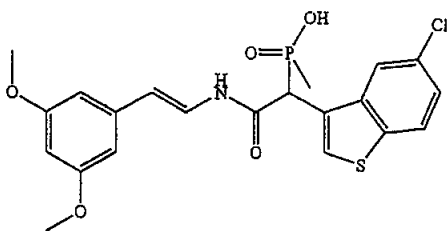
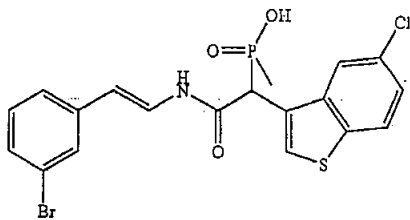
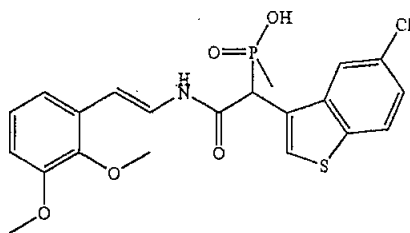


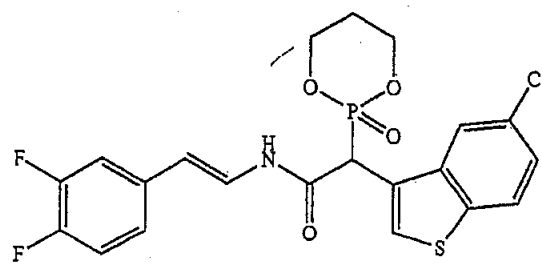
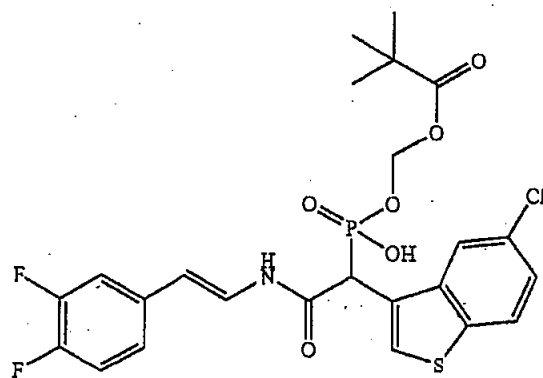
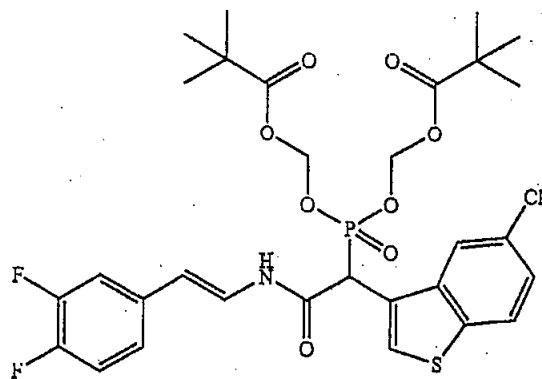
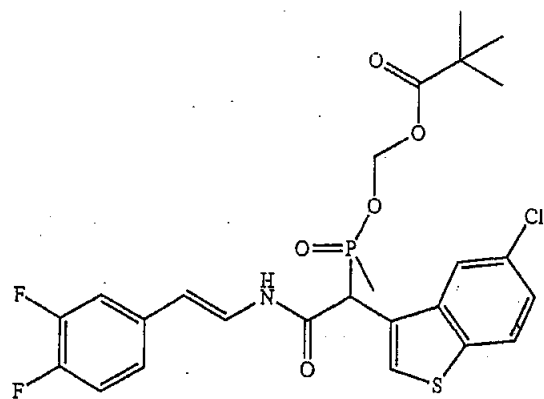




