HYDANTOIN DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY DISORDERS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates generally to novel hydantoin derivatives that can inhibit matrix metalloproteinases (MMPs), a disintegrin and metalloproteases (ADAMs) and/or tumor necrosis factor alpha - converting enzyme (TACE) and in so doing prevent the release of tumor necrosis factor alpha (TNF-α), pharmaceutical compositions comprising such compounds, and methods of treatment using such compounds.

Description

Osteo- and rheumatoid arthritis (OA and RA, respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A (1970) 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteases. The available evidence supports the belief that it is the metalloproteases that are responsible for the degradation of the extracellular matrix of articullar cartilage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, aggrecanase (a newly identified metalloprotease) has been identified that provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander L. S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Metalloproteases (MPs) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

MMPs are a family of over 20 different enzymes that are involved in a variety of biological processes important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as RA and OA, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMPs (tissue inhibitor of MPs), which form inactive complexes with the MMP's.

Tumor necrosis factor alpha (TNF-α) is a cell-associated cytokine that is processed from a 26 kDa precursor form to a 17 kd active form. *See* Black R.A. "Tumor necrosis factor-alpha converting enzyme" Int J Biochem Cell Biol. 2002 Jan; 34(1):1-5 and Moss ML, White JM, Lambert MH, Andrews RC."TACE and other ADAM proteases as targets for drug discovery" Drug Discov Today. 2001 Apr 1;6(8):417-426, each of which is incorporated by reference herein.

TNF-α has been shown to play a pivotal role in immune and inflammatory responses. Inappropriate or over-expression of TNF-α is a hallmark of a number of diseases, including RA, Crohn's disease, multiple sclerosis, psoriasis and sepsis. Inhibition of TNF-α production has been shown to be beneficial in many preclinical models of inflammatory disease, making inhibition of TNF-α production or signaling an appealing target for the development of novel anti-inflammatory drugs.

TNF-α is a primary mediator in humans and animals of inflammation, fever and acute phase responses, similar to those observed during acute infection and shock. Excess TNF-α has been shown to be lethal. Blocking the effects of TNF-α with specific antibodies can be beneficial in a variety of conditions, including autoimmune diseases such as RA (Feldman et al, Lancet, (1994) 344, 1105), non-insulin dependent diabetes mellitus (Lohmander L. S. et al., Arthritis Rheum. 36 (1993) 1214-22) and Crohn's disease (Macdonald T. et al., Clin. Exp. Immunol. 81 (1990) 301).

Compounds that inhibit the production of TNF-α are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that metalloproteases, such as TACE, are capable of converting TNF-α from its inactive to active form (Gearing et al Nature, 1994, 370, 555). Since excessive TNF-α production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF-α production may also have a particular advantage in diseases where both mechanisms are involved.

One approach to inhibiting the harmful effects of TNF-α is to inhibit the enzyme, TACE before it can process TNF-α to its soluble form. TACE is a member of the ADAM family of type I membrane proteins and mediates the ectodomain shedding of various membrane-anchored signaling and adhesion proteins. TACE has become increasingly important in the study of several diseases, including inflammatory disease, because of its role in cleaving TNF-α from its "stalk" sequence and thus releasing the soluble form of the TNF-α protein (Black R.A. Int J Biochem Cell Biol. 2002 34,1-5).

There are numerous patents and publications which disclose hydroxamate, sulphonamide, hydantoin, carboxylate and/or lactam based MMP inhibitors.

US 6,677,355 and US 6,534,491(B2), describe compounds that are hydroxamic acid derivatives and MMP inhibitors.

US 6,495,565 discloses lactam derivatives that are potential inhibitors of MMPs and/or TNF-α.

PCT Publications WO2002/074750, WO2002/096426, WO20040067996, WO2004012663, WO200274750 and WO2004024721 disclose hydantoin derivatives that are potential inhibitors of MMPs.

PCT Publications WO2004024698 and WO2004024715 disclose sulphonamide derivatives that are potential inhibitors of MMPs.

PCT Publications WO2004056766, WO2003053940 and WO2003053941 also describe potential inhibitors of TACE and MMPs.

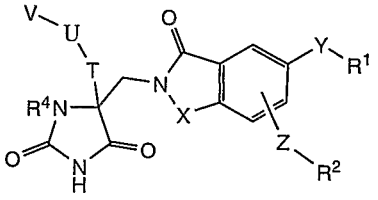
There is a need in the art for inhibitors of MMPs, ADAMs, TACE, and TNF-α, which can be useful as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of TNF-α, TACE and or other MMPs

can prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of OA and RA as well as many other auto-immune diseases.

SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of compounds as inhibitors of TACE, the production of TNF-α, MMPs, ADAMs or any combination thereof, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof using such compounds or pharmaceutical compositions.

In one embodiment, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein:

X is selected from the group consisting of –S-, $-C(R^4)_2-$ or $-N(R^4)-$;

T is selected from the group consisting of H (with U and V being absent), alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl, and arylalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of T is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can

be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

U is absent or present, and if present U is selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(R^4)_2-$, $-N(R^4)C(O)-$, $-O-$, $-N(R^4)S(O)_2-$, $-N(R^4)C(O)N(R^4)-$, and $-N(R^4)C(S)N(R^4)-$;

V is absent or present, and if present V is selected from the group consisting of alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2$, $-O-$,$-S-$, $-C(O)-$, $-S(O)-$, and $-S(O)_2-$;

Z is absent or present, and if present Z is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$,$-S-$, $-C(O)-$, $-S(O)-$, and $-S(O)_2-$;

n is 1 to 3;

R^1 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^1 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Y is present and Y is N, S or O, then R^1 is not halogen;

R^2 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^2 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Z is present and Z is N, S or O, then R^2 is not halogen;

each R^4 is the same or different and is independently selected from the group consisting of H and alkyl;

R^{10} is selected from the group consisting of $-OR^4$, $-N(R^4)_2$, -S(O)-, $-S(O)_2-$, $-N(R^4)S(O)_2-$, $-S(O)_2N(R^4)-$, -O(fluoroalkyl), halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of R^{10} is unsubstituted or optionally independently substituted with one to four R^{30} moieties which can be the same or different, each R^{30} moiety being independently selected from the group of R^{30} moieties below;

R^{20} is selected from the group consisting of halogen, alkyl, fluoroalkyl; and

R^{30} is selected from the group consisting of halogen, alkyl, and fluoroalkyl.

The compounds of Formula I can be useful as inhibitors of TACE and may be useful in the treatment and prevention of diseases associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof.

DETAILED DESCRIPTION OF THE INVENTION

In its several embodiments, the present invention provides a novel class of inhibitors of TACE, the production of TNF-α, MMPs, ADAMs or any combination thereof, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations

comprising one or more such compounds, and methods of treatment, prevention or amelioration of one or more of the symptoms of inflammation.

In one embodiment, the present invention provides compounds which are represented by structural Formula (I) above or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein the various moieties are as described above.

In another embodiment, the isomer referred to the in the preceding paragraph is a stereoisomer.

In one embodiment, T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is -O-.

In another embodiment, T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present, and if present Z is -O-; and R^2 is selected from the group consisting of alkylaryl and alkylheteroaryl.

In another embodiment, T is alkyl or aryl; X is $-N(R^4)-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is -O-.

In another embodiment, X is $-CH_2-$ or $-N(R^4)-$.

In yet another embodiment, X is $-CH_2-$.

In still another embodiment, X is $-N(R^4)-$.

In another embodiment, R^4 is H.

In another embodiment, T is alkyl.

In yet another embodiment, T is $-CH_3$.

In still another embodiment, T is aryl and said aryl is unsubstituted or optionally independently substituted with one to five R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.

In another embodiment, R^{10} is halogen.

In yet another embodiment, R^{10} is heteroaryl.

In still another embodiment, R^{10} is aryl.

In an embodiment U selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(O)-$, and $-N(R^4)S(O)_2-$.

In yet another embodiment U is a covalent bond.

In still another embodiment U is -N(R^4)-.

In yet still another embodiment, U is -N(R^4)C(O)-.

In another embodiment, V is selected from the group consisting of aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, and cycloalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of any of said aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.

In another embodiment, Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, -C(O)- and –O-.

In yet another embodiment, Y is –O-.

In still another embodiment, Y is $-(C(R^4)_2)_n-$.

In yet still another embodiment, Y is –C(O)-.

In another embodiment, Y is a covalent bond.

In an embodiment, R^1 is selected from the group consisting of $-OR^4$, H, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.

In another embodiment, R^1 is H.

In yet another embodiment, R^1 is alkylaryl.

In still another embodiment, R^1 is alkyl.

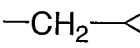
In yet still another embodiment, R^1 is fluoroalkyl.

In a further embodiment, R^1 is halogen.

In another embodiment, R^1 is $-OR^4$.

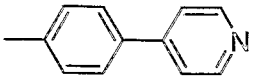
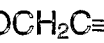
In another embodiment, where R^1 is $-OR^4$, R^4 is $-CH_2C{\equiv}CCH_3$.

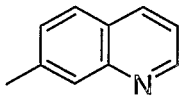
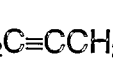
In another embodiment, where R^1 is $-OR^4$, R^4 is $-CH_2C{\equiv}CCH_2OH$.

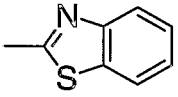
In another embodiment, where R^1 is $-OR^4$, R^4 is .

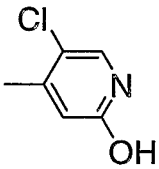
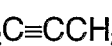
In another embodiment, the alkyl is $-CH_3$.

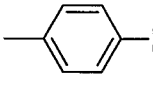
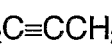
In still another embodiment, the alkyl is $-CH_2CH_3$.

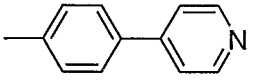
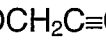
In another embodiment, in formula (I), T, U, and V are taken together to form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

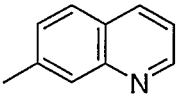
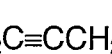
In another embodiment, in formula (I), T, U, and V are taken together to form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

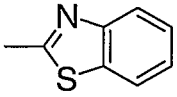
In another embodiment, in formula (I), T, U, and V are taken together to form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

In another embodiment, in formula (I), T, U, and V are taken together to form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

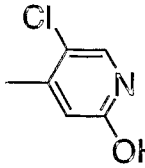
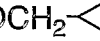
In another embodiment, in formula (I), T, U, and V are taken together to form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

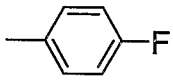
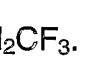
In another embodiment, in formula (I), T, U, and V are taken together to form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

In another embodiment, in formula (I), T, U, and V are taken together to form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

In another embodiment, in formula (I), T, U, and V are taken together to form  and R^2 is selected from the group consisting of F, Cl, OH,

$-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

In another embodiment, in formula (I), T, U, and V are taken together to form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

In another embodiment, in formula (I), T, U, and V are taken together to form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

In another embodiment, the fluoroalkyl is $-CH_2CF_3$.

In an embodiment, halogen is selected from the group consisting of –Br, -Cl and -F.

In another embodiment, R^4 is $-CH_3$.

In yet another embodiment, alkyl of R^1 is substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties.

In another embodiment, R^{20} is aryl.

In another embodiment, Z is selected from the group consisting of a covalent bond, $-N(R^4)-$, $-(C(R^4)_2)_n-$, -C(O)- and –O-.

In yet another embodiment, Z is –O-.

In still another embodiment, Z is a covalent bond.

In yet still another embodiment, Z is $-N(R^4)-$.

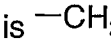
In a further embodiment, Z is -C(O)-.

In another embodiment, R^4 is alkyl.

In another embodiment, R^2 is selected from the group consisting of $-OR^4$, H, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.

In another embodiment wherein R^2 is $-OR^4$, R^4 is $-CH_2C{\equiv}CCH_3$.

In another embodiment wherein R^2 is $-OR^4$, R^4 is $-CH_2C{\equiv}CCH_2OH$.

In another embodiment wherein R^2 is $-OR^4$, R^4 is .

In yet another embodiment, R^2 is hydrogen.

In still another embodiment, R^2 is alkyl.

In yet still another embodiment, R^2 is alkylaryl.

In yet further embodiment, R^2 is fluoroalkyl.

In another embodiment, R^2 is $-CH_2CF_3$.

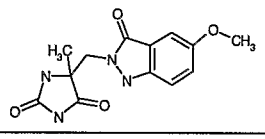
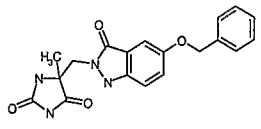
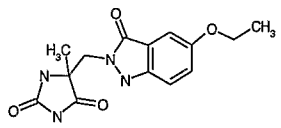
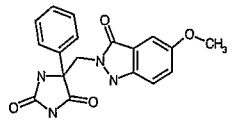
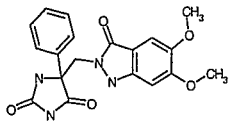
In yet another embodiment, R^2 is halogen.

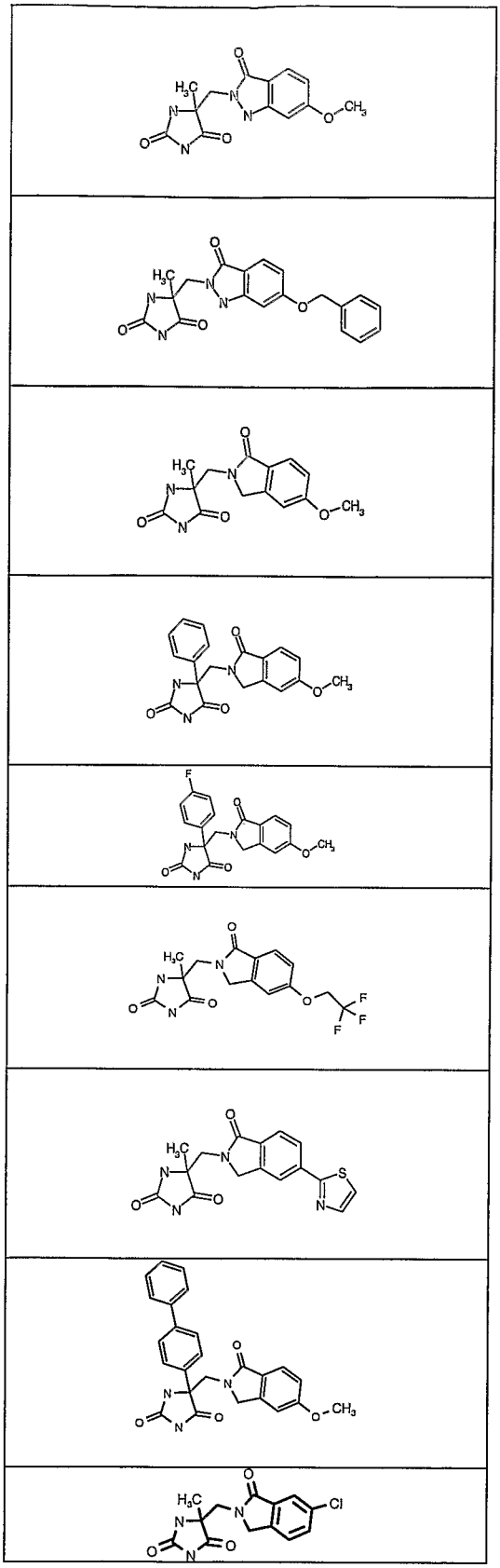
In another embodiment, R^2 is heteroaryl.

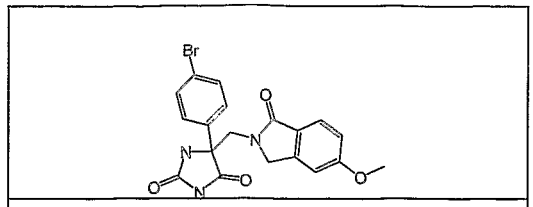
In another embodiment, R^4 is $-CH_3$.

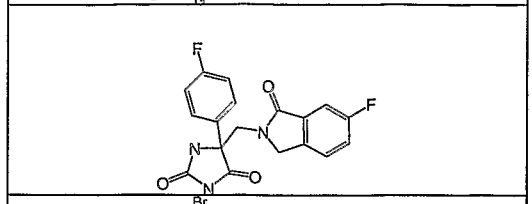
Another embodiment of the invention discloses the following compounds shown in **Table A** below.

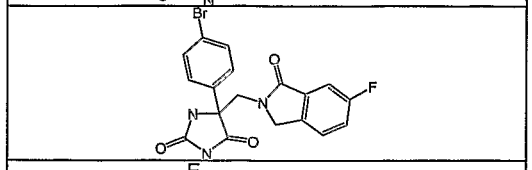
Table A

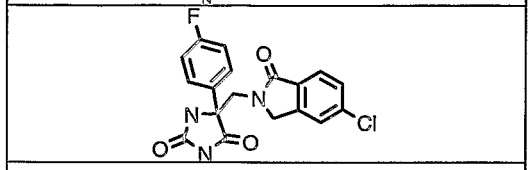
Structures






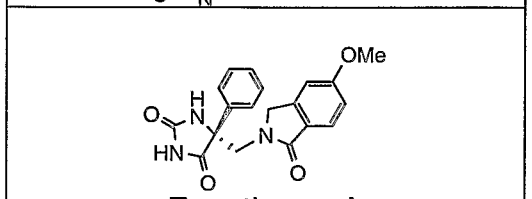




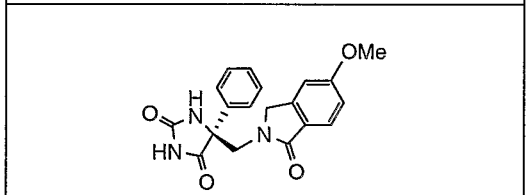




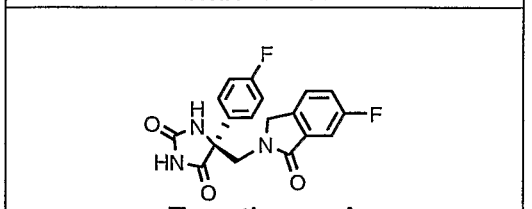




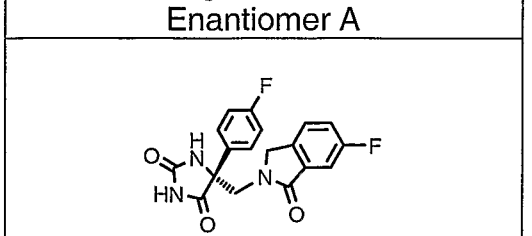
Enantiomer A



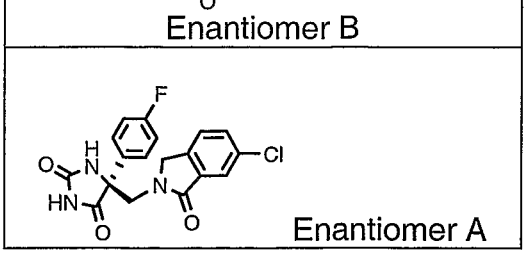
Enantiomer B



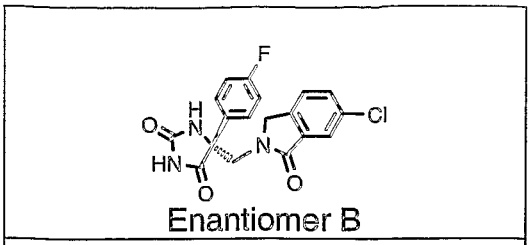
Enantiomer A



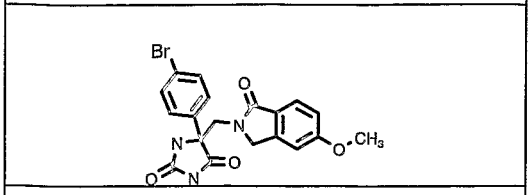
Enantiomer B

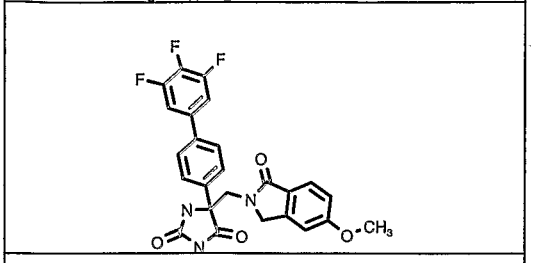


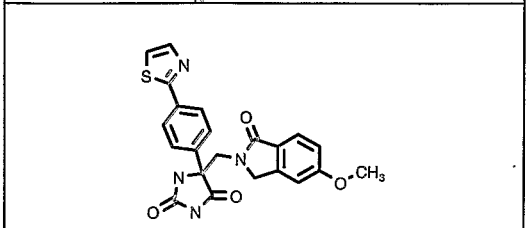
Enantiomer A

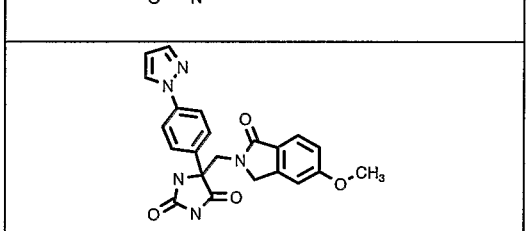


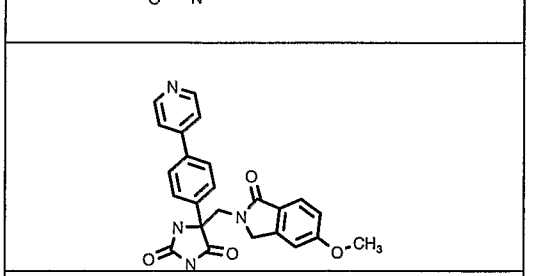
Enantiomer B

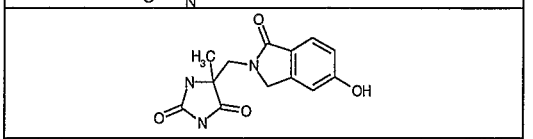


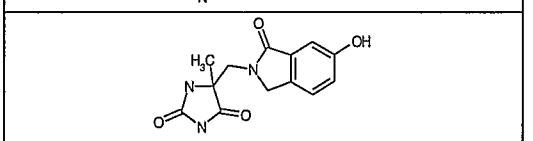


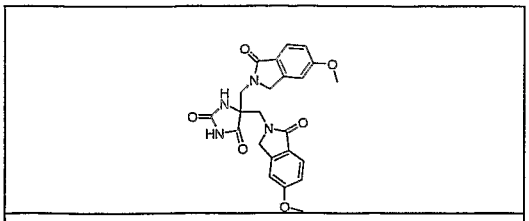


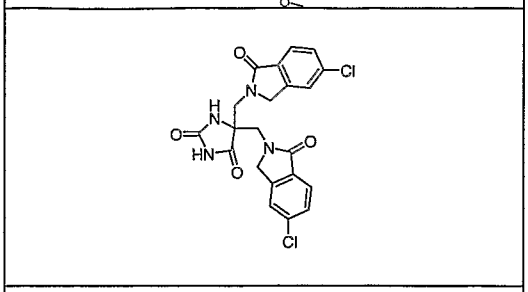


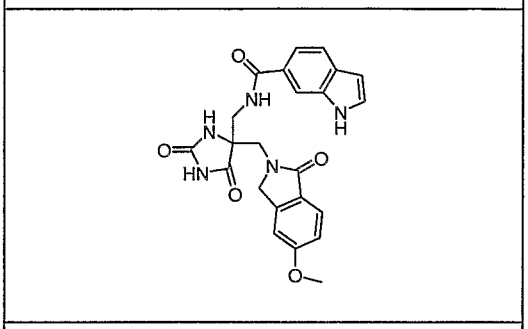


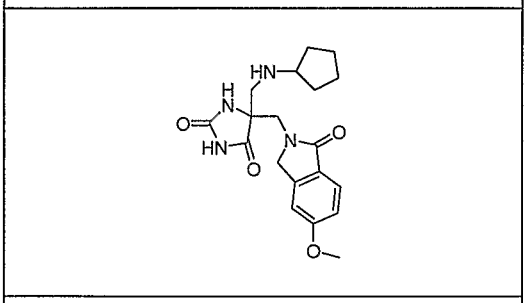


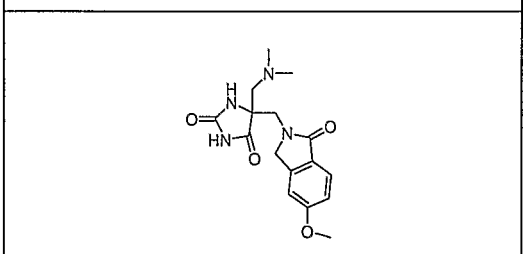


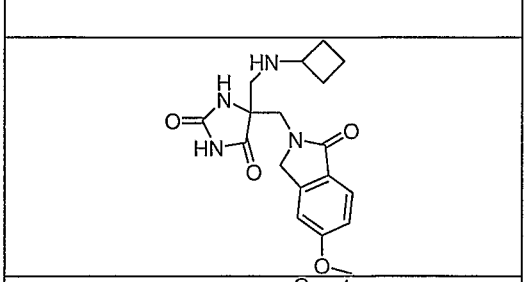


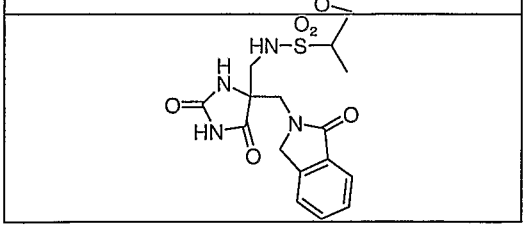


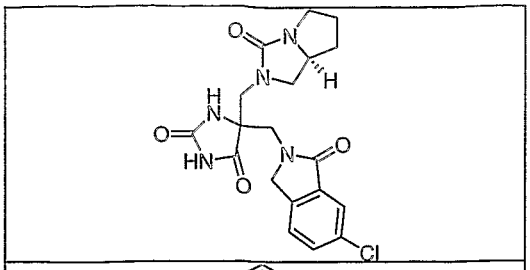


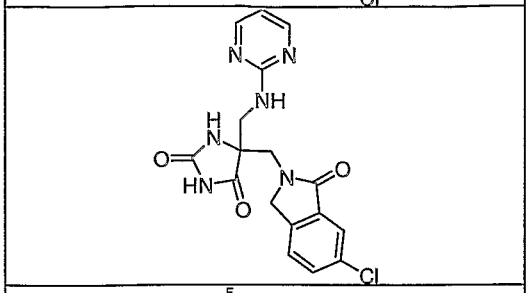


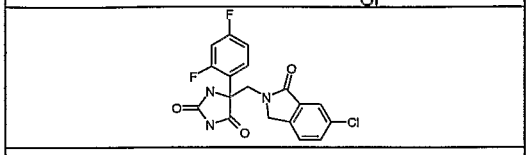


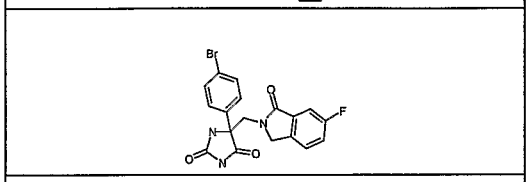


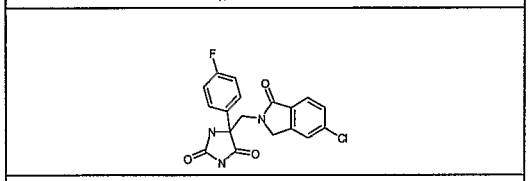


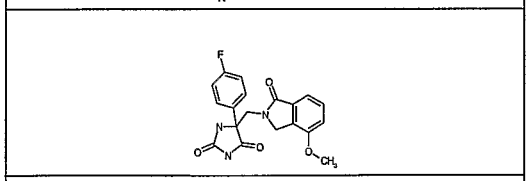


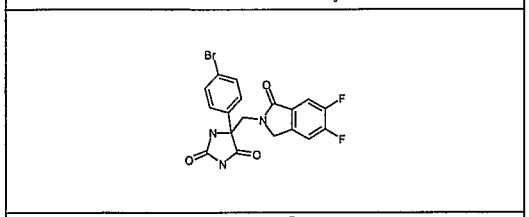


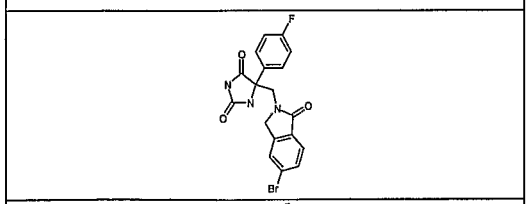


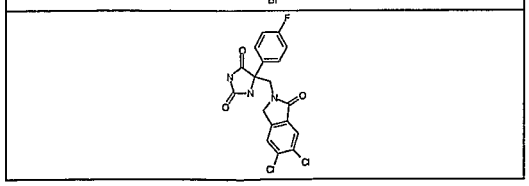


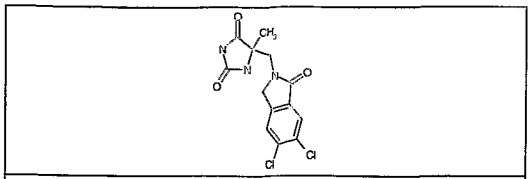


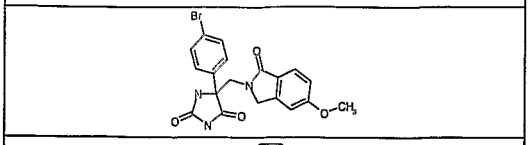


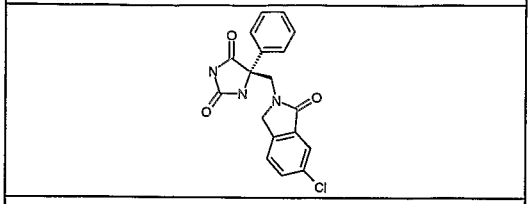


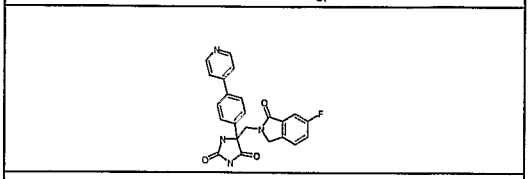


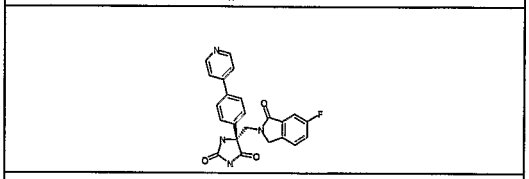


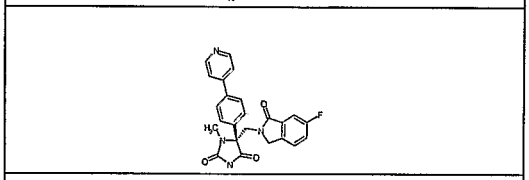


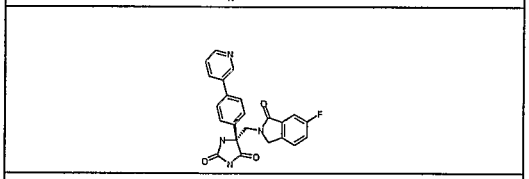


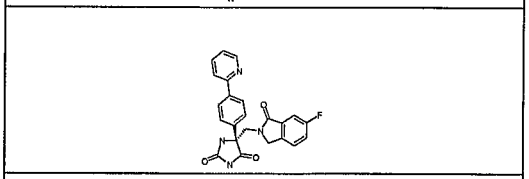


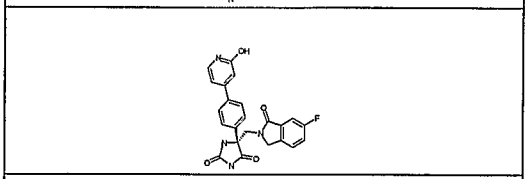


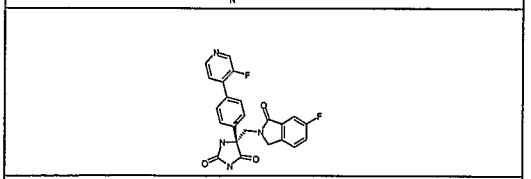


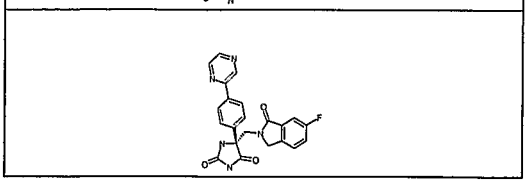


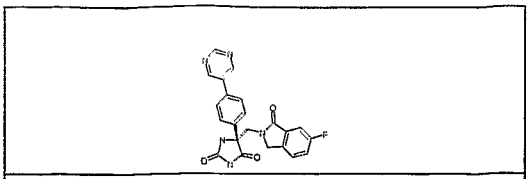


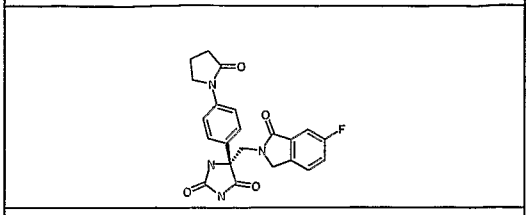


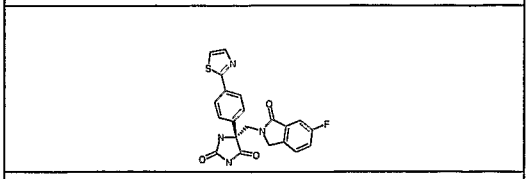


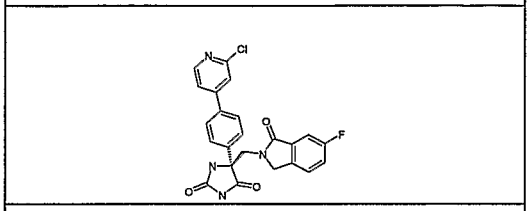


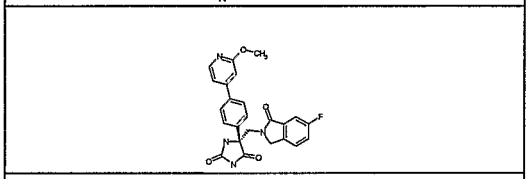


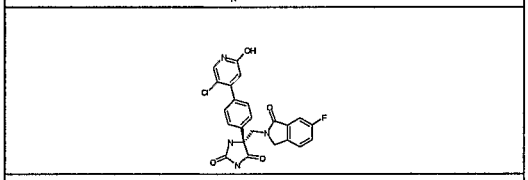


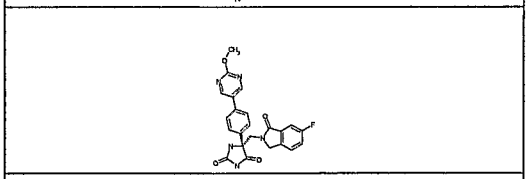


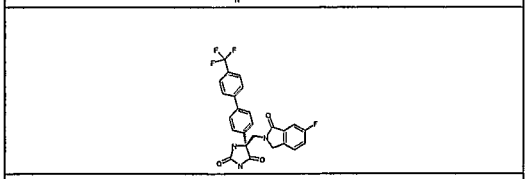


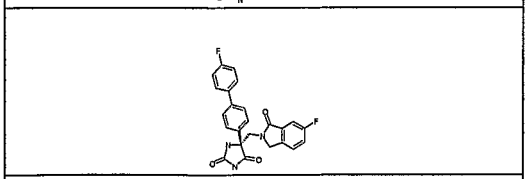


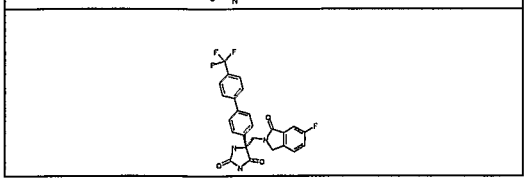


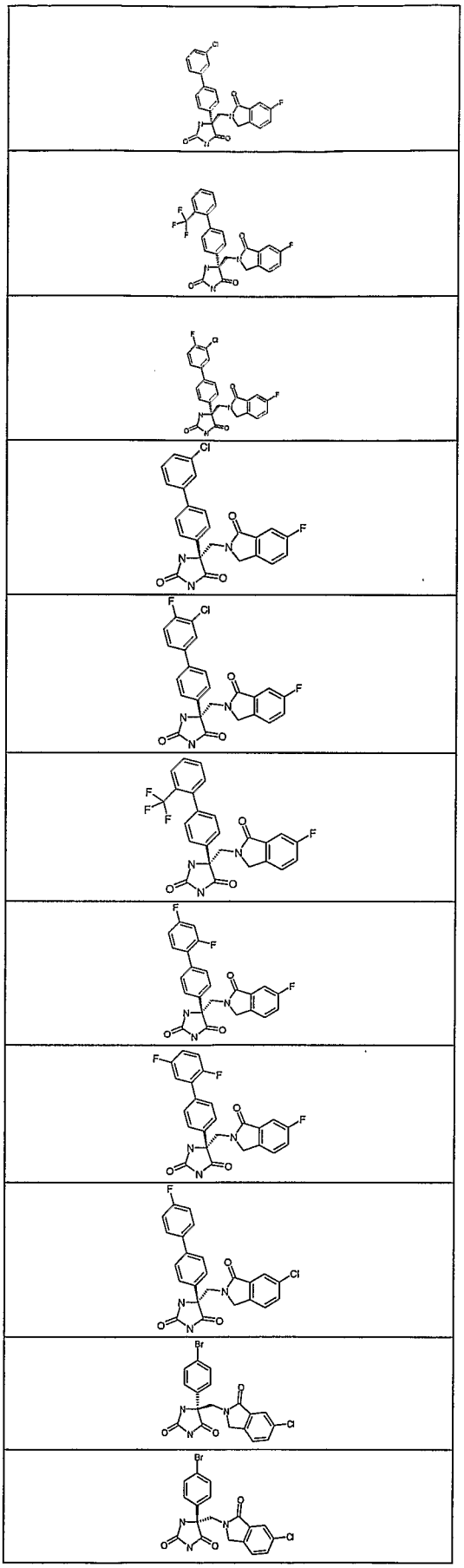


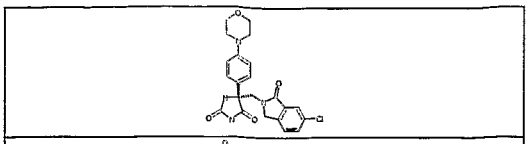


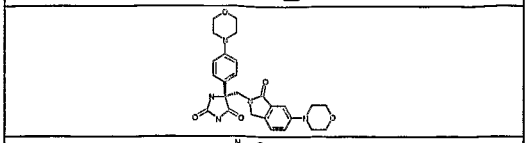


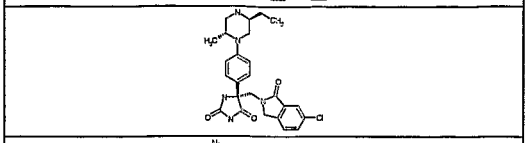


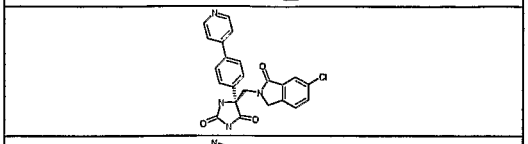


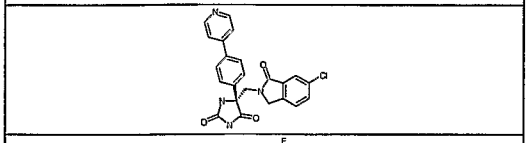


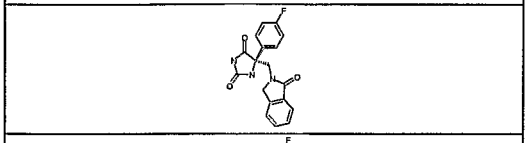


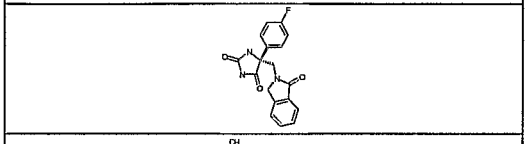


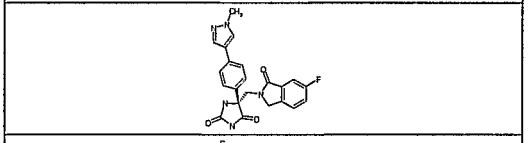


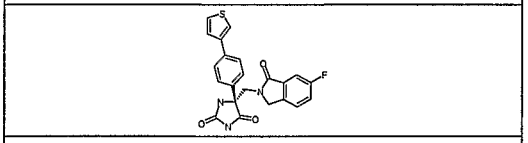


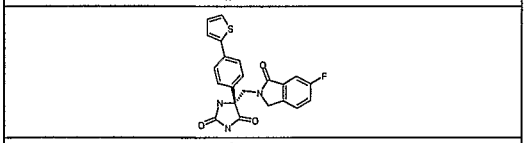


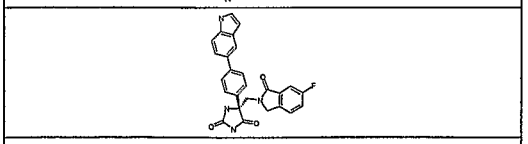


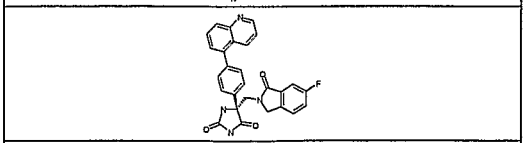


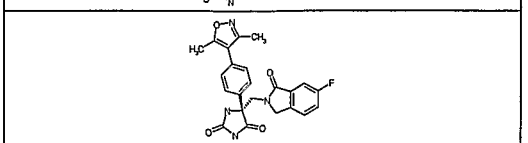


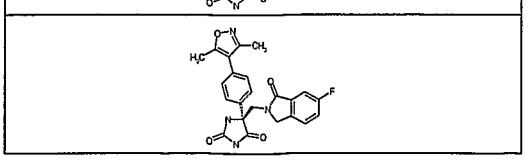


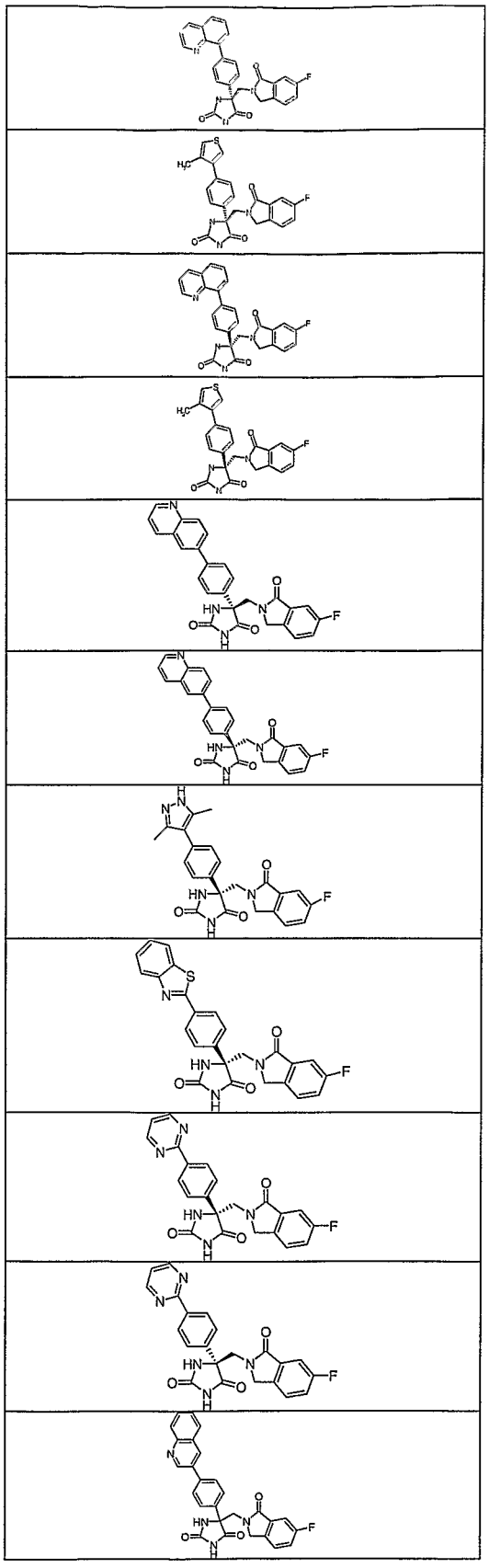


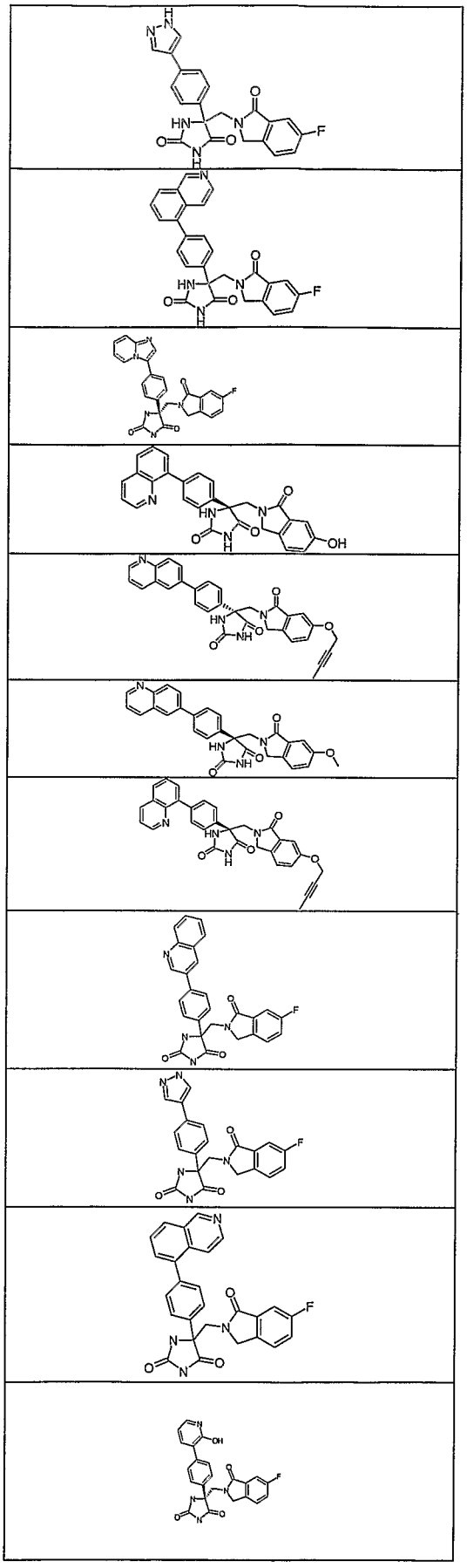


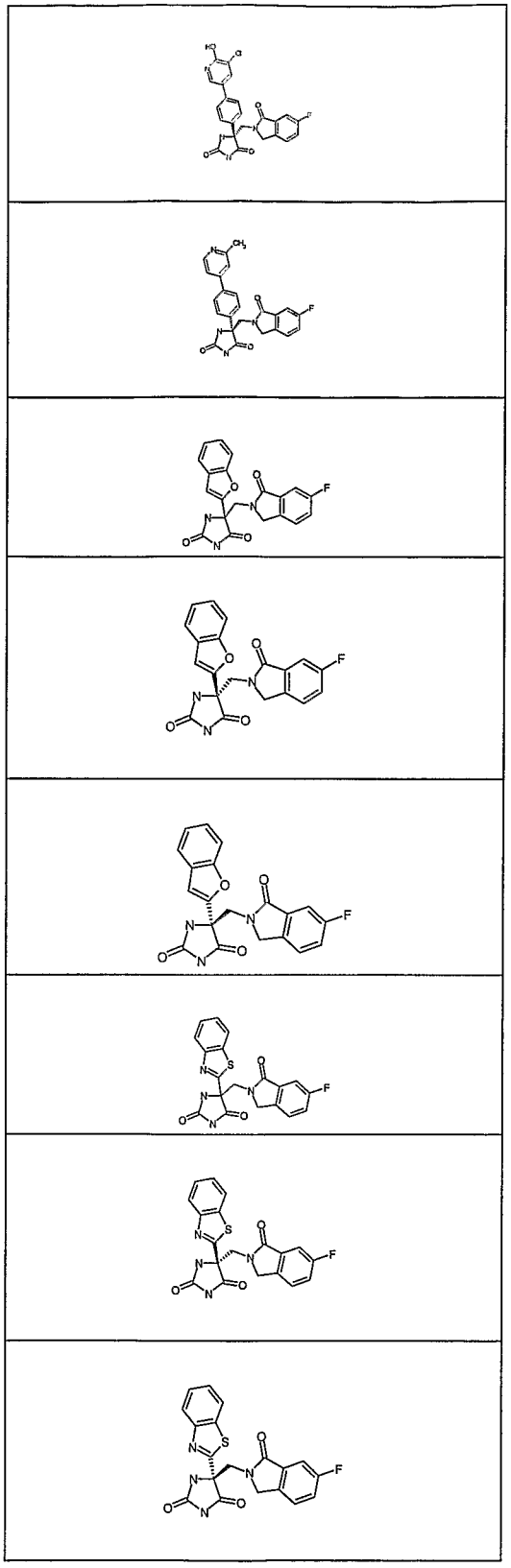


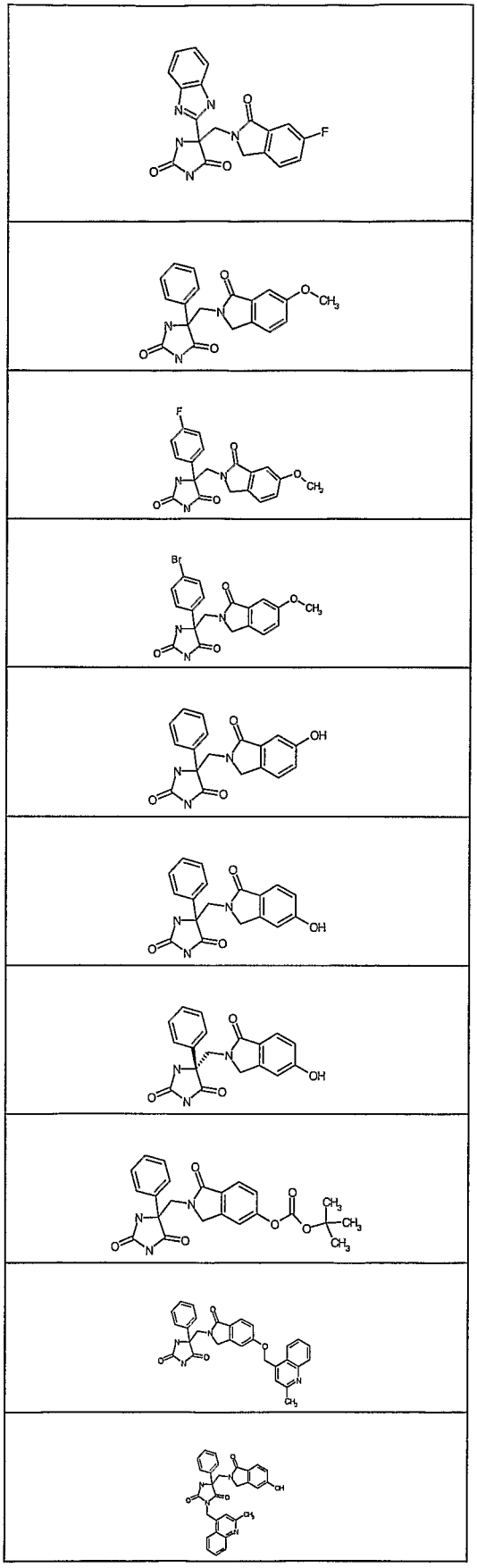


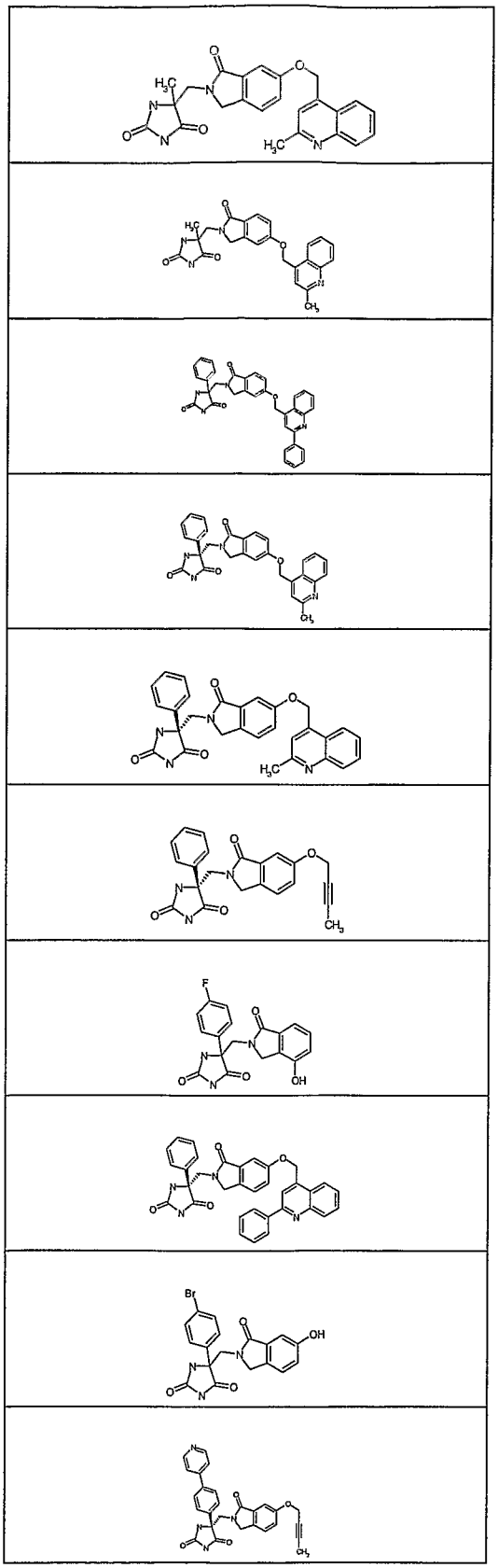


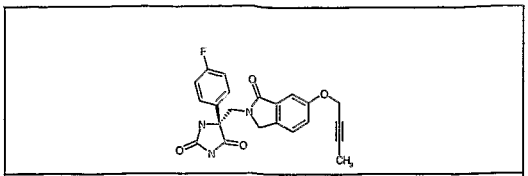


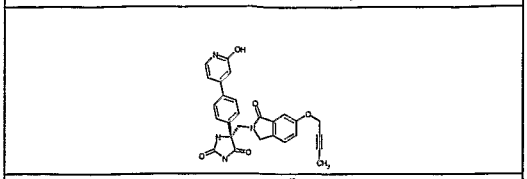


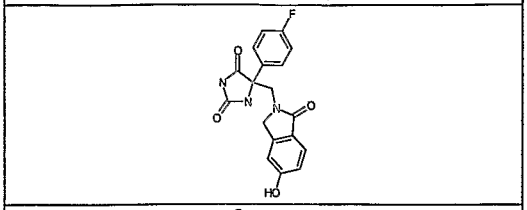


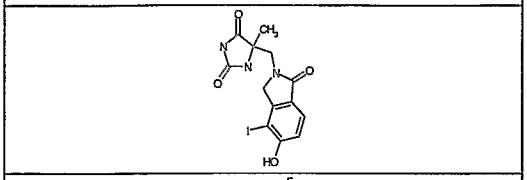


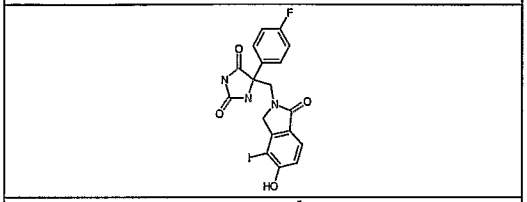


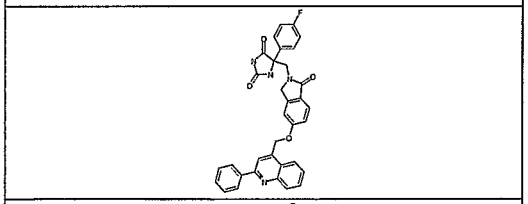


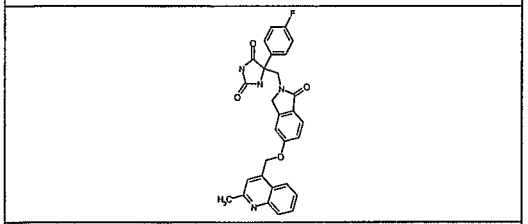


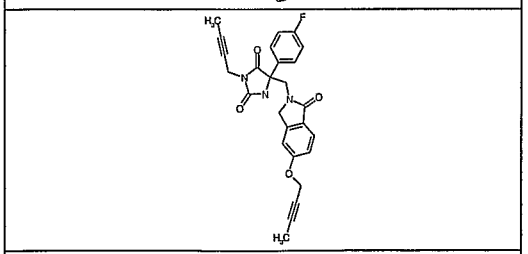


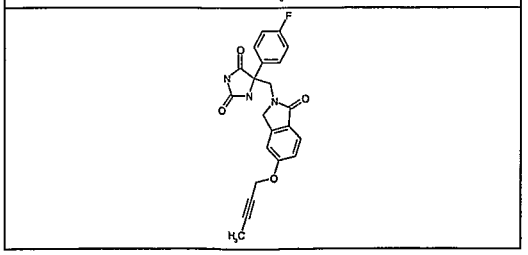


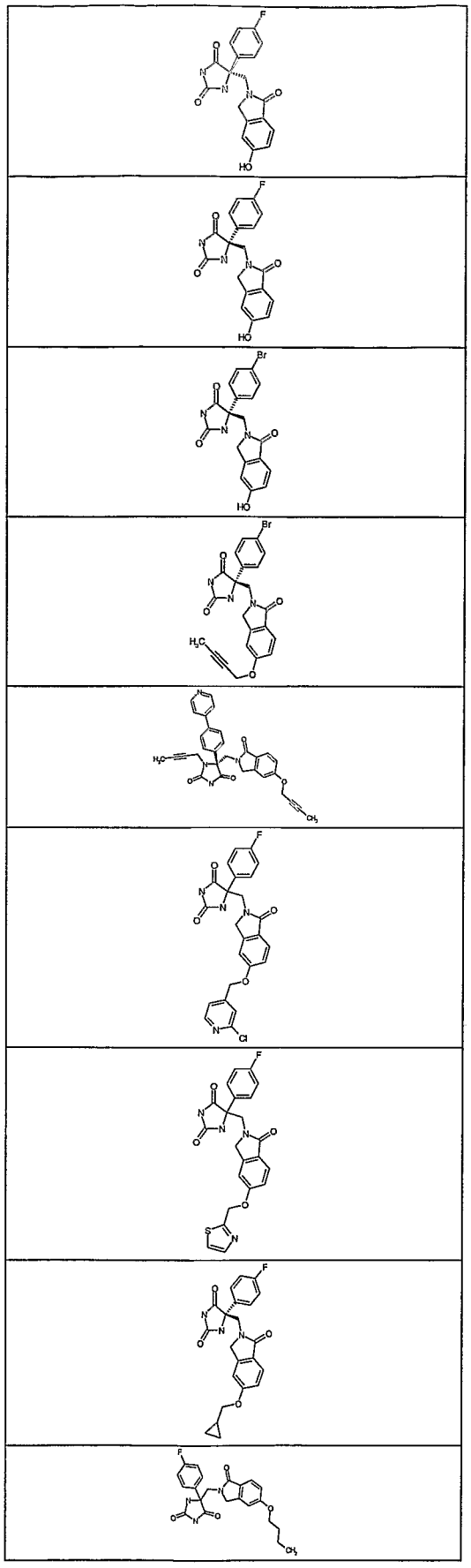


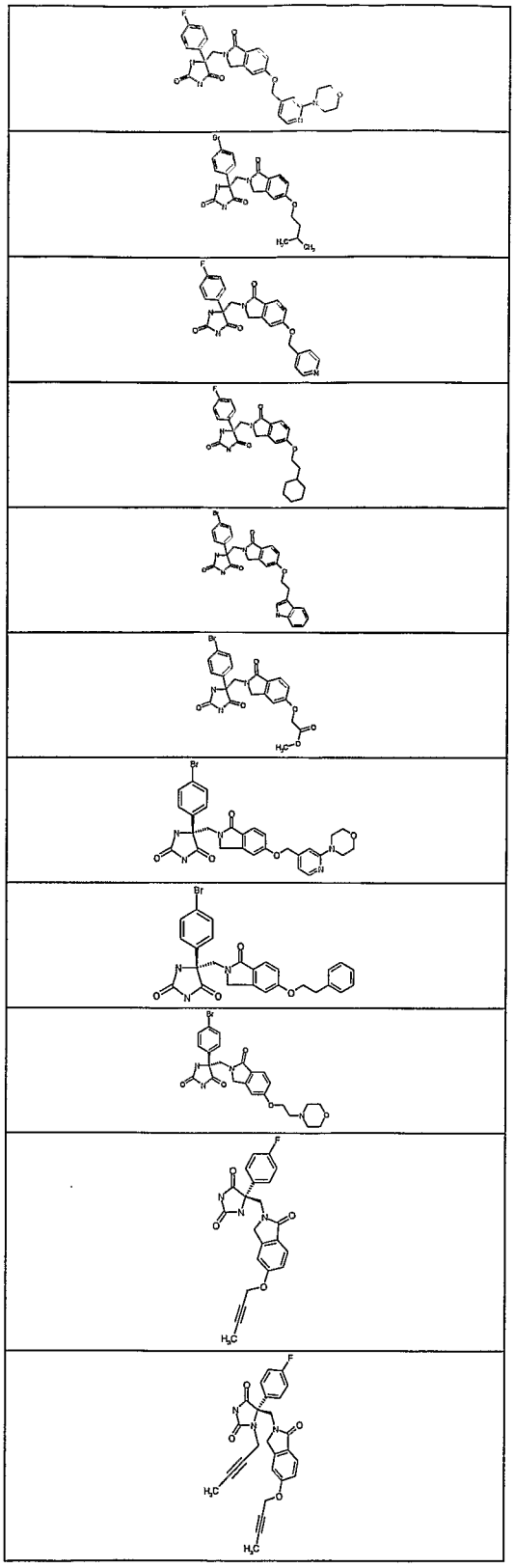


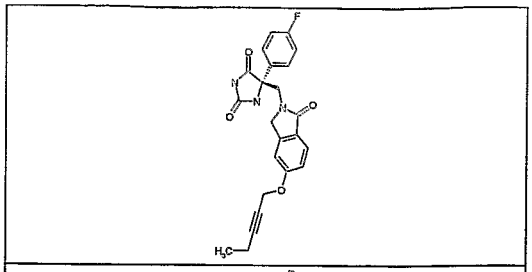


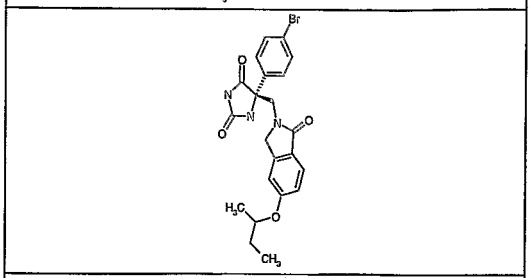


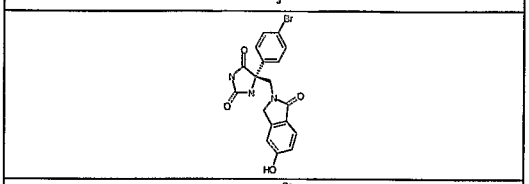


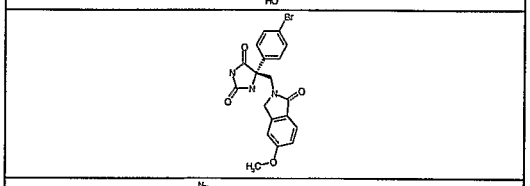


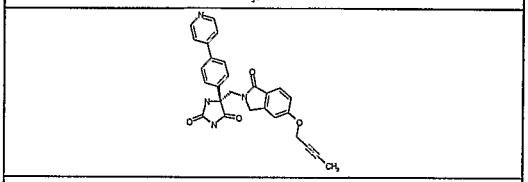


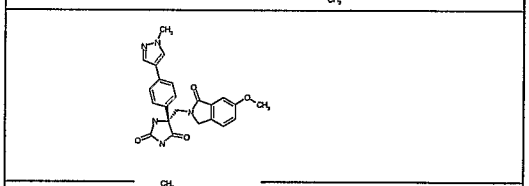


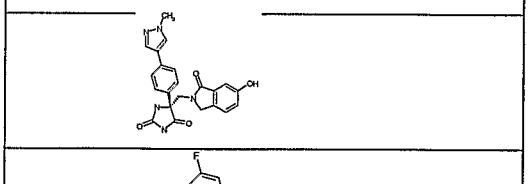


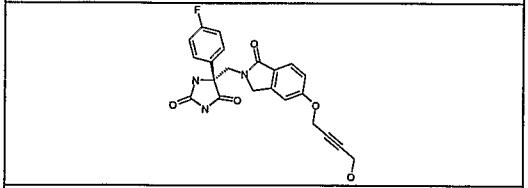


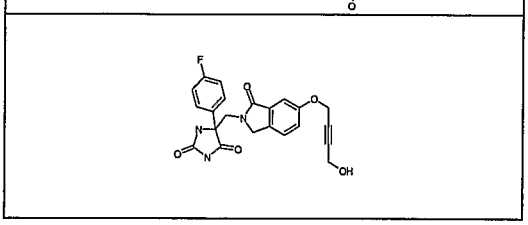


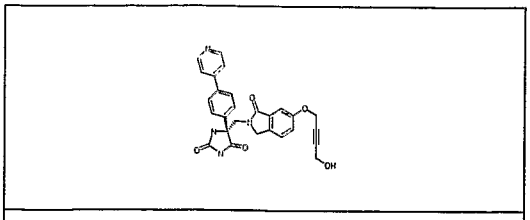


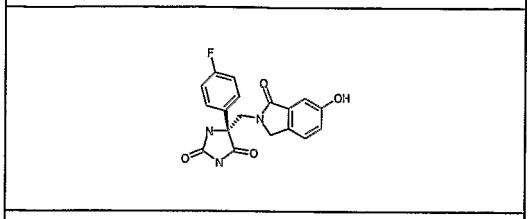


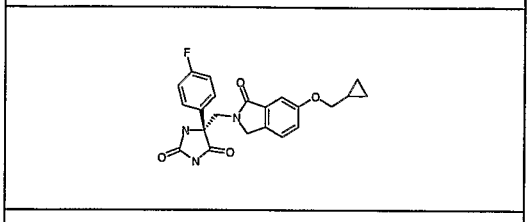


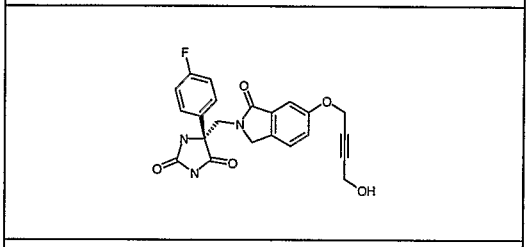


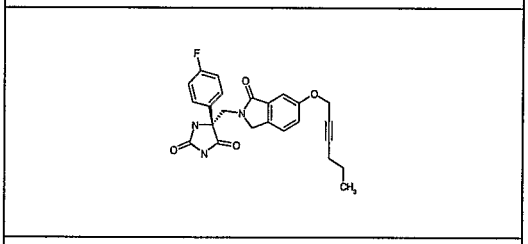


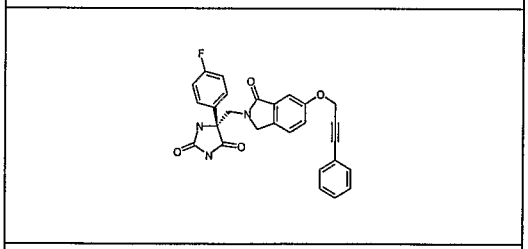


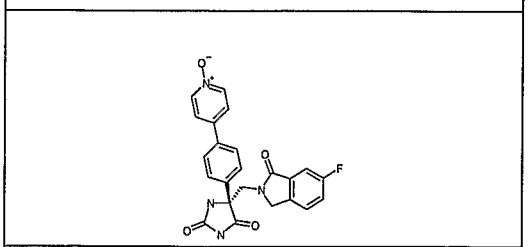


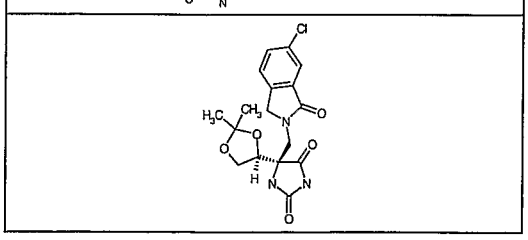


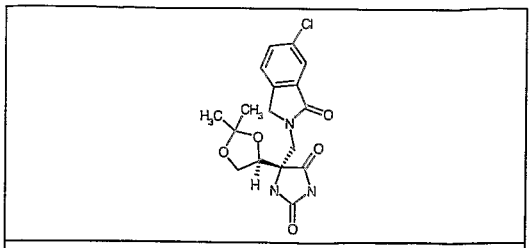


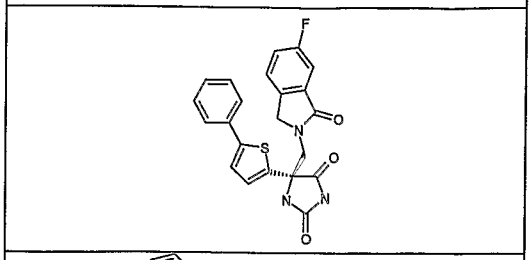


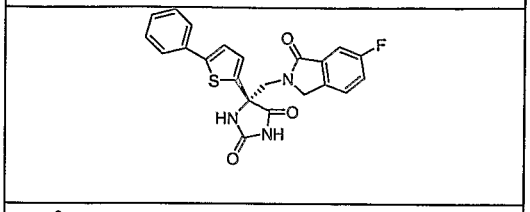


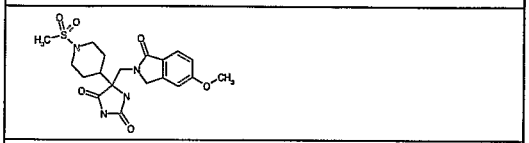


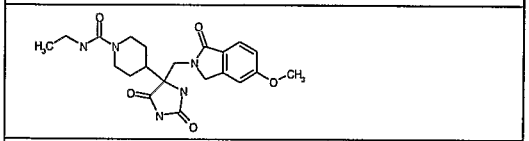


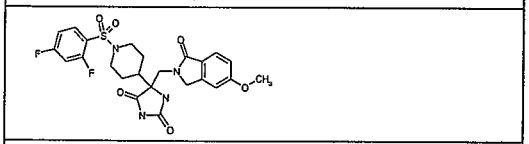


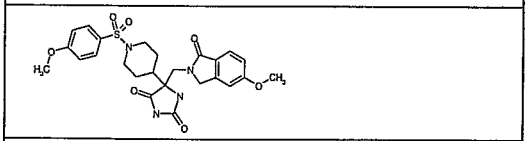


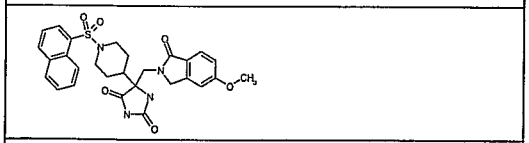


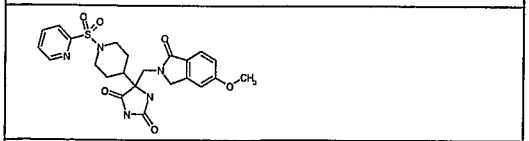


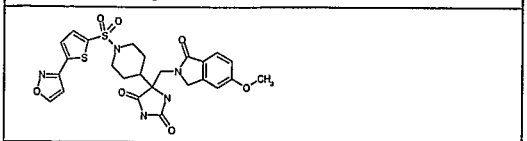


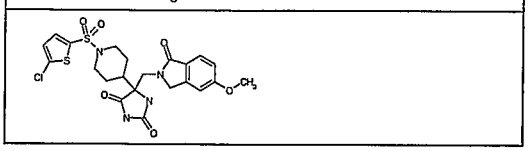


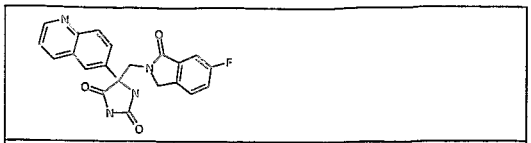


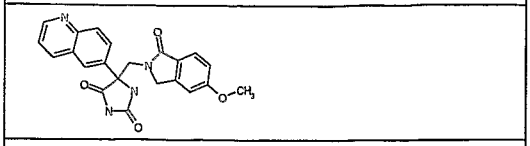


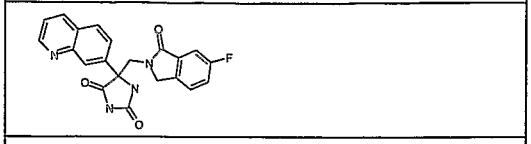


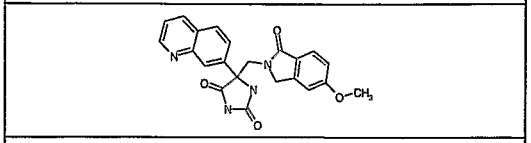


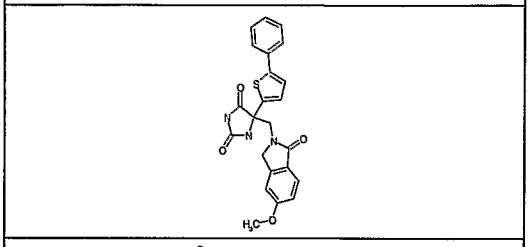


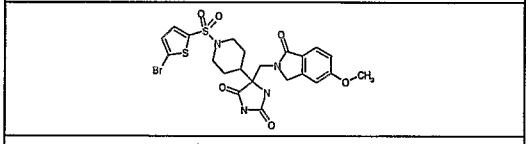


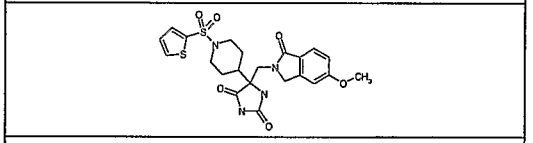


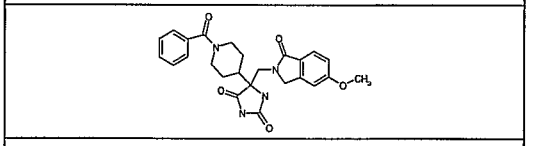


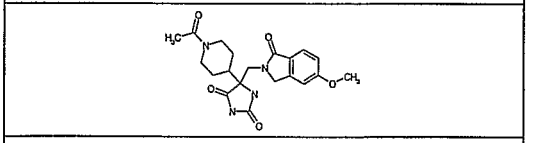


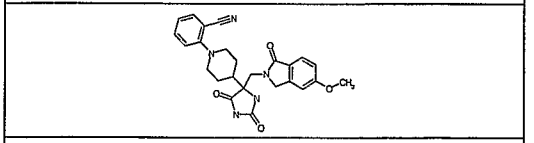


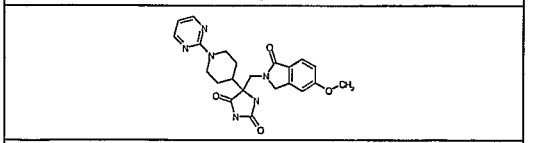


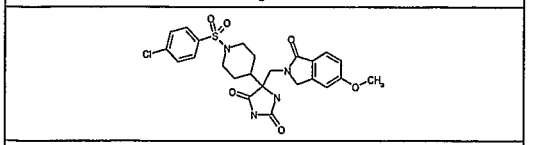


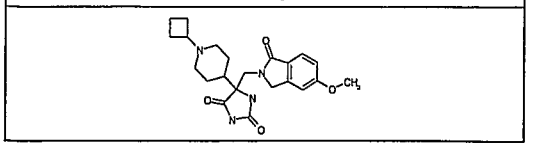


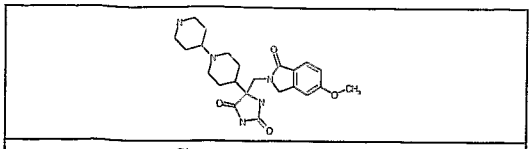


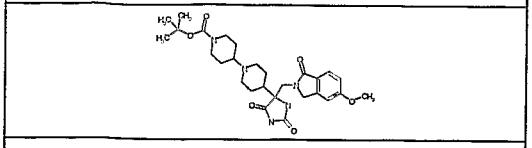


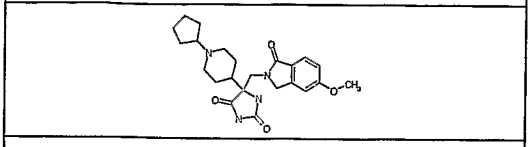


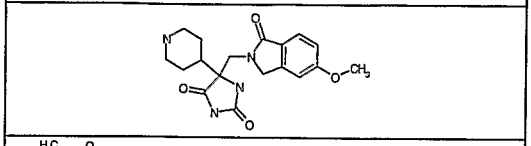


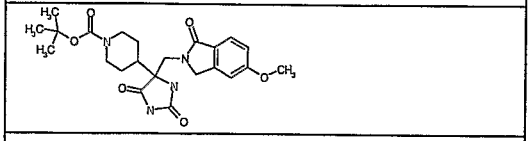


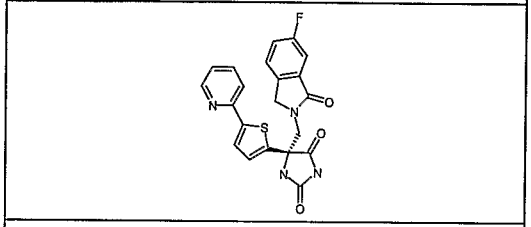


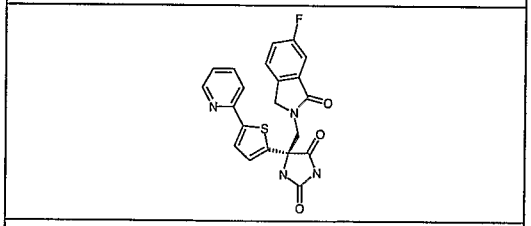


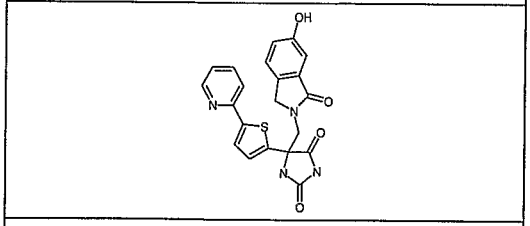


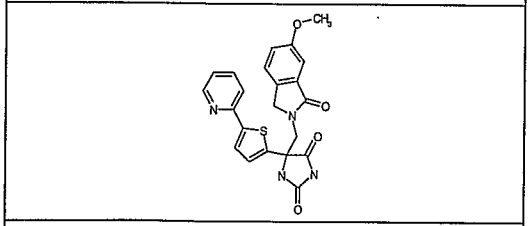


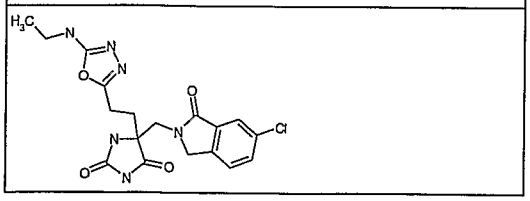


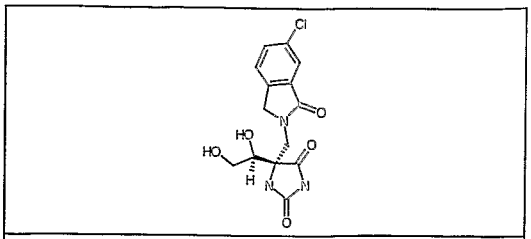


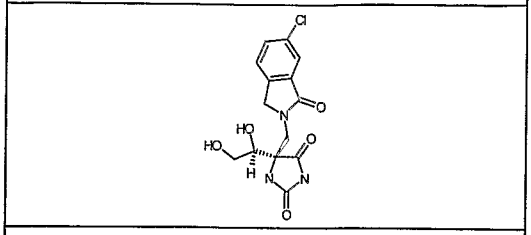


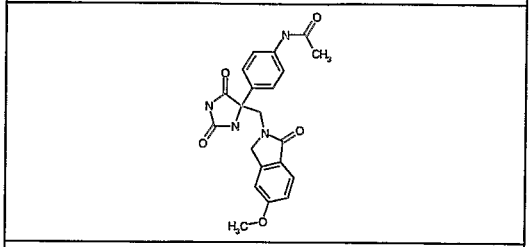


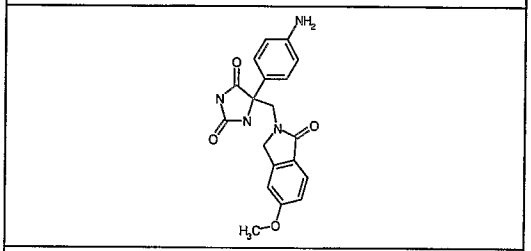


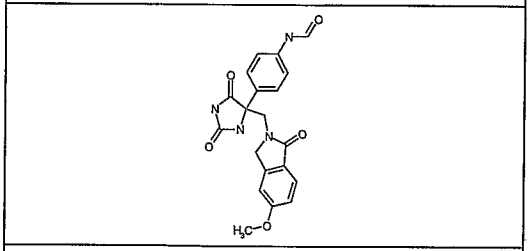


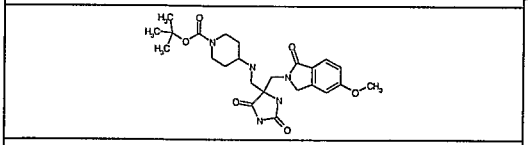


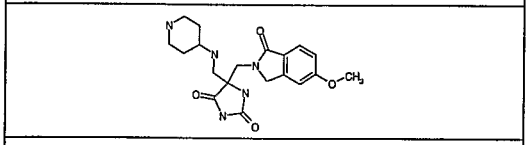


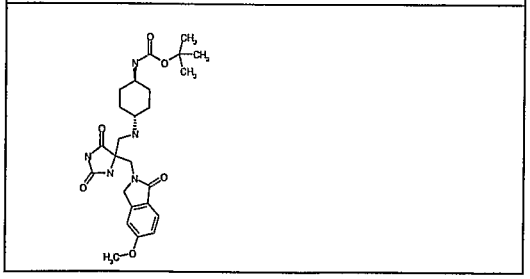


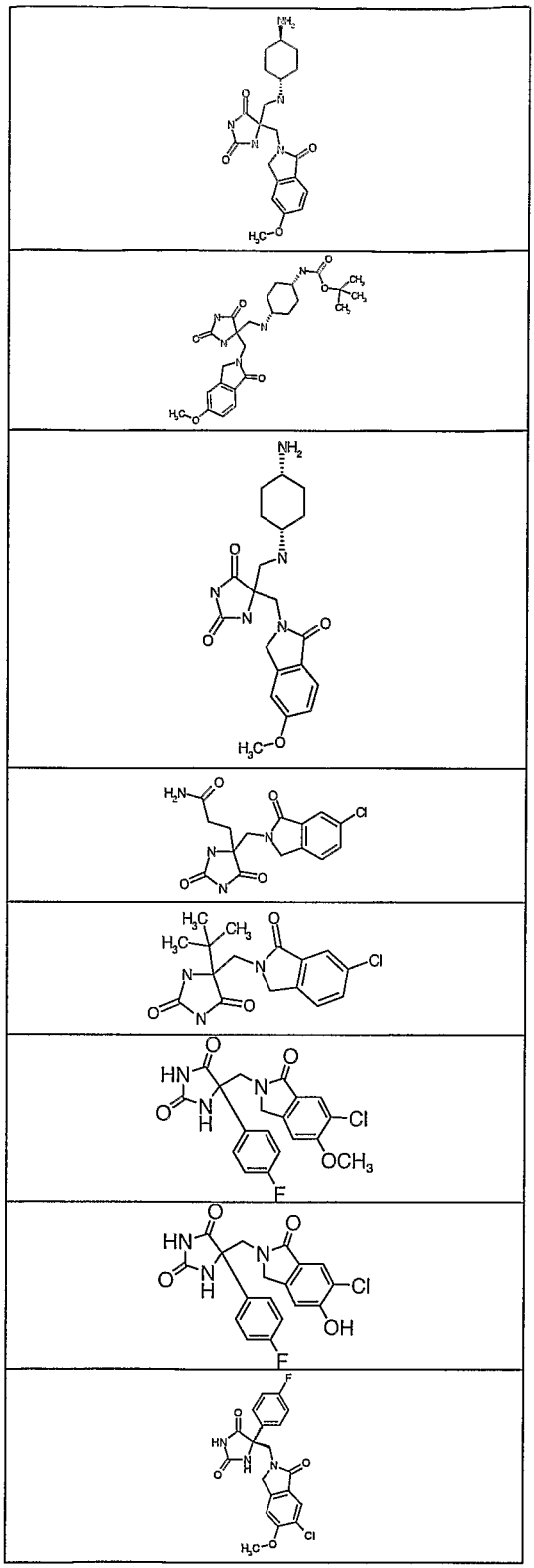






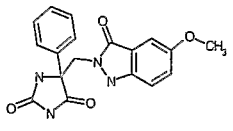
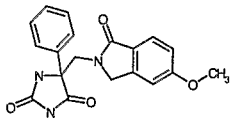
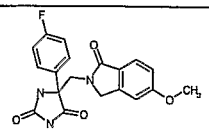
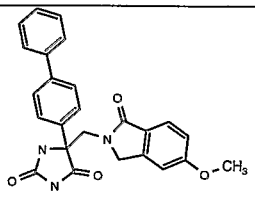
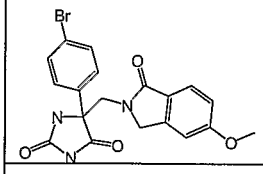
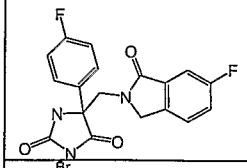
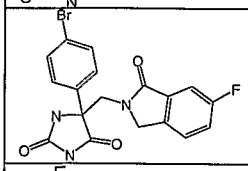
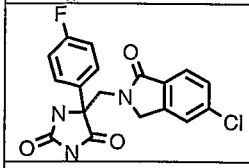
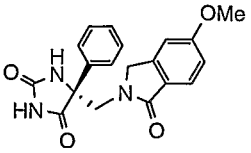


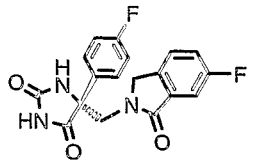


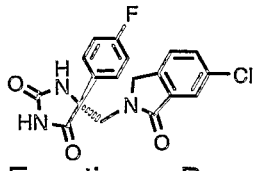


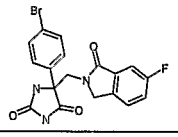
Another embodiment of the invention discloses the preferred compounds shown in Table B below:

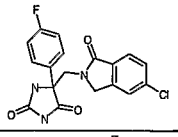
Table B

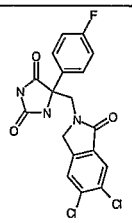
Structure








 Enantiomer A

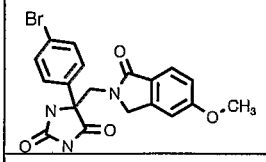

Enantiomer B

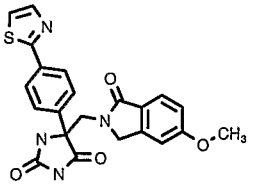

Enantiomer B

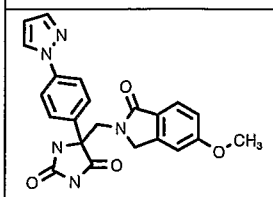


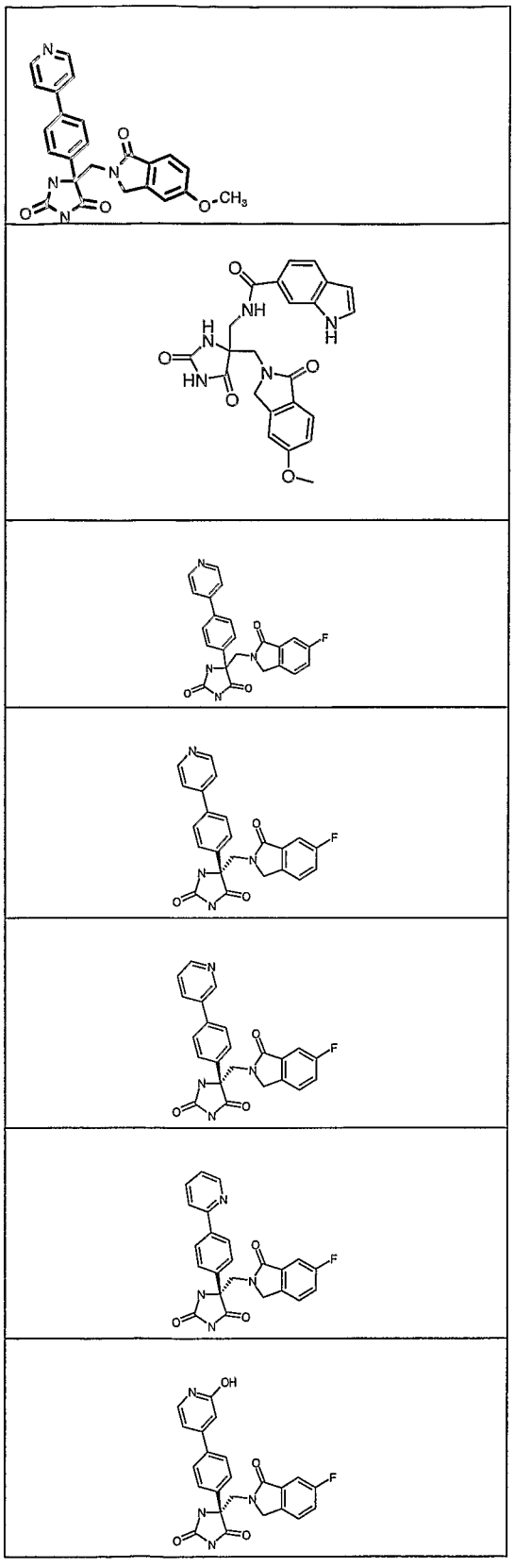


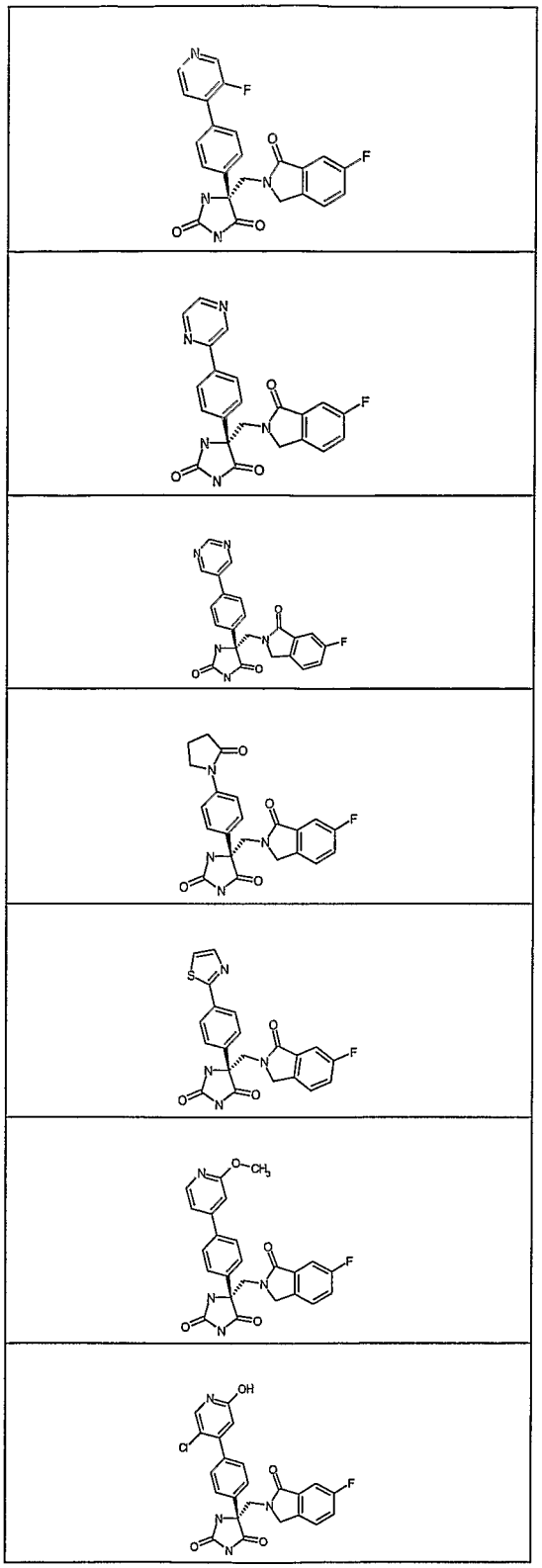


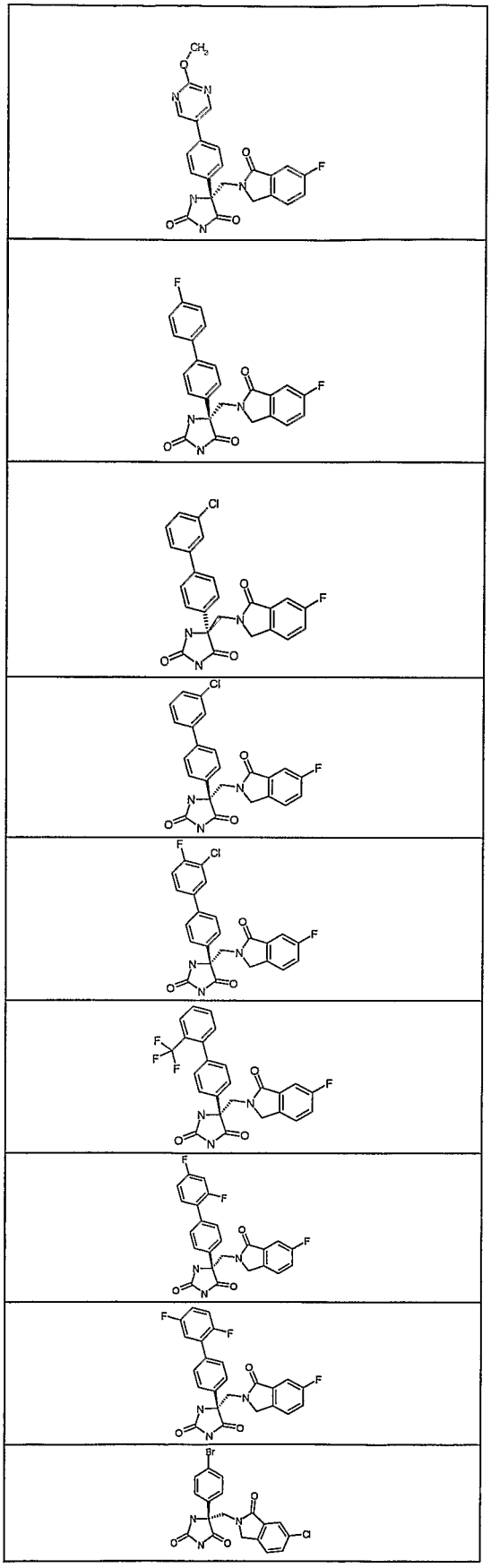


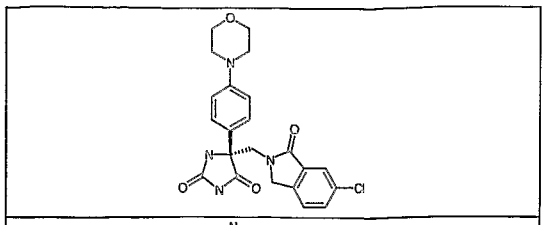


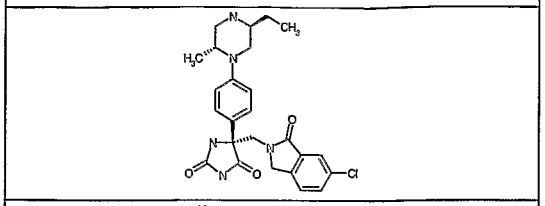


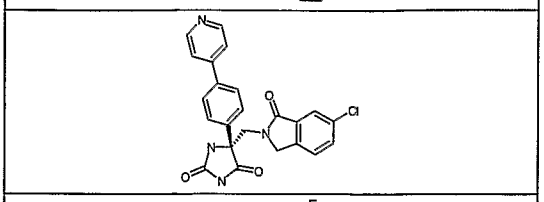


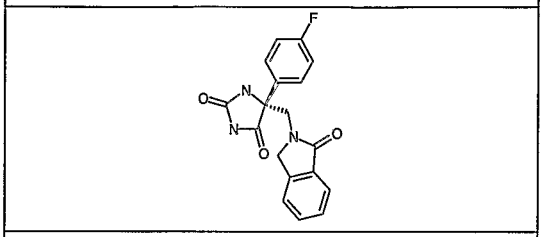


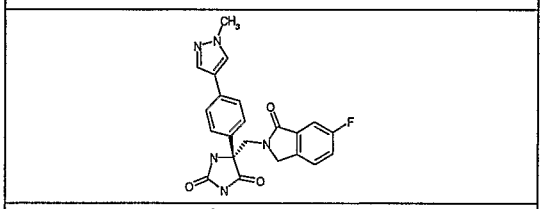


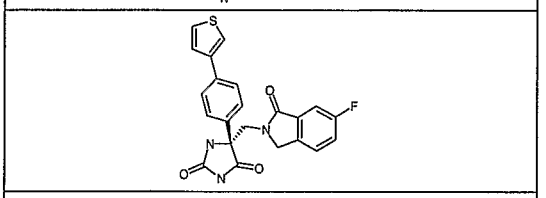


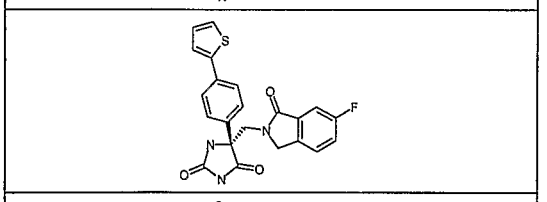


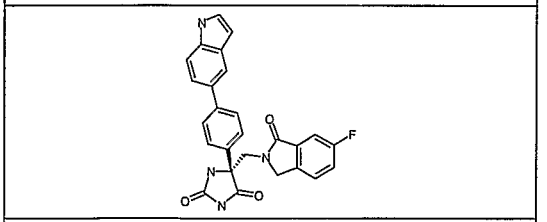


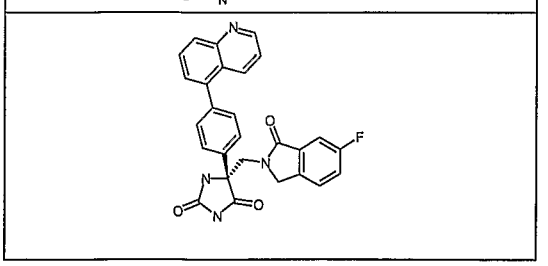


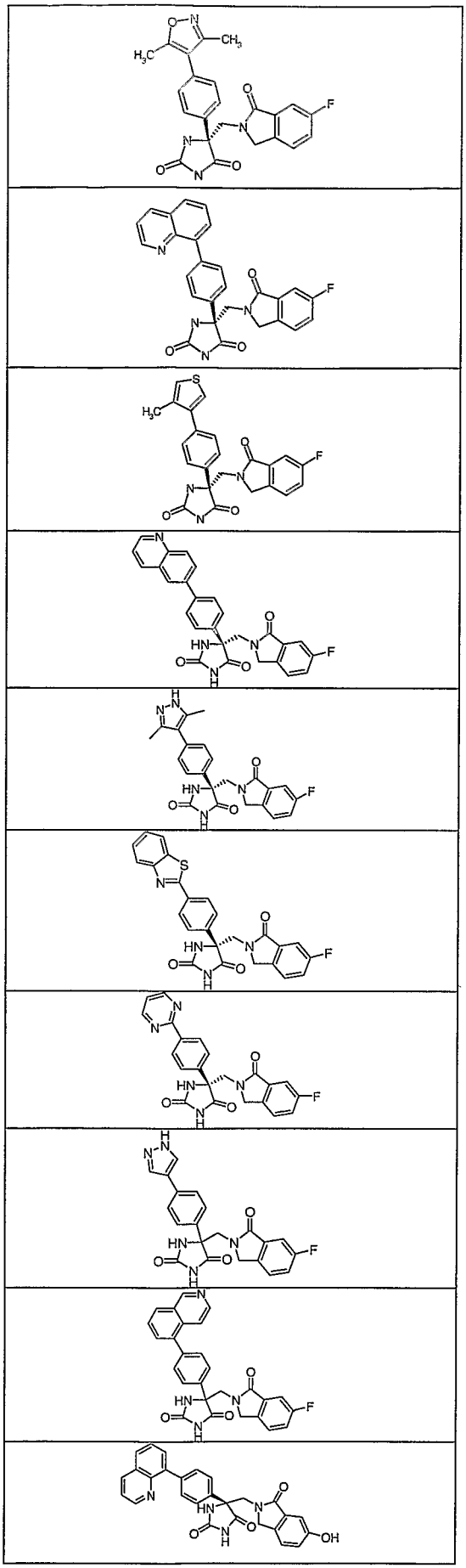


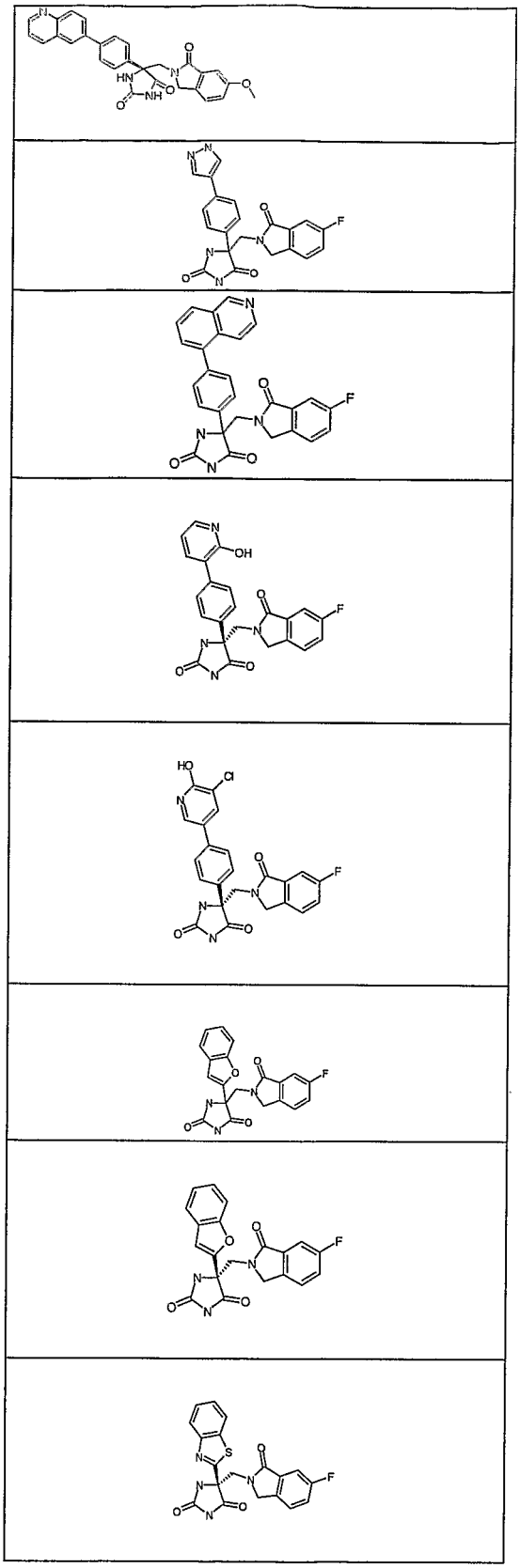


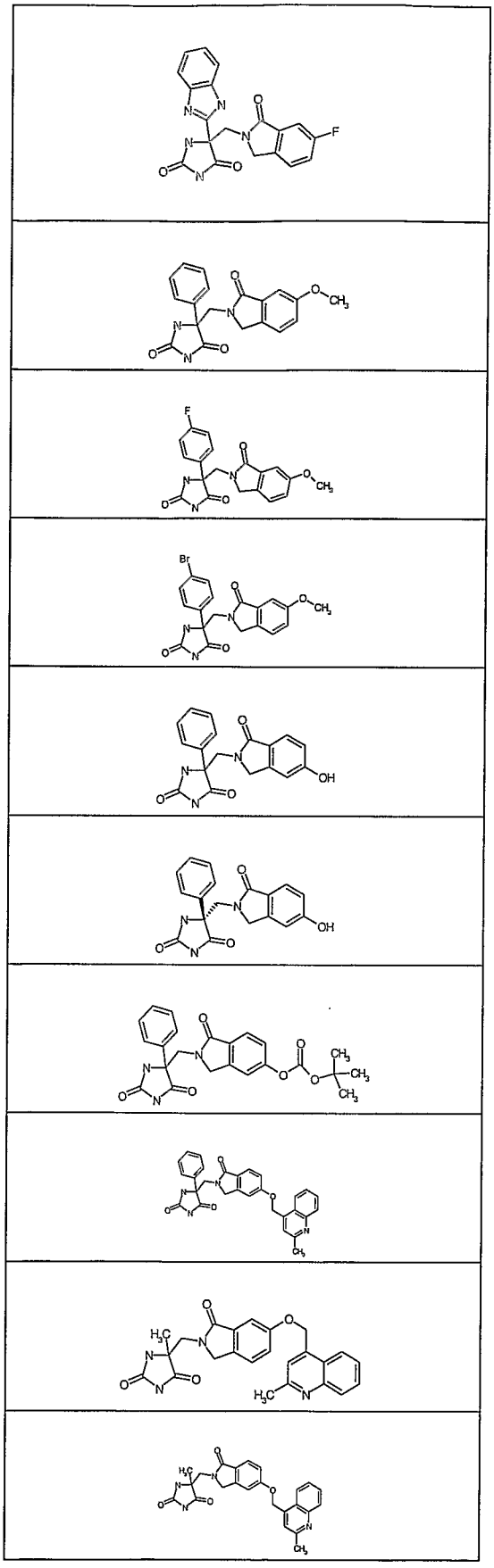


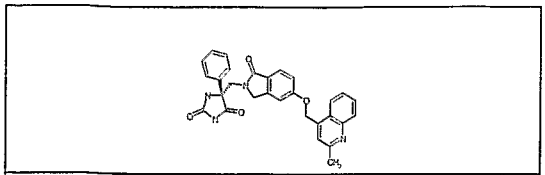


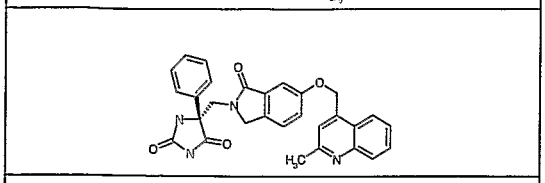


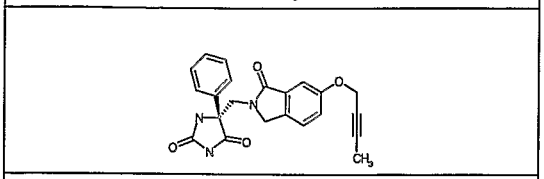


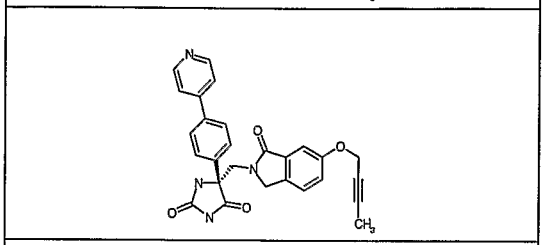


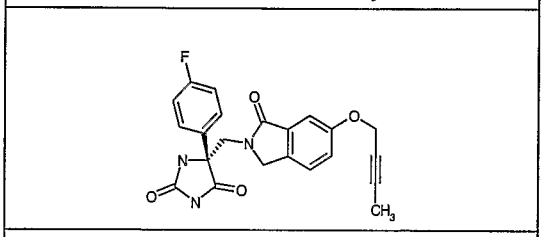


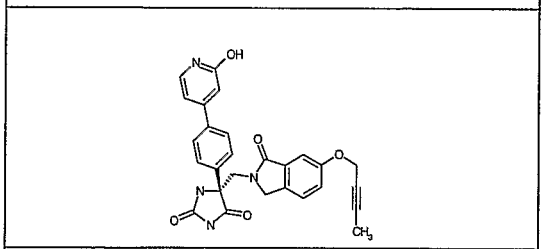


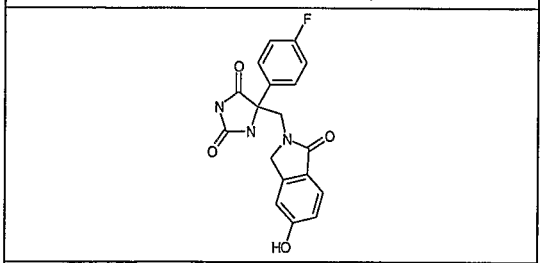


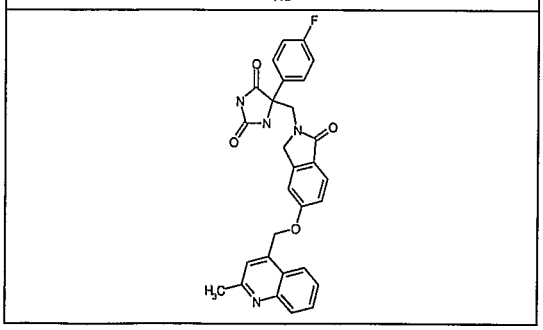


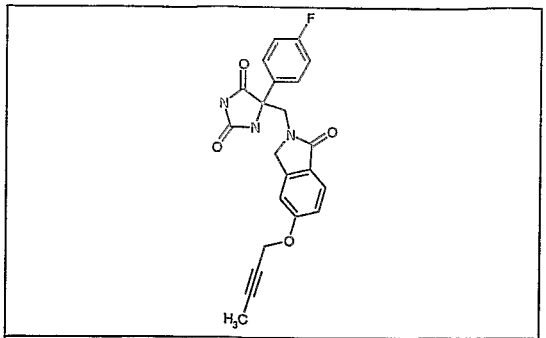


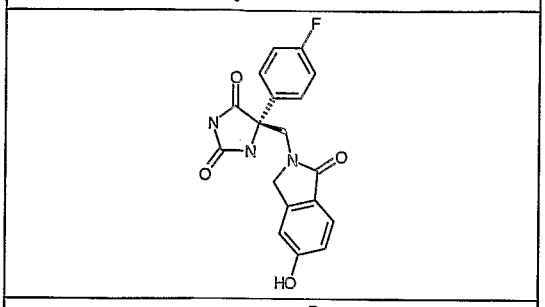


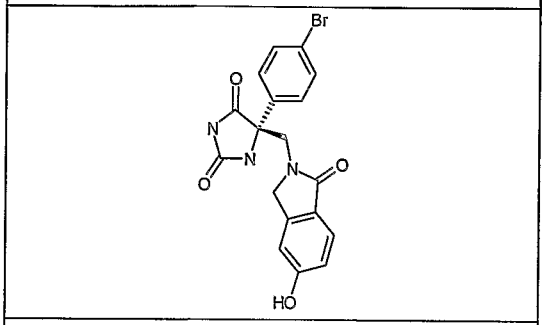


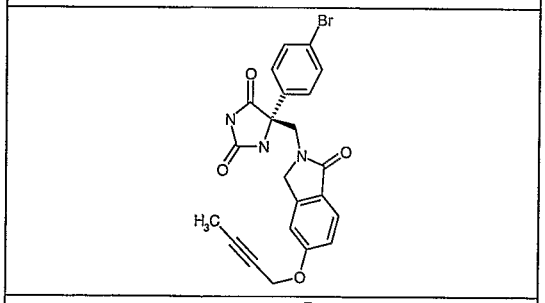


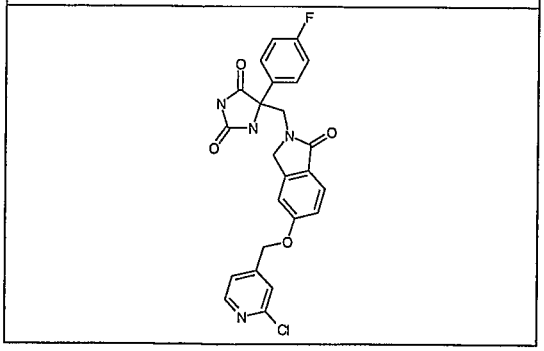


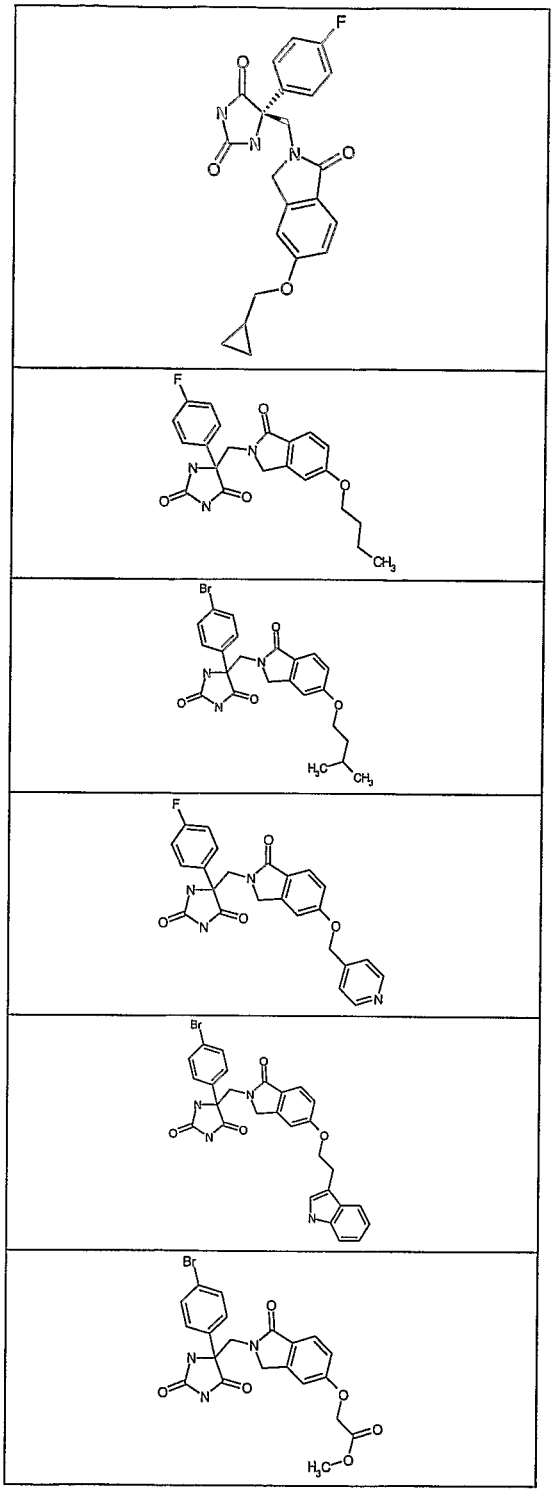


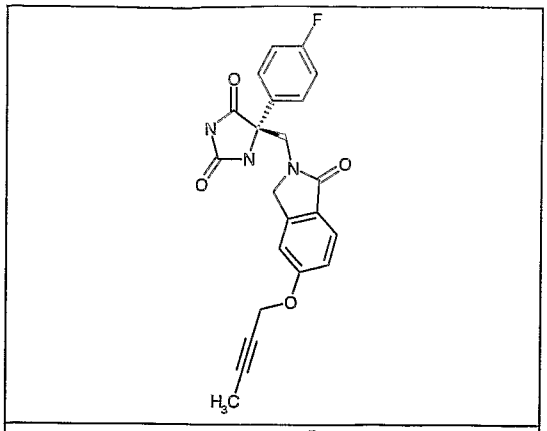


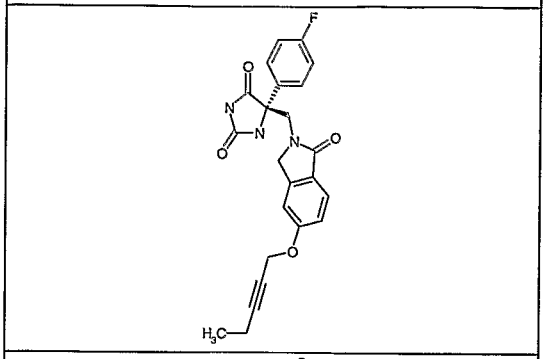


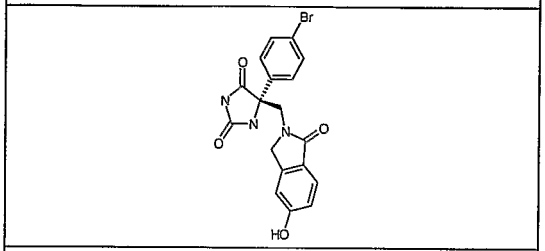


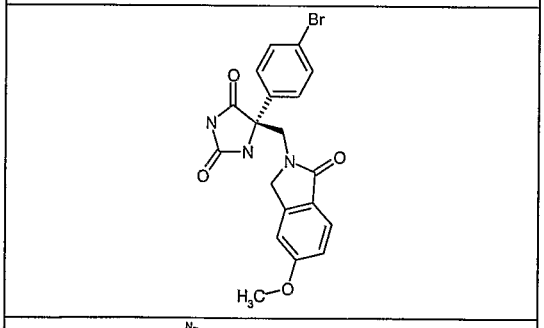


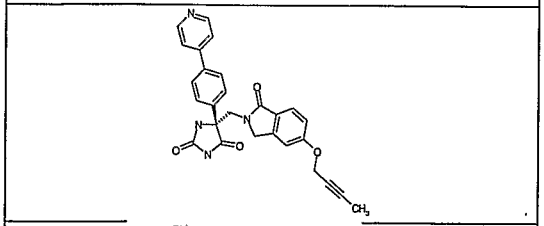


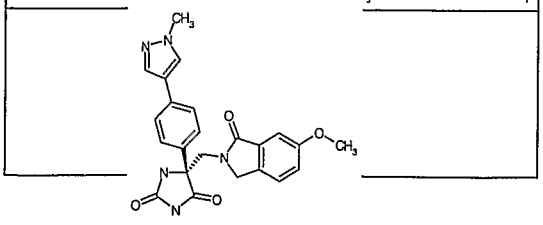


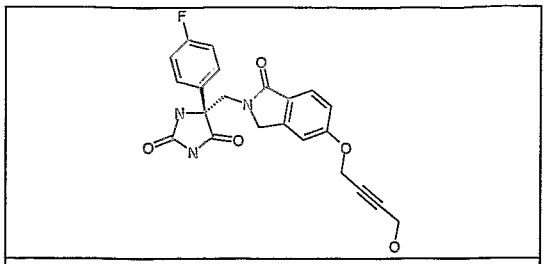


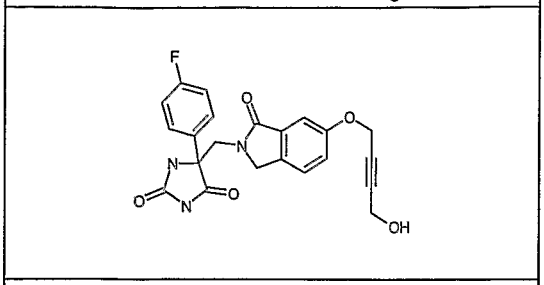


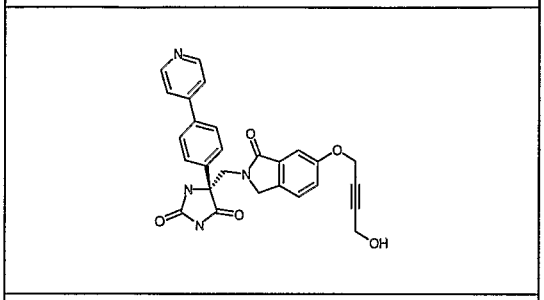


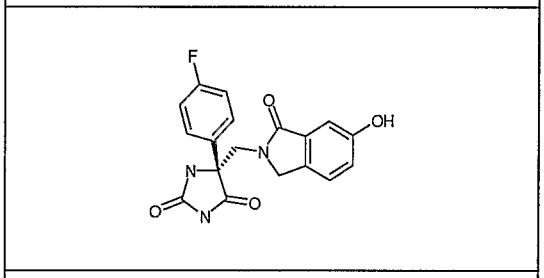


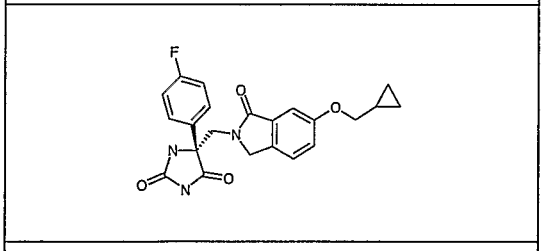


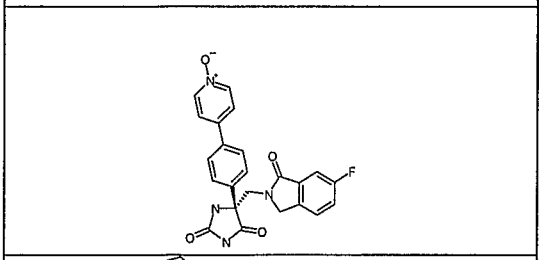


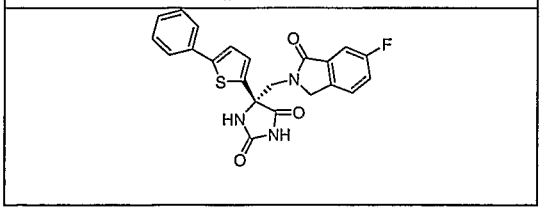


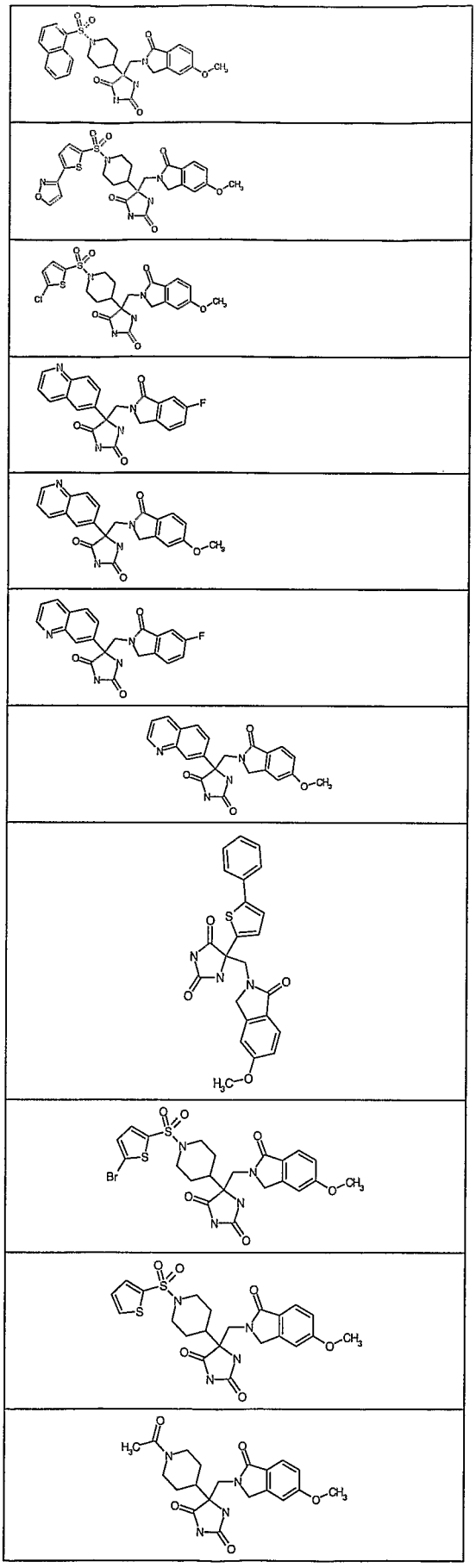


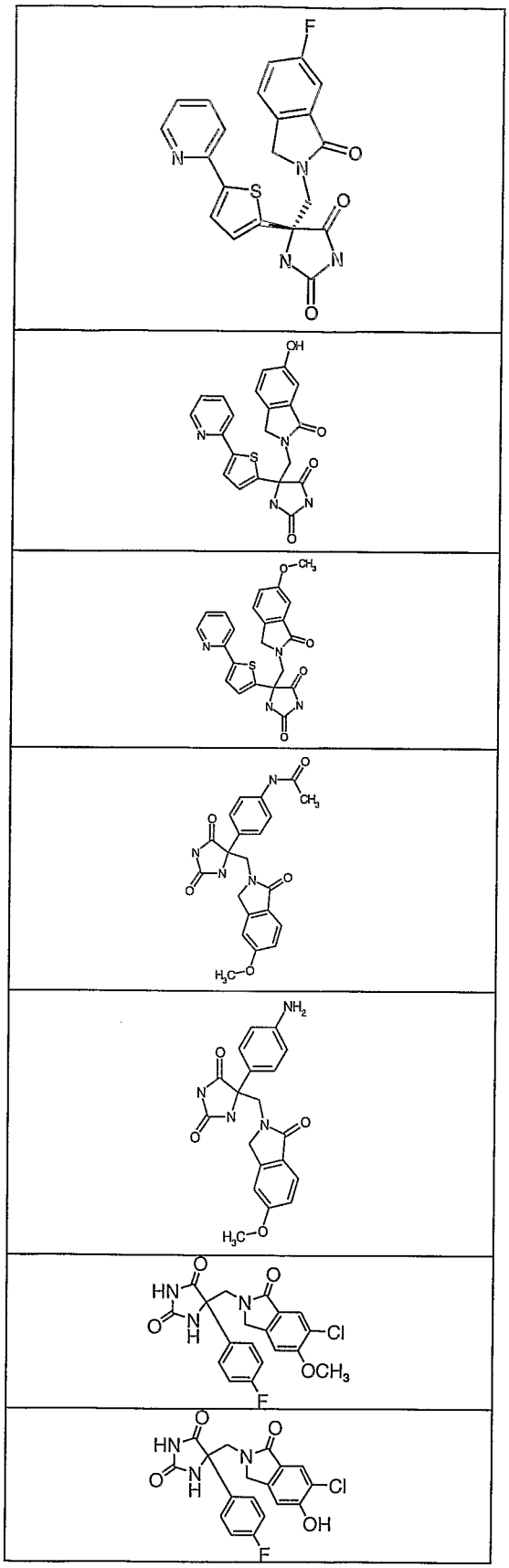






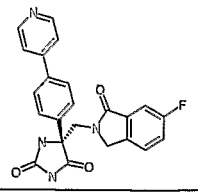
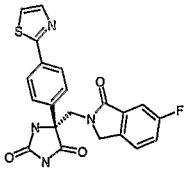
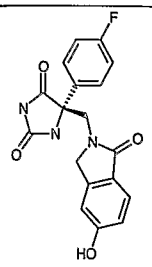
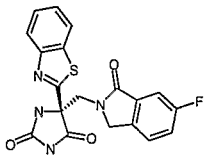
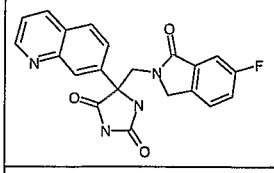
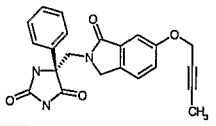
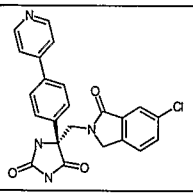


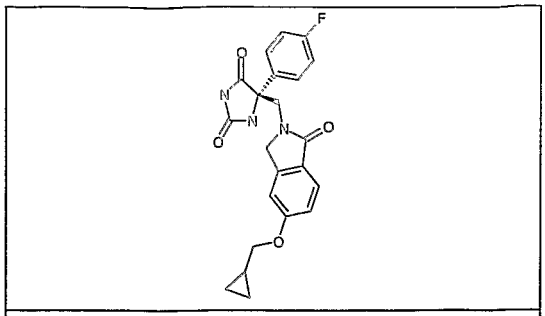


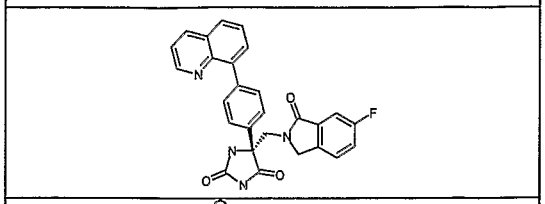


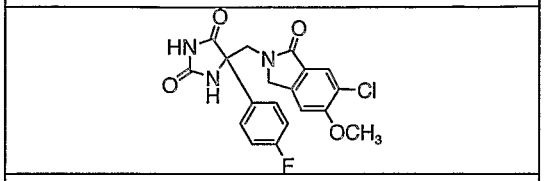
Another embodiment of the invention discloses the more preferred compounds shown in **Table C** below.

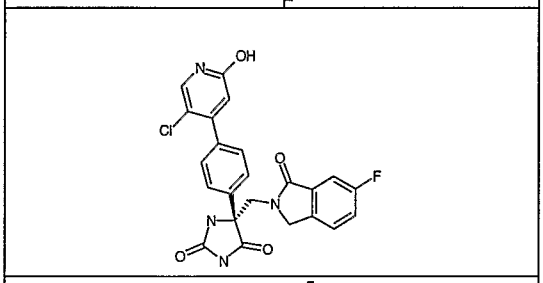
Table C

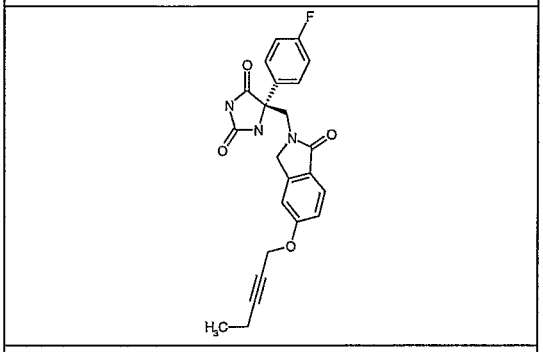
Structure








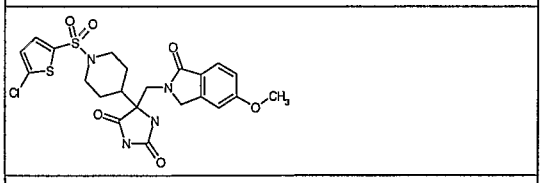


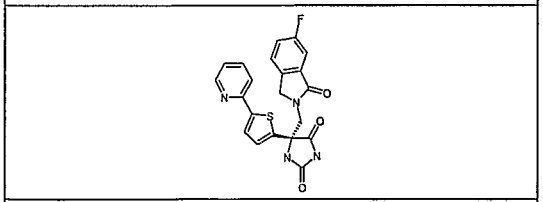


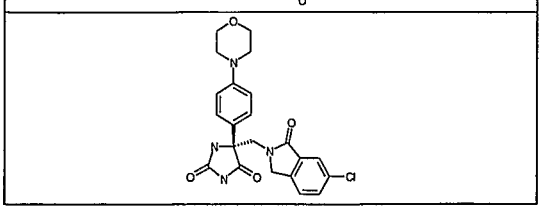


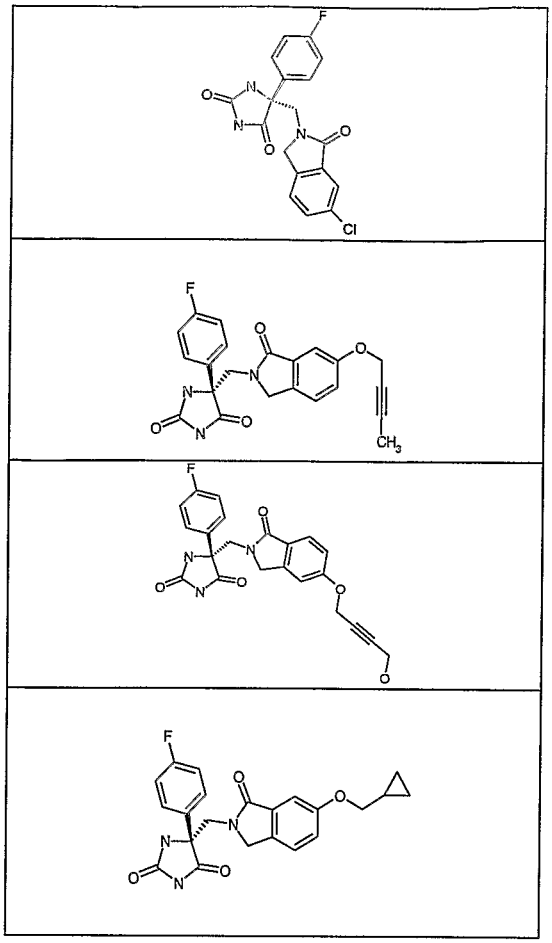












As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

“Mammal” means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl),

-NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring

atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term “heteroaryl” also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or “arylalkyl” means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

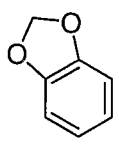
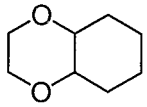
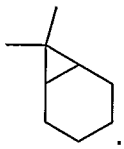
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include

cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

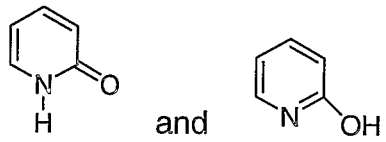
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), G_1G_2N-, G_1G_2N-alkyl-, $G_1G_2NC(O)$-, $G_1G_2NSO_2$- and -$SO_2NG_1G_2$, wherein G_1 and G_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:



and

.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to

about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent

moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is

assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

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 combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates,

methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting TACE, the production of TNF-α, MMPs, ADAMS or any combination thereof and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977)

66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula I, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as

racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be inhibitors of TACE, TNF-α and/or MMP activity.

In one aspect, the invention provides a pharmaceutical composition comprising as an active ingredient at least one compound of formula 1.

In another aspect, the invention provides a pharmaceutical composition of formula 1 additionally comprising at least one pharmaceutically acceptable carrier.

In another aspect, the invention provides a method of treating disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of formula 1.

In another aspect, the invention provides a use of a compound of formula 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof.

The compounds of Formula I can have anti-inflammatory activity and/or immunomodulatory activity and can be useful in the treatment of diseases including but not limited to septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, OA and

RA, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and/or bronchitis. It is contemplated that a compound of this invention may be useful in treating one or more of the diseases listed.

In another aspect, the invention provides a method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of formula 1 and at least one pharmaceutically acceptable carrier.

In another aspect, the invention provides a compound of formula (I) exhibiting TACE, TNF-α, MMPs, ADAMs or any combination thereof inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed in **Table A** set forth above.

In another aspect, the invention provides a pharmaceutical composition for treating disorders associated with TACE, TNF-α, MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a compound of formula 1 in purified form.

In another aspect, the invention provides a method of treating a condition or disease mediated by TACE, MMPs, TNF-α, aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome,

radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with ankylosing spondylitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof, in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

Additionally, a compound of the present invention may be co-administered or used in combination with disease-modifying antirheumatic drugs (DMARDS) such as methotrexate, azathioprine, leflunomide, pencillinamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. They may also be co-administered with or used in combination with non-steroidal anti-inflammatory drugs (NSAIDs) such as

piroxicam, naproxen, indomethacin, ibuprofen and the like; cycloxygenase-2 selective (COX-2) inhibitors such as Vioxx® and Celebrex®; immunosuppressives such as steroids, cyclosporin, Tacrolimus, rapamycin and the like; biological response modifiers (BRMs) such as Enbrel®, Remicade®, IL-1 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, other chemically different TACE inhibitors, chemokine receptor antagonists, Thalidomide and other small molecule inhibitors of pro-inflammatory cytokine production.

Also, a compound of the present invention may be co-administered or used in combination with an H1 antagonist for the treatment of seasonal allergic rhinitis and/or asthma. Suitable H1 antagonists may be, for example, Claritin®, Clarinex®, Allegra®, or Zyrtec®.

In another aspect, the invention provides a method of treating a condition or disease mediated by TACE, MMPs, TNF-α, aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of disease modifying anti-rheumatic drugs (DMARDS), NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1

inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method for treating RA comprising administering a compound of the formula I in combination with compound selected from the class consisting of a COX-2 inhibitor e.g.

Celebrex® or Vioxx®; a COX-1 inhibitor e.g. Feldene®; an immunosuppressive e.g. methotrexate or cyclosporin; a steroid e.g. β-methasone; and anti-TNF-α compound, e.g. Enbrel® or Remicade®; a PDE IV inhibitor, or other classes of compounds indicated for the treatment of RA.

In another aspect, the invention provides a method for treating multiple sclerosis comprising administering a compound of the formula I in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

TACE activity is determined by a kinetic assay measuring the rate of increase in fluorescent intensity generated by TACE catalyzed cleavage of an internally quenched peptide substrate (SPDL-3). The purified catalytic domain of recombinant human TACE (rhTACEc, Residue 215 to 477 with two mutation (S266A and N452Q) and a 6xHis tail) is used in the assay. It is purified from the baculovirus/Hi5 cells expression system using affinity chromatography. The substrate SPDL-3 is an internally quenched peptide (MCA-Pro-Leu-Ala-Gln-Ala-Val-Arg-Ser-Ser-Ser-Dpa-Arg-NH2), with its sequence derived from the pro-TNFα cleavage site. MCA is (7-Methoxycoumarin-4-yl)acetyl. Dpa is N-3-(2,4-Dinitrophenyl)-L-2,3-diaminopropionyl.

A 50 μl assay mixture contains 20 mM HEPES, pH 7.3, 5 mM $CaCl_2$, 100 μM $ZnCl_2$, 2 % DMSO, 0.04% Methylcellulose, 30 μM SPDL-3, 70 pM rhTACEc and a test compound. RhTACEc is pre-incubated with the testing compound for 90 min. at 25 °C. Reaction is started by addition of the substrate. The fluorescent intensity (excitation at 320 nm, emission at 405 nm) was measured every 45 seconds for 30 min. using a fluorospectrometer (GEMINI XS, Molecular Devices). Rate of enzymatic reaction is shown as Units per second. Effect of a test compound is shown as % of TACE activity in the absence of the compound.

Useful compounds for TACE inhibitory activity can exhibit K_i values of less than about 1000 nm, preferably about 0.01 nm to about 1000 nm, more preferably about 0.1 nm to about 100 nm, and most preferably less than about 15 nm. The TACE inhibitory activity (Ki values) of some representative

compounds of the present invention are listed in the "EXAMPLES" section hereinbelow.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for controlled release.

The term pharmaceutical composition is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage

unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules where in the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring

agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, e.g., sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, e.g., olive oil or arachis oil, or a mineral oil, e.g., liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, e.g., soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, e.g., polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, e.g., as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be

employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. The compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The compounds for the present invention can be administered in the intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. Preferably, doses of the compound of Formula I useful in the method of the

present invention range from 0.01 to 1000 mg per day. More preferably, dosages range from 0.1 to 1000 mg/day. Most preferably, dosages range from 0.1 to 500 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 milligrams of the active ingredient, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 1 mg/kg of body weight per day.

Advantageously, the active agent of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in dividend doses of two, three or four time daily.

The amount of active ingredient that may be combined with the carrier materials to produce single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route or administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the invention may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below.

EXAMPLES

The following abbreviations are used in the procedures and schemes:

ACN	Acetonitrile
AcOH	Acetic acid
Aq	Aqueous
BOC	tert-Butoxycarbonyl
BOC-ON	[2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitril]
BOC_2O	BOC Anhydride

C	degrees Celsius
CBZCl	Benzyl chloroformate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
(DHQ)2PHAL	Hydroquinine 1,4-phthalazinediyl diether
DIAD	Diisopropylazodicarboxylate
DIPEA	Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1h)-pyrimidinone
DMSO	Dimethyl sulfoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron ionization
Eq	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
g	grams
h.	hours
^{1}H	proton
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HOBT	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
M	Molar
mmol	milimolar
mCPBA	*meta*-Chloroperoxybenzoic acid

Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mg	Milligrams
MHZ	Megahertz
mL	Milliliter
MPLC	Medium Pressure Liquid Chromatography
NMR	Nuclear Magnetic Resonance
MS	Mass Spectroscopy
NBS	N-Bromosuccinimide
NMM	N-Methylmorpholine
NMP	1-methyl-2-pyrrolidone
ON	Overnight
PCC	Pyridinium Chlorochromate
PTLC	Preparative thin layer chromatography
PyBrOP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Pyr	Pyridine
RT	Room temperature
sgc	Silica gel 60 chromatography
tBOC	tert-Butoxycarbonyl
TACE	TNF-alpha converting enzyme
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

NMR spectra were acquired on the following instruments: 400 MHZ NMR (Bruker), 500 MHZ NMR (Bruker), 400 MHz NMR (Varian), 300 MHZ NMR (Varian) using CD_3OD, $CDCl_3$ or DMSO-d_6 as solvents. LC-MS data were obtained using a PESciex API 150EX quadropole mass spectrometer using electroscopy ionization.

Purification via reverse phase chromatography (Gilson) was accomplished using a C18 reverse phase column with a gradient of (0.1 %

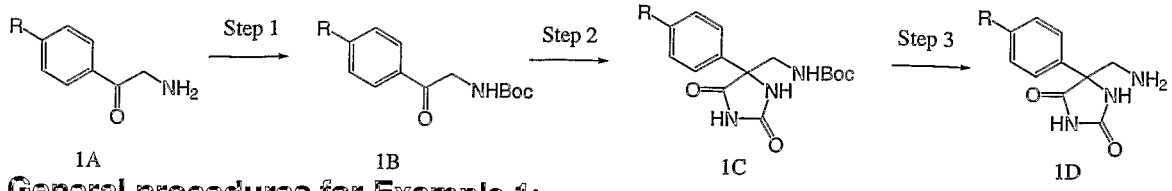
formic acid) 5:95 to 90:10 acetonitrile:water, at a flow rate of 14 mL/min. Samples were collected using UV detection. Alternatively an ISCO Companion with (0.1% formic acid) 5:95 to 95:5 acetonitrile:water, at a flow rate = 10 - 55 mL/min.

Normal phase silica gel chromatography was either accomplished on a Biotage instrument using a 60 Å 12/M, 25/M, or 40/M flash cartridges, or on a Jones Flash Master Personal instrument using Isolute flash SI 5g, 10g, 20g, 50g, or 70 g cartridges.

The compounds of formula (I) may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below. These preparations and examples should not be construed to limit the scope of the disclosure. Alternate mechanistic pathways and analogous structures may be apparent to those skilled in the art. Some of the compounds made by these processes are listed in the tables below. All kinds of isomeric forms of the compounds are considered to be within the scope of this invention.

SYNTHETIC ROUTES AND EXAMPLES

Example 1



1A 1B 1C 1D

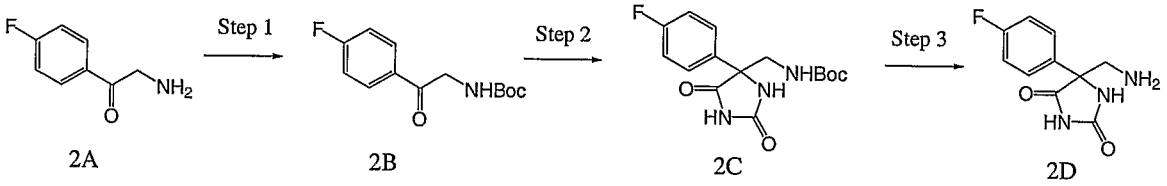
General procedures for Example 1:

In step 1, Compound 1A (either commercially available, or prepared by a procedure similar to that described by Abdalla, G. M. and Sowell, J. W. *Journal of Heterocyclic Chemistry*, 1987, *24*(2), 297-301) was treated with one equivalent of Di-tert-butyl dicarbonate in polar solvent, such as DMF, for 30 minutes to 12 hours. The solvent was removed and compound 1B could be used without further purification or purified by silica gel chromatography.

In step 2, compound 1B was reacted with potassium cyanide and ammonium carbonate in appropriated alcohol and water solution, at 50 °C to 90 °C, for 5 hours to 48 hours. After cooling down, water was added and compound **1C** could be collected by filtration.

In step 3, compound **1C** was stirred with 2 to 20 equivalents of hydrogen chloride in methanol for 5 to 48 hours. After ethyl ether was added, compound **1D** could be collected by filtration.

Example 2



2A 2B 2C 2D

Step 1

Compound **2A** (Abdalla, G. M. and Sowell, J. W. *Journal of Heterocyclic Chemistry*, **1987**, *24*(2), 297-301) (Hydrochloride salt, 8.60g, 45.4 mmol), triethyl amine (19.0 mL, 136 mmol), and di-tert-butyl dicarbonate (11.9g, 54.4 mmol) were stirred in methylene chloride (100 mL) at 25 °C for 16 hours.

Saturated aqueous $NaHCO_3$ (150 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (100 mL) twice. The organic phase was washed with brine (100 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporator to give compound **2B** which was used without further purification.

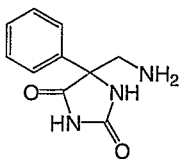
Step 2

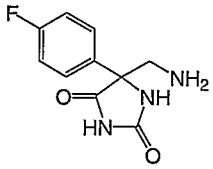
Compound **2B** (9.06g, 35.8 mmol), KCN (3.49g, 53.7 mmol), and $(NH_4)_2CO_3$ (12.0 g, 125.2 mmol) were suspended in a mixture of EtOH (35 mL) and water (35 mL). The solution was stirred at 70 °C for three days. After cooling down, water (35 mL) was added. The solid was filtered and washed with water three times. The solid was dried under vacuum at 40 °C for 16 hours to give compound **2C** (7.9 g, 68%).

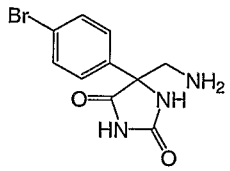
Step 3

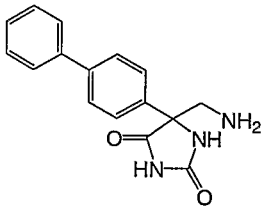
Compound **2C** (4.0 g) was suspended in methanol (50 mL) and HCl (4M in dioxane, 20 mL) was added. The solution was stirred at 25 °C for 3 hours. Ethyl ether (50 ml) was added. The solid was filtered, washed with ethyl ether twice, and dried under vacuum for 12 hours to give compound **2D** (2.7 g, 84%).

The following intermediates were prepared as described in **Examples 1 and 2.**

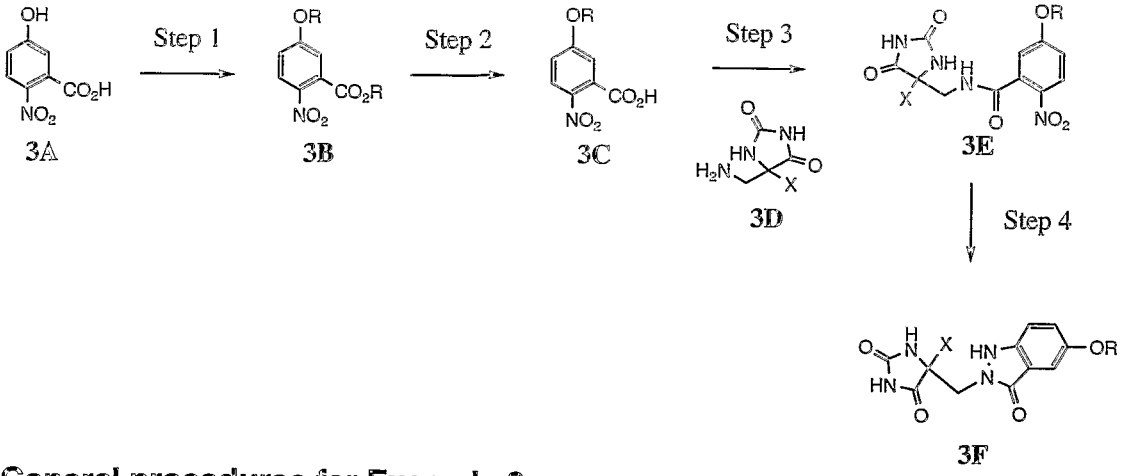








Example 3



General procedures for Example 3

In step 1, 5-Hydroxy-2-nitro-benzoic acid (compound 3A) was dissolved in a suitable solvent, such as DMF, and reacted with an alkyl chloride or alkyl bromide in the presence of cesium carbonate at room temperature for 2 to16 hours. Water and EtOAc were added. The organic phase was washed by water 1 to 5 times to remove DMF. The organic phase was washed with brine, dried, concentrated to give the crude product (compound **3B**) which was used without further purification.

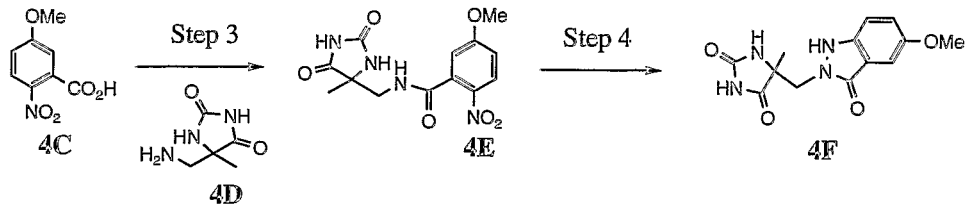
In step 2, compound **3B** was dissolved in dioxane/water (3:1) and treated with lithium hydroxide at room temperature for 3 to 6 hours. The solution was made acidic by addition of 1N HCl solution and extracted with EtOAc. The products (compound **3C**) were either used without further purification or purified by chromatography depending on the boiling point of the alcohol side products.

In step 3, compound **3C** was dissolved in a suitable solvent, such as DMF, and coupled with compound **3D** using EDCI and HOBT at room temperature overnight. After an aqueous/EtOAc work up, the product (compound **3E**) was isolated by chromatography.

In step 4, compound **3E** was suspended in MeOH/water (1:1) under N_2 atmosphere. NaOH and Zinc powder were added and the reaction mixture

was stirred at 70 °C to 80 °C for 8 to 24 hours. After cooling to room temperature, the solution was adjusted to pH=6~7 with 1N HCl solution. The product (compound 3F) was extracted with EtOAc and purified by reverse phase HPLC.

Example 4



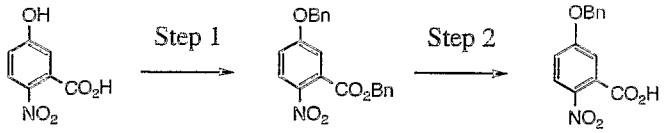
Step 3

A 25 mL flask was charged with compound 4C (331 mg, 1.68 mmol), compound 4D (Stratford, E. S. and Curley, R. W. Jr, *J. Med. Chem.* 1983, *26*, 1463-1469) (200 mg, 1.4 mmol), EDCI (403 mg, 2.1 mmol), HOBT (227 mg, 1.68 mmol), NMM (0.46 mL, 4.2 mmol), and DMF (7 mL). The solution was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (50 mL) were added. The organic phase was separated and washed with water (20 mL) and brine (20 mL), then dried over Na_2SO_4. The solvent was evaporated and the crude product was isolated by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH 20:1:0.1 to 10:1:0.1) to give compound **4E** (201 mg, 45%).

Step 4

To a 10 mL flask was added compound **4E** (50 mg, 0.155 mmol), NaOH (25 mg, 0.62 mmol), Zinc powder (62 mg, 0.47 mmol), MeOH (0.5 mL), and water (0.5 mL). The solution was stirred at 75 °C for 16 hours. After cooling to room temperature, solid was removed by filtration. The filtrate was adjusted to pH=5 by adding 2N HCl. The aqueous phase was extracted by EtOAc (10 mL). The organic solution was dried over Na_2SO_4 and concentrated. The product was isolated by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 40:1:0.1 to 20:1:0.1 to 10:1:0.1) to give compound **4F** 6.5 mg (14%).

Example 5



5A 5B 5C

Step 1

Compound 5A (1.33 g, 7.26 mmol), benzyl bromide (2.73 g, 16.0 mmol), and Cs_2CO_3 (7.1 g, 22.0 mmol) were mixed in DMF (30 mL) and stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (100 mL) was added and the aqueous phase was extracted with EtOAc (100 mL) twice. The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The product was isolated by silica gel chromatography (Hexane/EtOAc: 10:1 to 5:1) to give compound 5B (2.25 g, 89%).

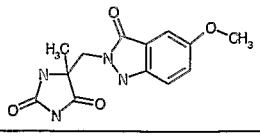
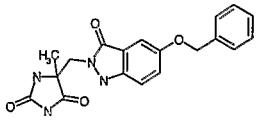
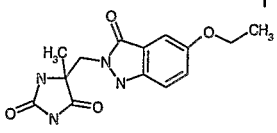
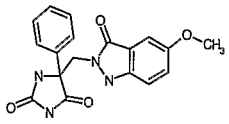
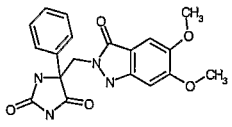
Step 2

Compound **5B** (2.25 g, 6.44 mmol) was dissolved in dioxane/water (3:1, 35 mL) and LiOH (810 mg, 19.3 mmol) was added. The solution was stirred at room temperature for 3 hours. Water (30 mL) was added followed by addition of 2N HCl (30 mL). The aqueous phase was extracted with EtOAc (50 mL) three times. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH/HCO_2H: 40:1:0.1 to 20:1:0.1) to give compound **5C** (1.6 g, 91%).

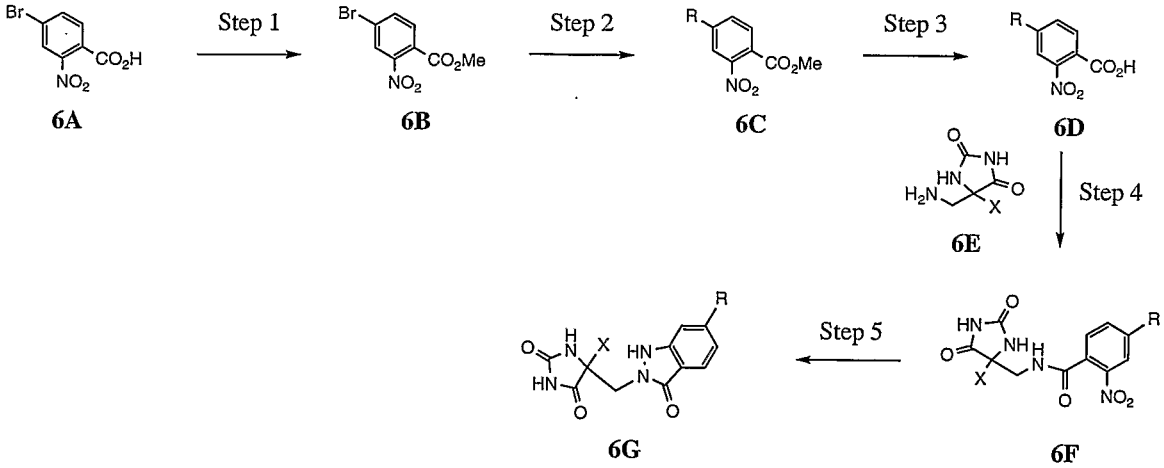
The following compounds were prepared as described in **Examples 3-5.**

In each of the tables below, those compounds having a Ki value of less than 10 nM (<10 nM) are designated with letter "A"; those with a Ki value of from 10 to less than 100 nM (10 - <100 nM) are designated with letter "B"; those with a Ki value of from 100 to 1000 nM are designated with letter "C"; and those with a Ki value of more than 1000 nM (>1000 nM) are designated with letter "D".

Table 1

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
1		290.27	291.1 $[M+H]^+$	B
2		366.13	367.1 $[M+H]^+$	C
3		304.12	305.0 $[M+H]^+$	C
4		352.12	353.1 $[M+H]^+$	A
5		382.13	383.1 $[M+H]^+$	B

Example 6



General procedures for Example 6

In step 1, 4-Bromo-2-nitro-benzoic acid (compound 6A) was dissolved in a suitable solvent, such as DMF, and reacted with methyl iodide in the presence of cesium carbonate at room temperature for 2-16 hours. Water and EtOAc were added and the organic phase was washed by water 1-5 times to remove DMF. The organic phase was washed with brine, dried, concentrated, and dried to give the crude product (compound 6B) which used without further purification.

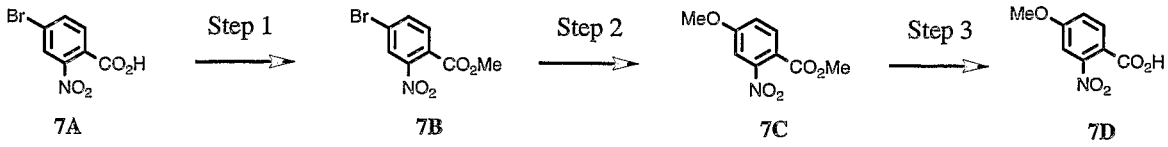
In step 2, the methyl ester (compound 6B) was mixed with $Pd(OAc)_2$, Cs_2CO_3, and an appropriate ligand, such as racemic-2-(Di-*t*-butylphosphino)-1,1'-binaphthyl. The mixture was placed under vacuum for 1 to 10 minutes to remove oxygen, and refilled with N_2. An alcohol and toluene were added and the solution was stirred at 50 °C to reflux temperature for 12 to 72 hours. After cooling to room temperature, the solid was removed by filtration and the solvent was removed. The product could be purified by chromatography. During this reaction, the methyl ester may be partially converted to the ester of the alcohol used. This side product was also collected and hydrolyzed in the next step.

In step 3, compound **6C** was dissolved in Dioxane/water (3:1) and treated with lithium hydroxide at room temperature for 3-6 hours. The solution was made acidic by addition of 1N HCl solution and subjected to aqueous/EtOAc work up. The products (compound **6D**) were either used without further purification or purified by chromatography depending on the boiling point of the alcohol side products.

In step 4, compound **6D** was dissolved in a suitable solvent, such as DMF, and coupled with compound **6E** under EDCI and HOBT conditions at room temperature overnight. After an aqueous/EtOAc work up, the product (compound **6F**) could be isolated by chromatography.

In step 5, compound **6F** was suspended in MeOH/water (1:1) under N_2 atmosphere. NaOH and zinc powder were added and the reaction mixture was stirred at 70 °C to 80 °C for 8 to 24 hours. After cooling to room temperature, the solution was adjusted to pH=6~7 with 1N HCl solution. Compound **6G** was extracted with EtOAc and isolated by reverse phase HPLC.

Example 7



7A **7B** **7C** **7D**

Step 1

Compound **7A** (10.0 g, 40.7 mmol) was dissolved in DMF (100 mL). Cs_2CO_3 (27.0g, 81.3 mmol) and methyl iodide (7.60 mL, 122.0 mmol) were added. The solution was stirred at room temperature overnight. EtOAc (250 mL) and water (100 mL) were added. The organic phase was separated and washed with water (100 mL) three times and brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator. The product was dried under vacuum to give compound **7B** (10.3 g, 97%).

Step 2

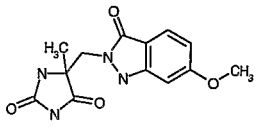
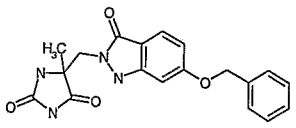
$Pd(OAc)_2$ (43 mg, 0.19 mmol), racemic-2-(di-*t*-butylphosphino)-1,1'-binaphthyl (92 mg, 0.23 mmol), and Cs_2CO_3 (1.88 g, 5.76 mmol) were placed in a 50 mL flask. The flask was placed under vacuum for 2 minutes and refilled with N_2. Compound **7B** (1.00 g, 3.84 mmol) and MeOH (0.311 mL, 7.69 mmol) were dissolved in toluene (10 mL). The resulting solution was added to the above flask by pipette. The reaction mixture was stirred at 70 °C oil bath for 48 hours. After cooling to room temperature, the solid was filtered and the solvent was removed using a rotary evaporator. The product was isolated by silica gel chromatography (Hexane/EtOAc 20:1 to 10:1) to give compound **7C** (380 mg, 47%).

Step 3

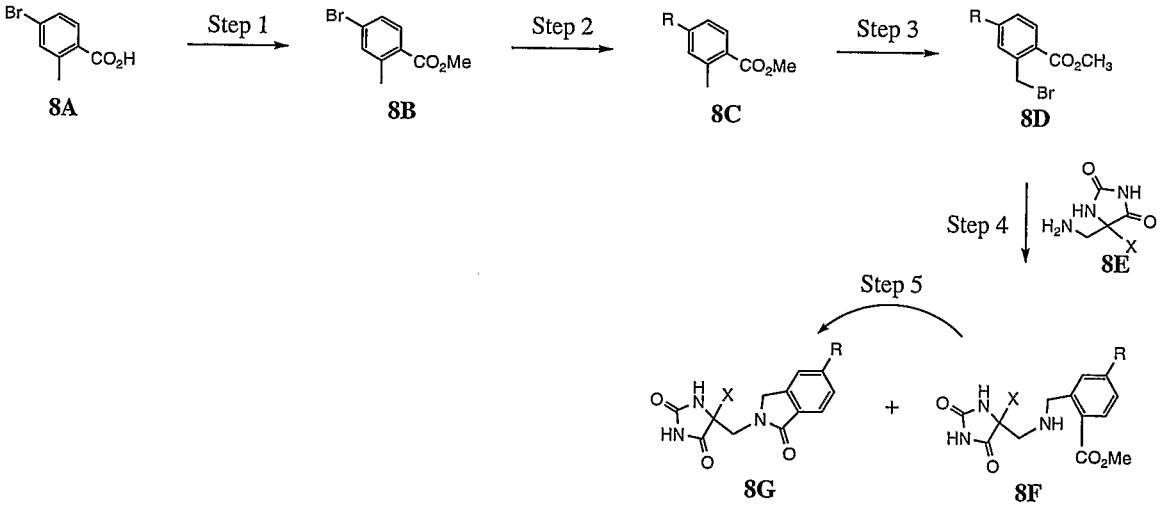
Compound 7C (380 mg, 1.80 mmol) was dissolved in dioxane/water (3:1, 8 mL) and LiOH (378 mg, 9.0 mmol) was added. The solution was stirred at room temperature for 3 hours. Water (5 mL) was added followed by addition of 2N HCl to adjust the pH = 2~4. The aqueous phase was extracted with EtOAc (10 mL) three times. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was dried under vacuum to give compound 7D which was used without further purification.

The following compounds were prepared as described in Examples 6-7

Table 2

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
6		289.11	291.1 $[M+H]^+$	B
7		366.13	367.1 $[M+H]^+$	C

Example 8



General procedure for Example 8

In step 1, Compound 8A was dissolved in a suitable solvent, such as DMF, and reacted with methyl iodide in the presence of cesium carbonate at room temperature for 2-16 hours. Water and EtOAc were added and the organic phase was washed by water 1-5 times to remove DMF. The organic phase was washed with brine, dried, concentrated, and dried to give the crude product (compound 8B) which was used without further purification.

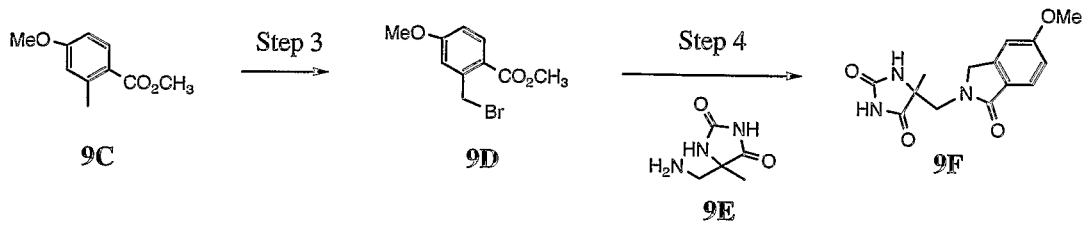
In step 2, when alcohol was used, the reaction was operated in a similar manner as step 2 in example 6. When an aromatic or heterocyclic stannane was used, the reaction was operated in the following manner. The aromatic or heterocyclic stannane was added into a dry flask, followed by addition of the 4-Bromo-2-methyl-benzoic acid methyl ester (compound 8B), a base, such as Cs_2CO_3, K_3PO_4, and a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$. The flask was placed under vacuum for 1 to 10 minutes to remove oxygen and was refilled with N_2. An appropriate solvent, such as dry CH_3CN, was added and the solution was stirred at 60 °C to reflux temperature overnight to 3 days. The solid was removed by filtration and the solvent was removed. Compound **8C** was isolated by chromatography.

In step 3, compound **8C** was dissolved in a suitable inert solvent, such as benzene, CCl_4 or α,α,α-Trifluorotoluene. NBS and benzoyl peroxide were added and the solution was stirred at 50 °C to 90 °C for 1 to 24 hours. The solid was filtered and the solvent was removed. The residue was dissolved in ether and washed by water. The ether was removed to afford the compound **8D** which was used without further purification.

In step 4, the benzyl bromide (compound **8D**) was mixed with hydantoin methyl amine **8E**, K_2CO_3, and DMF. The solution was stirred at room temperature for 12 to 24 hours. Then the solid was removed by filtration. The product could be purified by reverse phase HPLC. Compounds **8F** and **8G** could be obtained in a variable ratio.

Step 5 is used when the compound 8F was isolated in step 4. Compound 8F was dissolved in an appropriate solvent, such as MeOH, and stirred at 50 °C to reflux temperature for 1 to 12 hours. The product could be obtained by removing the solvent by rotary evaporator or purifying via reverse phase chromatography.

Example 9



9C 9D 9E 9F

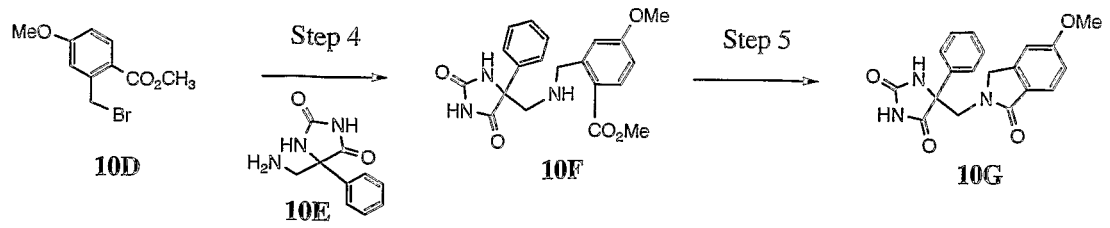
Step 3

Compound 9C (prepared according to the procedure described by Wyrick, S. D. et al. *Journal of Medicinal Chemistry*, **1987**, 30(*10*), 1798-806) (3.33 g, 18.5 mmol) was dissolved in dry benzene (40 mL). NBS (3.45 g, 19.4 mmol) and benzoyl peroxide (134 mg, 0.55 mmol) were added. The solution was stirred in a 75 °C oil bath for about 2 hours. After cooling down, the solid was filtered and washed with Et_2O (150 mL). The organic solution was then washed with water (50 mL) twice, dried over Na_2SO_4 or $MgSO_4$, filtered, and concentrated by rotary evaporator. The crude product was dried under vacuum to give compound **9D** which was used without further purification. ^{1}H-NMR appeared to indicate that approximately 75% of this material was compound **9D**.

Step 4

Compound **9D** (4.62 mmol), Compound **9E** (824 mg, 4.62 mmol), and K_2CO_3 (1.28 g, 9.24 mmol) were mixed in DMF (30 mL). The solution was stirred at room temperature for 20 hours. DMF (15 mL) was added and the solid was filtered and washed with DMF. All the DMF solution was combined and concentrated to 25 mL. The resulting solution was applied to reverse phase MPLC (CH_3CN/water, 5% to 90%, containing 0.1%HCO_2H) to give compound **9F** (198 mg, 15%).

Example 10



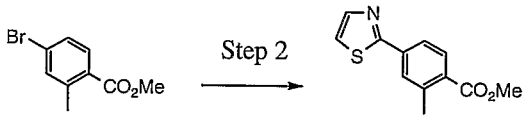
Step 4

Compound **10D** (prepared in example 9) (902 mg, 2.07 mmol, factor = 0.75), Compound **10E** (prepared as described in **Example 1**, 500 mg, 2.07 mmol), and K_2CO_3 (629 mg, 4.56 mmol) were mixed in DMF (15 mL). The solution was stirred at room temperature for 20 hours. DMF (15 mL) was added and the solid was filtered and washed with DMF. All the DMF solution was combined and concentrated to 20 mL. It was applied to reverse phase MPLC (CH_3CN/water: 5% to 90%, containing 0.1% HCO_2H) to give compound **10F**.

Step 5

Compound **10F** (prepared in step 4) was dissolved in MeOH (5 mL), stirred at 65 °C for 5 hours, then concentrated to dryness. The compound was suspended in water and dried with lyophilizer to give compound **10G** (68.3 mg, 9.4%).

Example 11

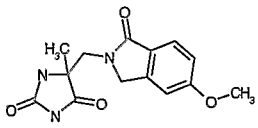
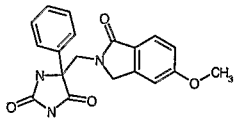
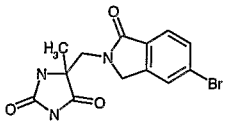
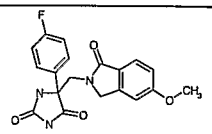
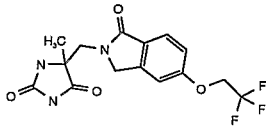
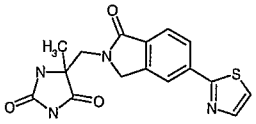
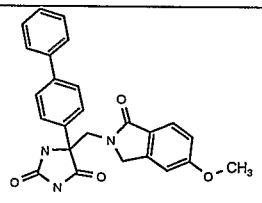
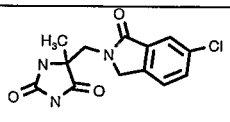


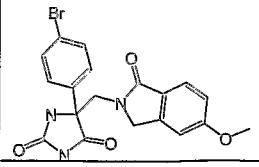
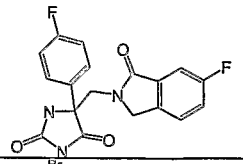
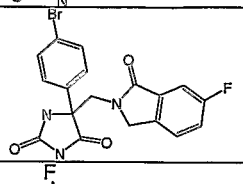
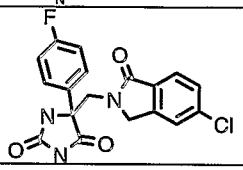
Step 2

Compound **11B** (500 mg, 2.18 mmol), 2-tributylstannylthiazole (0.97 mL, 2.84 mmol), $Pd(PPh_3)_2Cl_2$, and dry CH_3CN were stirred under nitrogen at reflux temperature overnight. After cooling to room temperature, the solid was filtered. The product was isolated by silica gel chromatography (Hexane/EtOAc: 20:1 to 10:1 to 5:1) to give compound **11C** (480 mg, 94%).

The following compounds were prepared as described in Examples 8-11.

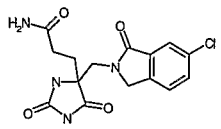
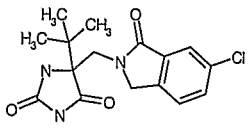
Table 3

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
8		289.11	290.1 $[M+H]^+$	B
9		351.12	352.1 $[M+H]^+$	A
10		337.01	338 $[M+H]^+$ 340.1	C
11		369.11	370.1 $[M+H]^+$	A
12		357.09	358.1 $[M+H]^+$	B
13		342.08	343.1 $[M+H]^+$	C
14		427.2	428.2 $[M+H]^+$	A
15		293.06	294.1 $[M+H]^+$	B

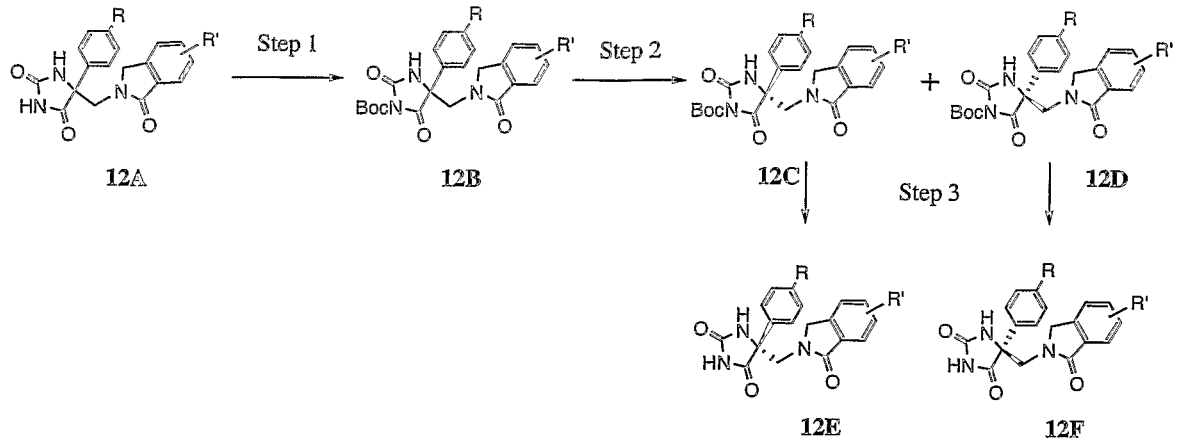
16		431.0	432.1 $[M+H]^+$	A
17		357.1	358.1 $[M+H]^+$	A
18		417.0	418.1 $[M+H]^+$	A
19		373.1	374.2 $[M+H]^+$	A

The following additional compounds were prepared as described in **Examples 8 to 11.**

Table 4

Compound #	Structures	Exact Mass	Mass Obsvd	Ki (nM)
294		**350.08**	**351.1[M+H]$^+$**	**B**
295		**335.10**	**336.1[M+H]$^+$**	**B**

Example 12



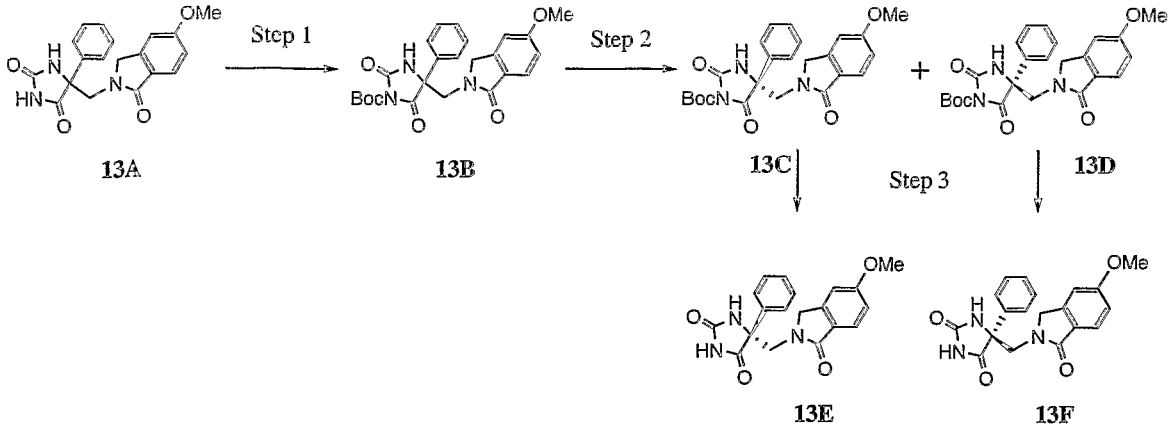
General procedures for Example 12:

In step 1, racemic compound 12A was treated with one equivalent of di-tert-butyl dicarbonate and 4-N,N-dimethylaminopyridine in polar solvent, such as DMF, for 30 minutes to 12 hours. The solvent was removed and the product (compound **12B**) was isolated by silica gel (pretreated with 1% triethylamine in Hexane) chromatography.

In step 2, compound **12B** was dissolved in proper solvents allowed by HPLC column, and resolved by HPLC using a preparative Chiralpak AD or Chiralcel OD column to give compound **12C** and **12D**.

In step 3, compound **12C** and **12D** were treated with excess HCl in methanol at 25 °C to 60 °C for one hour to 12 hours. The solvent was concentrated to give compound **12E** and **12F**.

Example 13



Step 1

Compound 13A (810 mg, 2.07 mmol), di-tert-butyl dicarbonate (429 mg, 1.97 mmol), and 4-dimethylaminopyridine (20 mg) were dissolved in a mixture of DMF (10 mL) and THF (20 mL). The solution was stirred at 25 °C overnight. Solvents were removed by rotary evaporator. The product was isolated by C18 chromatography (CH_3CN/water: 5% to 90%) to give product **13B** (650 mg, 70%).

Step 2

Compound **13B** (600 mg) was dissolved in a mixture of iso-propanol (6 mL) and $CHCl_3$ (4 mL). 2.5 mL was separated via HPLC with preparative chiralcel OD column (Mobile phase: iso-propanol/Hexane: 1:4). Fractions for each peak were collected and concentrated by rotary evaporator to give compound **13C** (First peak, 197 mg) and compound **13D** (second peak, 178 mg).

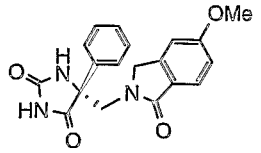
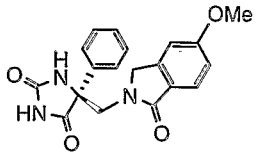
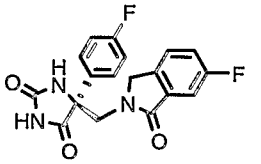
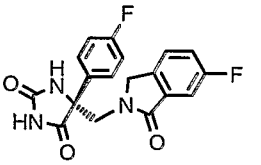
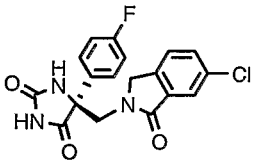
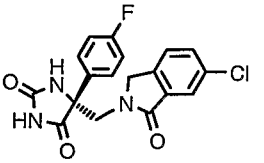
Step 3

Compound **13C** (197 mg) was dissolved in methanol (3 mL). HCl (4M in Dioxane, 0.5 mL) was added. The solution was stirred in a 60 °C oil bath for three hours. Methanol was removed by rotary evaporator to give compound **13E**.

Compound **13F** was prepared in the same way as compound **13D** (178 mg).

The following compounds were prepared as described in **Examples 12-13**

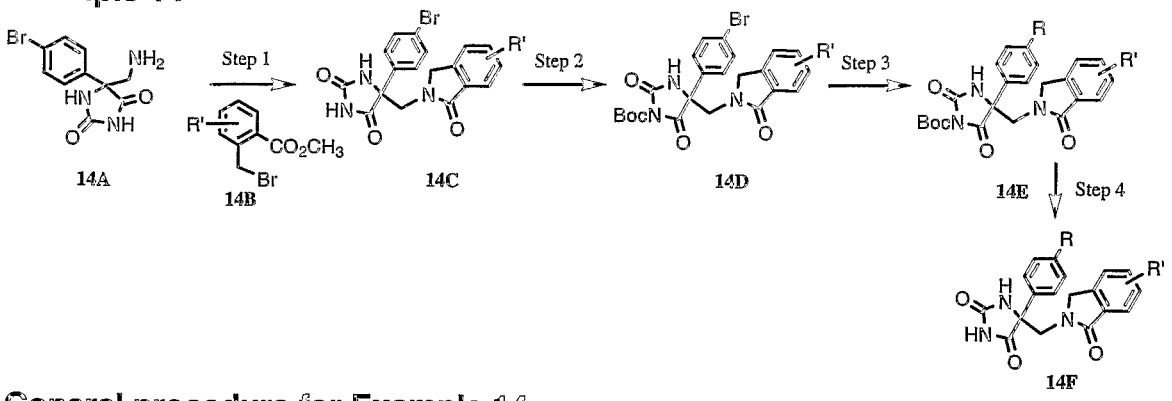
Table 5

Compound #	Structures	Exact Mass	Mass Obsvd	Ki (nM)
20	 Enantiomer A	351.1	352.2 $[M+H]^+$	A
21	 Enantiomer B	351.1	352.2 $[M+H]^+$	C
22	 Enantiomer A	357.1	358.1 $[M+H]^+$	C
23	 Enantiomer B	357.1	358.1 $[M+H]^+$	A
24	 Enantiomer A	373.06	374.2 [M+H]	C
25	 Enantiomer B	373.06	374.2 [M+H]	A

Proton NMR Spectral Data for Selected Compounds in Table 5.

Compound 25. ^{1}H NMR (500 Hz, DMSO-d_6) δ 4.06 (d, J = 14Hz, 1H), 4.20 (d, J = 14 Hz, 1H), 4.32 (d, J = 18 Hz, 1H), 4.38 (d, J = 18 Hz, 1H), 7.19-7.39 (m, 2H), 7.55-7.80 (m, 5H), 8.93 (s, 1H), 10.96 (s, 1H).

Example 14



General procedure for Example 14

In step 1, compound 14A (prepared as described in **Example 1**) was treated with a benzyl bromide (Compound **14B**) and DIPEA base in DMF at 25 °C to 60 °C for 12 to 24 hours. The reaction solution was purified via C18 reverse phase chromatography to give compound **14C**.

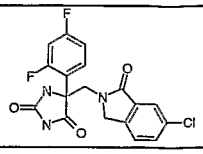
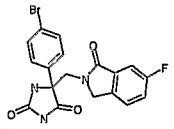
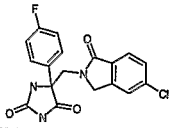
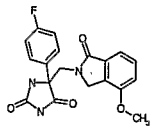
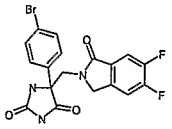
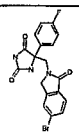
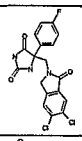
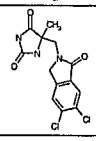
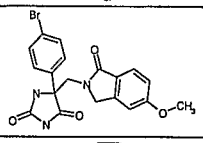
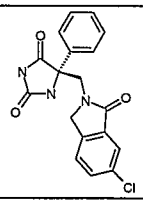
In step 2, compound **14C** was treated with one equivalent di-tert-butyl dicarbonate in polar solvent, such as DMF, for 30 minutes to 12 hours. The solvent was removed and the product (compound **14D**) was isolated by silica gel (pretreated with 1% triethylamine in Hexane) chromatography.

In step 3, compound **14D** was subjected to either a Pd catalyzed reaction with a heterocyclic boronic acid or a heterocyclic stannane, or a copper catalyzed reaction with a heterocyclic amine. The reaction were heated in appropriate solvents, such as DMF and acetonitrile, at 60 °C to 150 °C, for 5 minutes to 12 hours. In some cases, a microwave reactor was used. The product was purified by silica gel chromatography to give compound **14E** or compound **14F.**

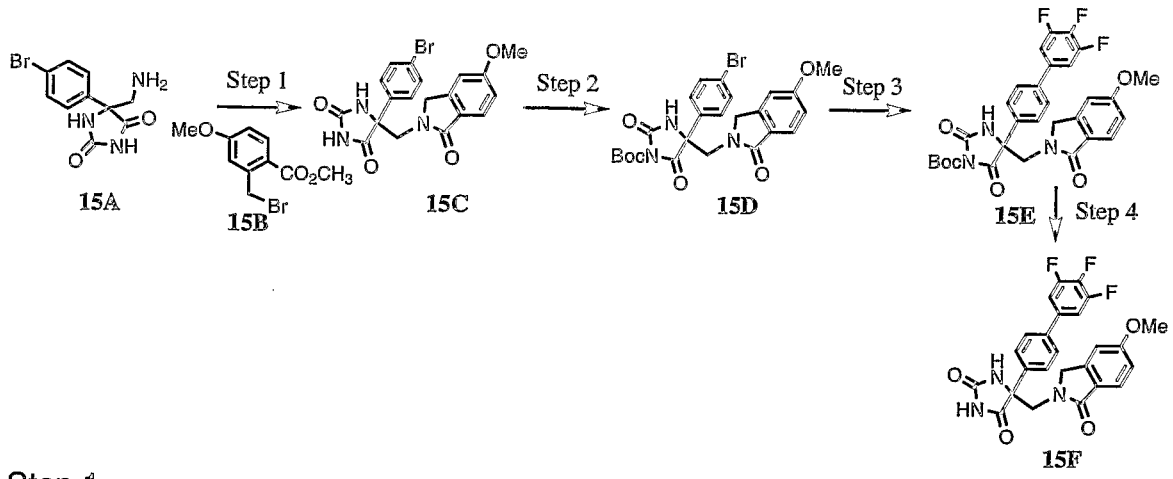
In step 4, compound **14E** was dissolved in methanol and was stirred with HCl for 1 hour to 12 hours at 25 °C to 60 °C. The solvent was removed to give compound **14F**.

The following compounds were prepared as described in step 1 of **Example 14** above.

Table 6

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
100		391.05	392.07 $[M+H]^+$	n/a
101		417.01	418.1 $[M+H]^+$	A
102		373.06	374.2 $[M+H]^+$	A
103		369.11	370.1 $[M+H]^+$	D
104		435.00	436.1 $[M+H]^+$	B
105		417.01	418.420 $[M+H]^+$	B
106		407.0	408 $[M+H]^+$	A
107		327.0	328 $[M+H]^+$	B
108		429.03	430.432 $[M+H]^+$	B
109		355.07	378.2 $[M+Na]^+$	B

Example 15



Step 1

Compound **15A** (prepared as described in **Example 1**, 1.0 g, 3.12 mmol), Compound **15B** (prepared in **Example 9**, 1.06 g, 3.12 mmol, factor = 0.76), and DIPEA base (1.14 mL, 6.55 mmol) were mixed in DMF (22 mL). The solution was stirred at 55 °C for 20 hours. The reaction solution was purified via C18 reverse phase MPLC (130g column, CH_3CN/water/0.1% HCO_2H, 5% to 90%, two separations) to give compound **15C** (900 mg, 67%).

Step 2

Compound **15C** (2.7 g, 6.28 mmol) was suspended in a mixture of DMF (20 mL) and THF (40 mL). Di-tert-butyl dicarbonate (1.51 g, 6.91 mmol) and 4-dimethyaminopyridine (38 mg, 0.31 mmol) were added. The solution was stirred at 25 °C for 16 hours. The solvents were removed by rotary evaporator. The residue was subjected to silica gel chromatography (Hexane/EtOAc: 2:1 to 1:1) to give compound **15D** (2.36 g, 71%).

Step 3

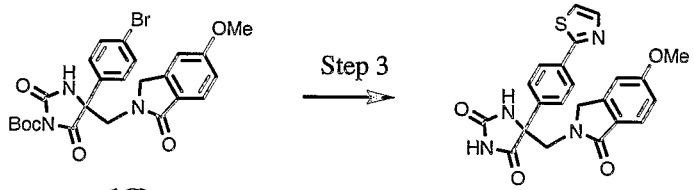
Compound **15D** (100 mg, 0.19 mmol), 3,4,5-trifluorophenyl boronic acid (40 mg, 0.23 mmol), 1,1'-bis(triphenylphosphino)ferrocene palladium (II) chloride (15 mg, 0.02 mmol), potassium carbonate (1M in water, 1 mL) and acetonitrile (1 mL) were added to a microwave reactor tube. The tube was sealed and reacted in the microwave reactor at 150 °C for 10 minutes. After cooling down, the aqueous layer was removed and the organic layer was

concentrated. The crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_3: 40:1:0.1) to give compound **15E**.

Step 4

Compound **15E** obtained from step 3 was suspended in MeOH. HCl (2M in ethyl ether, 0.5 mL) was added. The reaction mixture was stirred at 50 °C for five hours. The solvent was removed. The product was purified via C18 reverse phase chromatography (CH_3CN/water/0.1% HCO_2H, 5% to 90%) to give compound **15F** (8 mg, 8.8% from compound **15D**).

Example 16

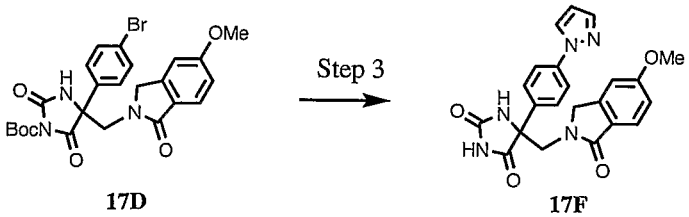


16D 16F

Step 3

Compound **16D** (50 mg, 0.094 mmol, prepared in example 13), 2-tributylstannylthiazole (53 mg, 0.14 mmol), dichlorobis(triphenylphosphine) palladium (II) (7 mg, 0.01 mmol), and acetonitrile (1 mL) were added to a microwave reactor tube. The tube was sealed and reacted in a microwave reactor at 150 °C for 10 minutes. The solvent was evaporated and the product was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_3: 40:1:0.1 to 20:1:0.1) to give compound **16F** (15 mg, 37%).

Example 17



17D 17F

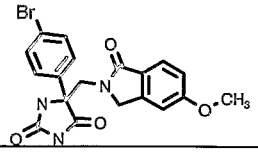
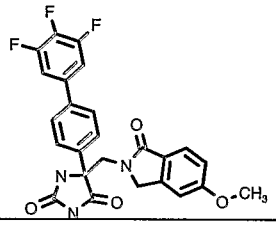
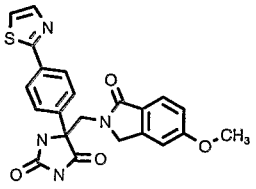
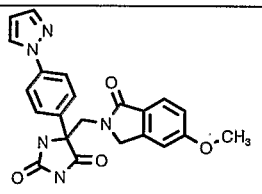
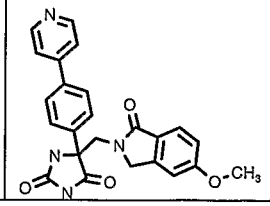
Step 3

Compound **17D** (100 mg, 0.19 mmol, prepared in example 13), pyrazole (15.4 mg, 0.23 mmol), cesium carbonate (124 mg, 0.38 mmol), copper iodide (7.2 mg, 0.038 mmol), 1,10-phenanthroline (14 mg, 0.076 mmol), and N,N-dimethylacetamide (0.5 mL) were added to a dry reaction tube and filled with

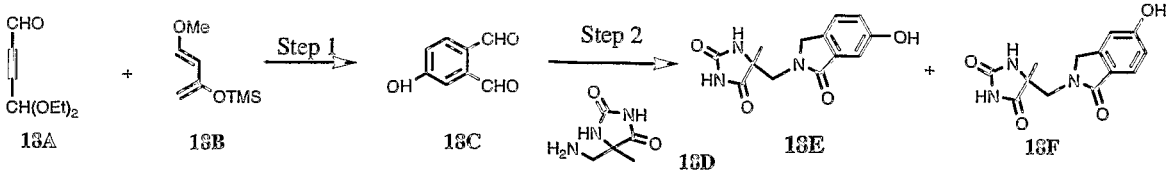
nitrogen. The reaction tube was sealed and heated in a 120 °C oil bath for two days. After cooling down, the reaction solution was purified by C18 chromatography (CH_3CN/water/0.1% HCO_2H, 5% to 90%) to give compound **17F** (5 mg, 6.4%).

The following compounds were prepared as described in **Examples 14-17**

Table 7.

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
26		429.0	430.1 $[M+H]^+$	A
27		481.1	482.3 $[M+H]^+$	B
28		434.1	435.1 $[M+H]^+$	A
29		417.1	418.2 $[M+H]^+$	A
30		428.2	429.1 $[M+H]^+$	A

Example 18



Step 1:

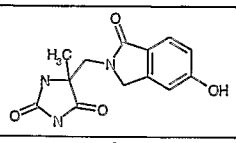
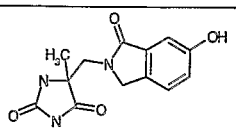
Compound **18A** (1.0 g, 6.4 mmol) and compound **18B** (1.324 g, 7.68 mmol) were dissolved in toluene (4 mL) and stirred at 80 °C for 24 hours. After cooling to room temperature, the solvent was removed by rotary evaporator. Half of the crude product was dissolved in THF/1N HCl (1:1, 14 mL) and stirred at room temperature for 2 hours. EtOAc (15 mL) and water (5 mL) were added. The organic phase was separated and the aqueous phase was extracted with EtOAc (15 mL) twice. The combined organic phase was dried over Na_2SO_4 and concentrated by rotary evaporator to give compound **18C** which was used without further purification.

Step 2

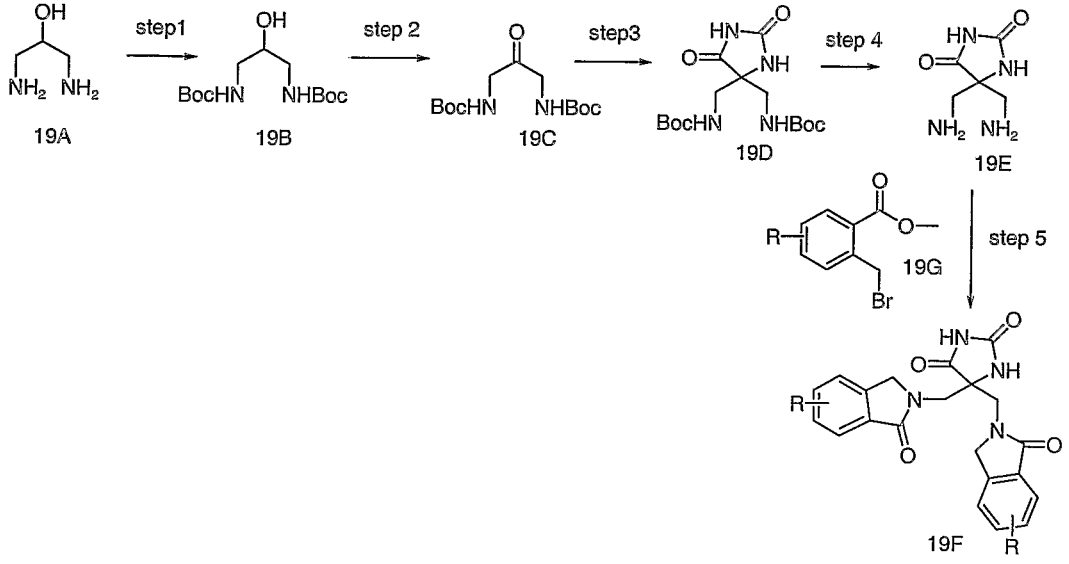
Compound **18C** (prepared in step 1) was dissolved in DMF (15 mL) and was cooled to 0 °C in an ice-water bath. Compound **18D** (571 mg, 3.2 mmol) was added in one portion. The solution was allowed to warm up to room temperature over 2 hours, and stirred at room temperature for 3 days. A 2N HCl solution (20 mL) was added and the aqueous phase was extracted with EtOAc (50 mL) three times. The organic phases were combined, dried over Na_2SO_4, and concentrated to dryness. The product was isolated by reverse phase LC (CH_3CN/water/0.1% HCO_2H: 5% to 90%) to give compound **18E** (65 mg, 7.4% from step 1) and Compound **18F** (16 mg, 1.8% from step 1).

The following compounds were prepared as described in **Example 18**

Table 8

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
31		275.09	276.0 $[M+H]^+$	B
32		275.09	276.0 $[M+H]^+$	C

Example 19



General procedures for **Example 19**:

In step1, compound **19A** was treated with two equivalent of Boc_2O in a suitable solvent, such as dichloromethane, for 30 min. to 12 h. The solvent was removed and the compound **19B** could be used without further purification or purified by silica gel chromatography.

In step 2, compound **19B** was treated with PCC and celite in a suitable solvent such as dichloromethane, for 2 hr to 12 hr. Compound **19C** was purified by silica gel chromatography.

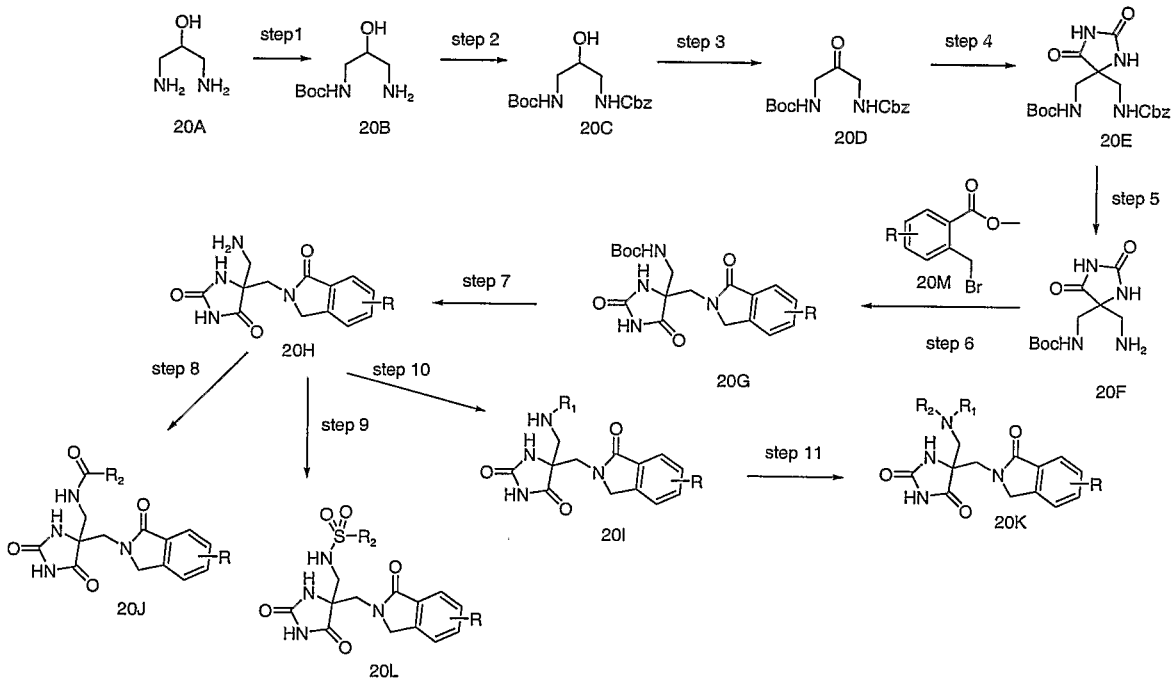
In step 3, compound **19C** was reacted with potassium cyanide and ammonium carbonate in appropriated alcohol and water solution, at 50 °C to

90 °C, for 5 hours to 48 hours. After cooling down, water was added and compound **19D** could be collected by filtration.

In step 4, compound **19D** was stirred with 2 to 20 equivalents of hydrogen chloride in methanol for 5 to 48 hours. The solvent was removed and the compound **19E** could be used without further purification.

In step 5, the benzyl bromide (compound **19G**) was mixed with hydantoin methyl amine **19E**, DIPEA, and DMF. The solution was stirred at room temperature for 12 to 24 hours. The product (**19F**) was either removed by filtration or purified by silica gel chromatography.

Example 20.



General procedures for **Example 20**:

In step 1, Compound **20A** was treated with BOC-ON in a suitable solvent such as dichloromethane, for 2 hr to 12 hr. Compound **20B** was purified by silica gel chromatography.

In step 2, Compound 20B was treated with CbzCl and a base such as DIPEA, in a suitable solvent, such as dichloromethane, for 2 hr to 12 hr. Compound 20C was purified by silica gel chromatography.

In step 3, compound 20C was treated with PCC and celite in a suitable solvent such as dichloromethane, for 2 hr to 12 hr. Compound 20D was purified by silica gel chromatography.

In step 4, compound 20D was reacted with potassium cyanide and ammonium carbonate in appropriated alcohol and water solution, at 50 °C to 90 °C, for 1 hour to 48 hours. After cooling down, water was added and compound 20E could be collected by filtration.

In step 5, Compound 20E was treated with Pd/C in a suitable solvent such as methanol, in a par shaker under H_2 atmosphere. After filtering off the catalyst and concentration of solvent, the product was used without further purification.

In step 6, the benzyl bromide (compound **20M**) was mixed with hydantoin methyl amine **20F**, DIPEA, and DMF. The solution was stirred at at room temperature to 80 °C for 12 to 24 hours. The product was either removed by filtration or purified by silica gel chromatography.

In step 7, compound **20G** was stirred with 2 to 20 equivalents of hydrogen chloride in dioxane for 1 to 12 hours. The solvent was removed and the compound **20H** was used without further purification.

In step 8, Compound **20H** was coupling with carboxylic acid to give compound **20J** which was purified by silica gel chromatography.

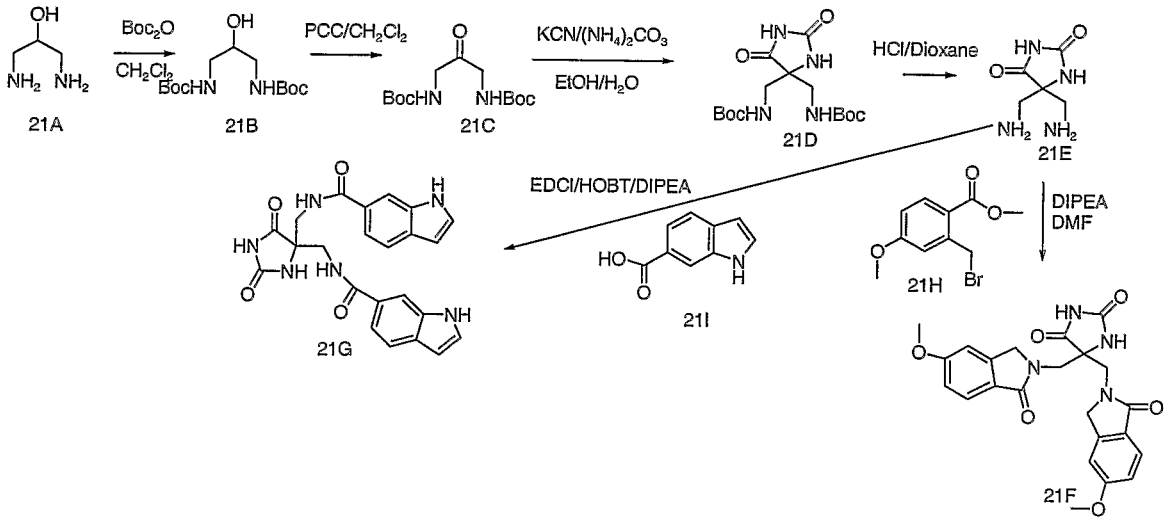
In step 9, Compound **20H** was coupling with sulphonyl chloride compound to give compound **20L** which was purified by silica gel chromatography.

In step 10, Compound **20H** was reacted with carbonyl compound under reductive amination condition to give compound **20I**. Alternatively, compound

20H was treated with a suitable electrophile and a base to give the product 20I, which was purified by silica gel chromatography.

In step 11, compound 20I was reacted with carbonyl compound under reductive amination condition to give product 20K. Alternatively, compound 20I was treated with a suitable electrophile and a base to give the product 20K, which was purified by silica gel chromatography.

Example 21:



Compound **21B**: Compound **21A** (7 g, 77.7 mmol), and di-tert-butyl dicarbonate (35.6 g, 163 mmol) were stirred in methylene chloride (100 mL) at 25 °C for 2 hr. Saturated aqueous NaCl (150 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (100 mL) twice. The organic phase was washed with brine (100 mL), dried over Na_2SO_4. The solvent was removed by rotary evaporator to give compound **21B** (17g, 76%) which was used without further purification.

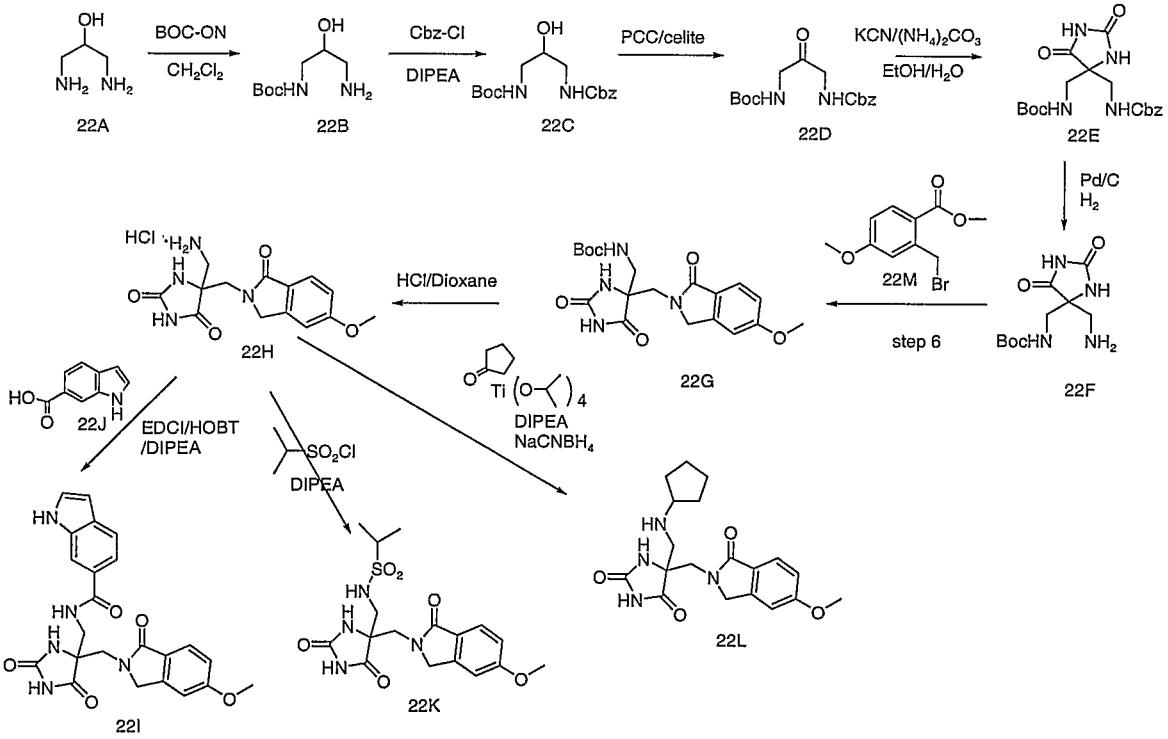
Compound **21C**: compound **21B** (17 g, 58.6 mmol) was dissolved in methylene chloride (100 mL). PCC (25.2 g, 117 mmol) and celite (15 g) were added and the reaction mixture was stirred at 25 °C overnight. The solid was filtered off and the resulting solution was concentrated and purified via sgc (40% EtOAc/Hexanes) to give 3.62 g (22%) of compound **21C**.

Compound **21D**: Compound **21C** (3.62, 12.6 mmol), KCN (1.23g, 18.9 mmol), and $(NH_4)_2CO_3$ (3.62 g, 37.7 mmol) were suspended in a mixture of EtOH (30 mL) and water (30 mL). The solution was stirred at 80 °C overnight. After cooling down, water (35 mL) was added. The solid was filtered and washed with water three times. The solid was dried under vacuum to give compound **21D** (3 g, 67%).

Compound **21E**: Compound **21D** (3.0 g) was suspended in methanol (50 mL) and HCl (4M in dioxane, 20 mL) was added. The solution was stirred at 25 °C for 3 hours. Ethyl ether (50 ml) was added. The solid was filtered, washed by ethyl ether twice, and dried under vacuum compound **21E** (1.34 g, 70%).

Compound **21F**: Compound **21E** (130 mg, 0.82 mmol), compound **21H** (0.27 g, 1 mmol) and DIPEA (0.55 mL, 2 mmol) were mixed in DMF (5 mL). The solution was stirred at room temperature overnight. Solvent was removed and the crude material was and purified via sgc (5% NH_3•MeOH/CH_2Cl_2) to give 129 mg (35%) of compound **21E**.

Example 22:



Compound 22B: Compound 22A (7.3 g, 81 mmol) was treated with BOC-ON (21.9 g, 89 mmol) in dichloromethane for 3 hr. Solvent was removed and the crude material was purified via sgc (10% NH_3◦MeOH/CH_2Cl_2) to give 6.5 (42%) of compound 22B.

Compound 22C: Compound 22B (1.5g, 7.9 mmol) was dissolved in dichloromethane (50 mL) at 0 °C. CbzCl (1.24 ml, 8.7 mmol) and DIPEA (1.52 ml, 8.7 mmol) were added and the reaction was stirred at 0 °C for 30 min. The reaction mixture was washed by HCl (1N, 50 mL) and brine (50 mL). The organic layer was dried and concentrated to give crude compound 22C (2.6 g, 99%) which was used without further purification.

Compound 22D: Compound 22C (2.78g, 8.57 mmol) was dissolved in methylene chloride (100 mL). PCC (4.62 g, 21.4 mmol) and celite (4.6 g) were added and the reaction mixture was stirred at 25 °C overnight. Another 0.5 eq. of PCC (923 mg, 4.3 mmol) was added and it was stirred for 3 hr at room temperature. The solid was filtered off and the resulting solution was concentrated and purified via sgc (50% EtOAc/Hexanes) to give 1.86 g (73%) of compound **22D**.

Compound **22E**: Compound **22D** (1.86, 5.8 mmol), KCN (0.56 g, 8.65 mmol), and $(NH_4)_2CO_3$ (1.66 g, 17.3 mmol) were suspended in a mixture of EtOH (20 mL) and water (20 mL). The solution was stirred at 80 °C overnight. After cooling down, EtOH was removed. The solid was filtered and washed with water three times. The solid was dried under vacuum to give compound **22E** (1.45 g, 64%).

Compound **22F**: Compound **22E** (1.45 g, 3.68 mmol) was treated with Pd/C in methanol in a par shaker under H_2 atmosphere of 50 psi for 60 hr. After filtering off the catalyst and concentration of solvent, Compound **22E** (0.95 g, 99%) was used without further purification.

Compound 22G: Compound 22F (150 mg, 0.58 mmol), compound 22M (170 mg, 0.64 mmol) and DIPEA (0.22 mL, 1.28 mmol) were mixed in DMF (5 mL). The solution was stirred at 70 °C overnight. Solvent was removed and the crude material was and purified via sgc (5% NH_3•MeOH/CH_2Cl_2) to give 166 mg (71%) of compound 22G.

Compound 22H: Compound 22G (166 mg) was suspended in methanol (10 mL) and HCl (4M in dioxane, 4 mL) was added. The solution was stirred at 25 °C for 2 hours. Ethyl ether (50 ml) was added. Solvent was removed and give compound 22H (0.14 g, 99%).

Compound 22I: Compound 22H (42 mg, 0.12 mmol) and compound 22J (26 mg, 0.16 mmol) were dissolved in DMF (20 mL). EDCI (30 mg, 0.16 mmol), HOBT (21 mg, 0.16 mmol) and DIPEA (0.05 mL, 0.28 mmol) were added and the reaction mixture was stirred at room temperature for 2 hr. Solvent was removed and the crude material was and purified via sgc (10% NH_3•MeOH/CH_2Cl_2) to give 7 mg (13%) of compound **22I**.

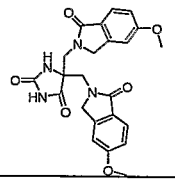
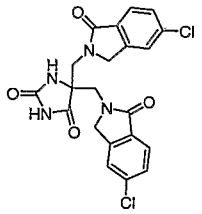
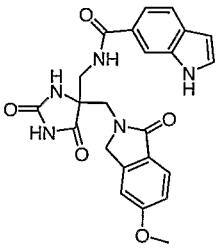
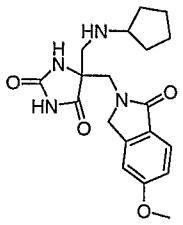
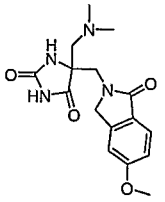
Compound **22L**: Compound **22H** (25 mg, 0.073 mmol) and cyclopentanone (7.5 mg, 0.088 mmol) were stirred in methylene chloride (5 mL). Titanium tetraisopropoxide (0.043 mL, 0.15 mmol) was added followed by addition of DIPEA (0.015 mL, 0.088 mmol). The reaction mixture was stirred at room temperature for 2h. Then, $Na(OAc)_3BH$ (31 mg, 0.15 mmol) was added and the mixture was stirred at rt overnight. Saturated K_2CO_3 aq. (20 mL) was added, and the mixture was stirred at rt briefly. The solid was filtered off through a celite pad. The filtrate was diluted with methylene chloride (30 mL), and it was extracted with brine. The organic layer was dried and concentrated to dryness. The crude material was purified via PTLC (10% NH_3•MeOH/CH_2Cl_2) to give 7 mg (26%) of compound **22L.**

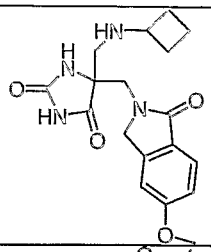
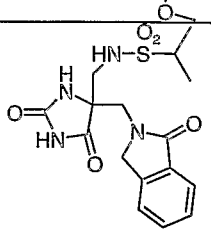
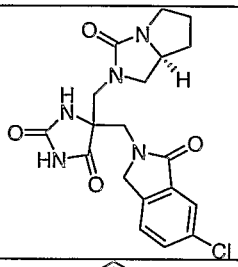
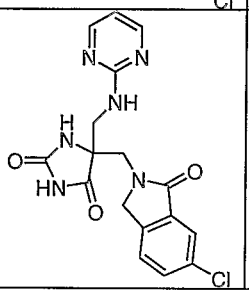
Compound **22K:** Compound **22H** (20 mg, 0.06 mmol) and isopropyl sulphonyl (27 mg, 0.18 mmol) were dissolved in methylene chloride (10 mL). DIPEA (0.04 mL, 0.26 mmol) were added and the reaction mixture was stirred at

room temperature for 48 hr. Solvent was removed and the crude material was and purified via sgc (10% NH_3•MeOH/CH_2Cl_2) to give 2 mg (8%) of compound 22K.

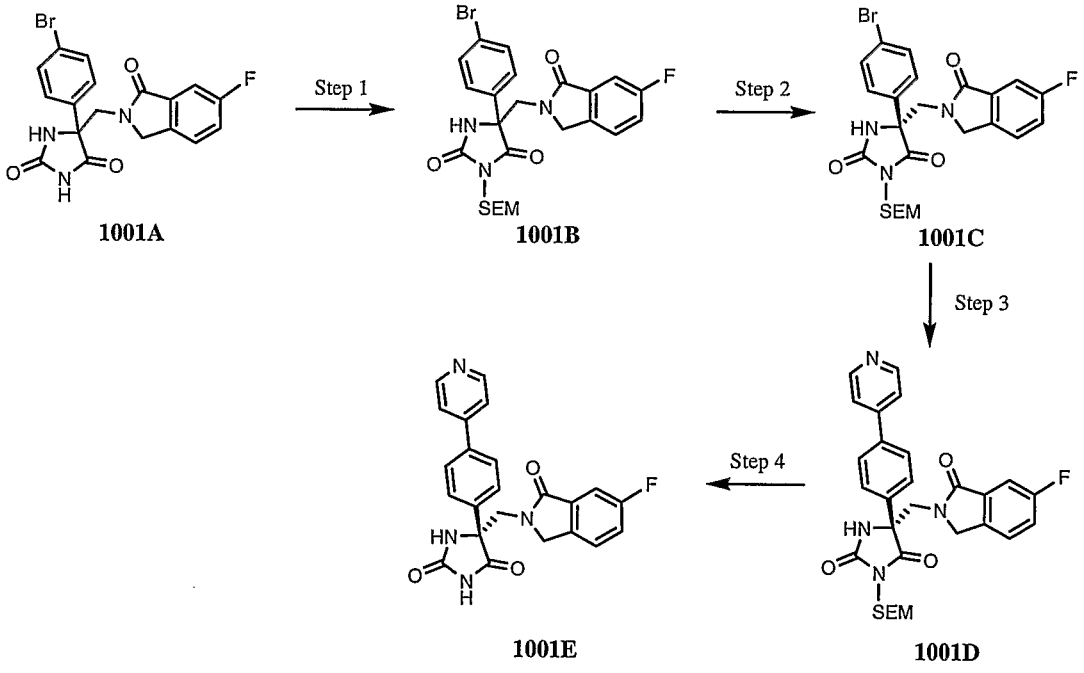
The following compounds were prepared as described in Examples 19-22.

Table 9

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
33		450.15	451.1 $[M+H]^+$	B
34		458.05	459.3 $[M+H]^+$	B
35		447.15	448.2 $[M+H]^+$	A
36		372.18	373.2 $[M+H]^+$	B
37		332.15	333.1 $[M+H]^+$	C

38		358.16	359.2 $[M+H]^+$	B
39		380.12	381.2 $[M+H]^+$	C
40		417.12	418.1 $[M+H]^+$	D
41		386.09	387.2 $[M+H]^+$	C

Example 1001:



Step 1

To a solution of compound **1001A** (1.65 g, 3.95 mmol) in anhydrous DMF (35 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl, 0.93 mL, 4.73 mmol) and DIPEA (0.9 mL, 5.14 mmol). The solution was stirred at 25 °C for overnight. DMF was removed under vacuum. The product **1001B** was purified by SGC (Hexane/EtOAc, 2:1. yield: 1.6 g, 74%).

Step 2

Compound **1001B** was resolved by Chiralcel OD column (Mobile phase: Hexane/2-propanol 3:1). The first peak was collected and concentrated to give compound **1001C**.

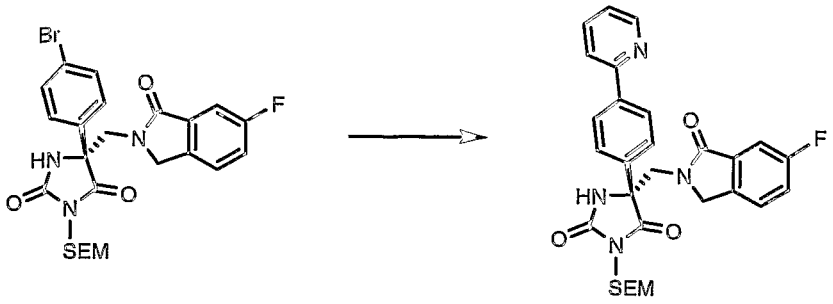
Step 3

To a dry flask was added compound **1001C** (1.5 g, 2.73 mmol) and 4-pyridyl boronic acid (670 mg, 5.50 mmol). The flask was vacuumed and refilled with nitrogen three times. $Pd(dppf)Cl_2$ (220 mg, 0.30 mmol) was added and followed by addition of CH_3CN (20 mL) and aq. K_2CO_3 (1 M, 15 mL). The solution was stirred at 80 °C (oil bath) for 16 hours. After cooling down, CH_3CN (100 mL) was added and the solid was removed by filtration. The aqueous layer was separated and extracted with EtOAc (20 mL) once. The organic solution was combined and concentrated. The product was purified by SGC (CH_2Cl_2/MeOH/NH_4OH: 20:1:0.1) to give compound **1001D**.

Step 4

Compound **1001D** was dissolved in a mixture of methanol and HCl (4M in dioxane) (2:1, 30 mL) and was stirred overnight in a sealed pressure flask at 90 °C (oil bath). After the solution was cooled, the solution was transferred into a 250 mL round bottom flask. It was concentrated and dried under vacuum. The crude mixture was dissolved in methanol (50 mL) and Et_3N (0.5 mL) was added and stirred overnight at 25 °C. The solvent was then removed and the product was purified by C18 reverse phase chromatography (CH_3CN/water 5% to 90%, with addition of 0.1% HCO_2H) to give compound **1001E** (815g, 71% from compound **1001C**).

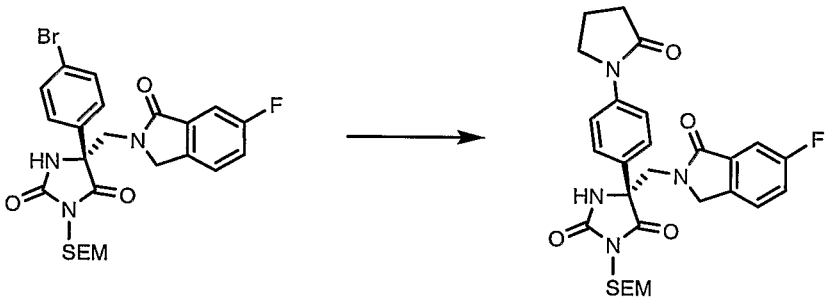
Example 1002



1003A 1003B

To a flamed dried flask was added compound **1003A** (100 mg, 0.182 mmol), [1,4-bis(diphenylphosphino)butane] palladium(II) dichloride [Pd(dppb)Cl_2, 12 mg, 0.02 mmol], and copper (II) oxide (15 mg, 0.18 mmol). The flask was vacuumed and refilled with nitrogen. 2-Tri-n-butylstannylpyridine (0.076 mL, 0.237 mmol) and DMF (1 mL) were added. The solution was stirred at 100 °C oil bath for 5 hours. After cooling, the DMF was removed by rotary evaporator. The product was purified by SGC (Hexane/EtOAc 2:1) to give **1003B** (84 mg, 84%).

Example 1003

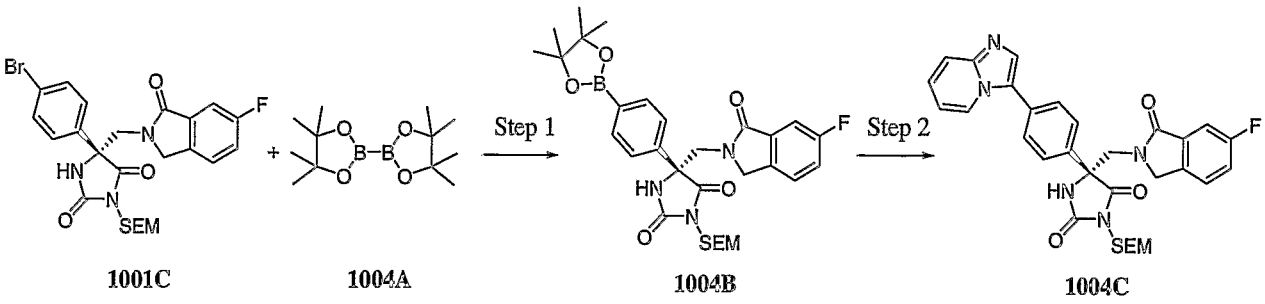


1003A 1003B

To a dry pressure tube was added compound **1003A** (50 mg, 0.091 mmol), bis(dibenzylideneacetone) palladium [Pd(dba)$_2$, 1.6 mg, 0.0018 mmol], 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos, 3.0 mg, 0.0055 mmol), and Cs_2CO_3 (60 mg, 0.182 mmol). The pressure tube was vacuumed and refilled with nitrogen. Pyrrolidinone (14 mg, 0.16 mmol) and dioxane(0.5 mL) were added. The tube was sealed and stirred overnight at 100 °C (oil bath). After cooling, dioxane (2 mL) was added and the solid was removed by

filtration. The solution was concentrated and purified by SGC (CH_2Cl_2/MeOH: 40:1) to give compound **1003B** (27 mg).

Example 1004:



Step 1

Compound **1001C** was prepared as described in Example 1001.

A mixture of compound **1001C** (0.3 g, 0.55 mmol), bis(pinacolato)diboron (**1004A**; 170 mg, 0.65 mmol), potassium acetate (170 mg, 1.70 mmol), and $[PdCl_2(dppf)]CH_2Cl_2$ (50 mg, 0.05 mmol) in 1,4-dioxane (10 mL) was vacuumed and refilled with argon three times. The reaction mixture was stirred at 