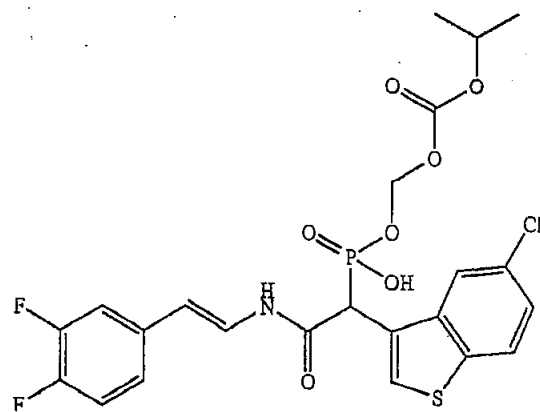




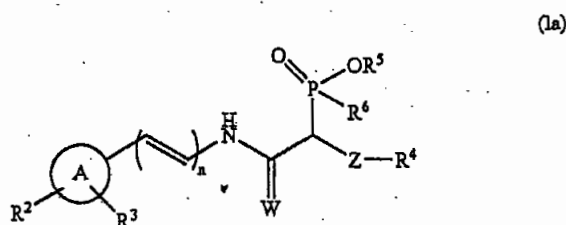




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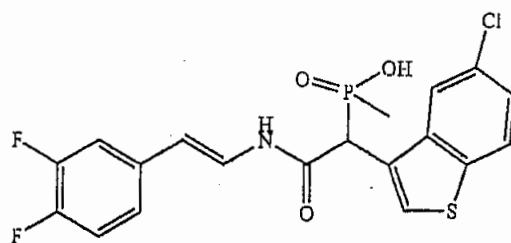


50. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.
51. A composition made by mixing the compound of claim 1 and a pharmaceutically acceptable carrier.
52. A composition comprising the compound of claim 30 and a pharmaceutically acceptable carrier.
53. A composition made by mixing the compound of claim 30 and a pharmaceutically acceptable carrier.
54. A compound of formula Ia selected from the group consisting of:

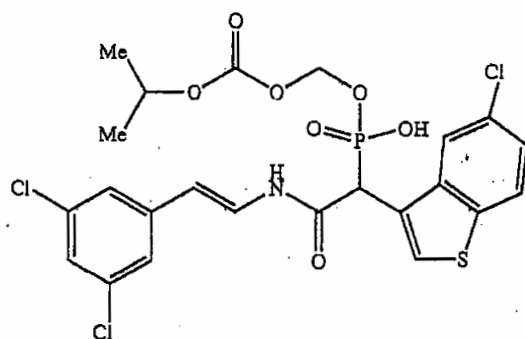


CPD	R ²	R ³	R ⁵	R ⁶	n	W	Z—R ⁴
2	3,4-difluoro-phenyl	H	H	OH	1	O	5-Cl-benzothio-phen-3-yl
17	3,4-difluoro-phenyl	H	H	CH ₃	1	O	5-Cl-benzothio-phen-3-yl
170	3,5-dichloro-phenyl	H	H	CH ₃	1	O	5-Cl-benzothio-phen-3-yl
187	3,4-difluoro-phenyl	—CH ₂ OC(=O)t-butyl	H	OH	1	O	5-Cl-benzothio-phen-3-yl
191	3,4-difluoro-phenyl	—CH ₂ OC(=O)isopropoxy	H	OH	1	O	5-Cl-benzothio-phen-3-yl
207	3,5-dichloro-phenyl	H	H	OH	1	O	5-Cl-benzothio-phen-3-yl
261	3,5-dichloro-phenyl	—CH ₂ OC(=O)t-butyl	H	OH	1	O	5-Cl-benzothio-phen-3-yl
297	3,5-dichloro-phenyl	—CH ₂ OC(=O)isopropoxy	H	OH	1	O	5-Cl-benzothio-phen-3-yl

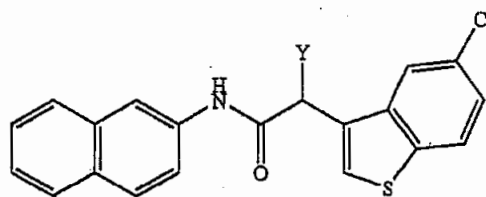
55. A compound of claim 54 that is



56. A compound of claim 54 that is:



57. A compound of claim 1 of Formula II



wherein Y is $-\text{SO}_3\text{H}$.

58. A compound of claim 54 that is:

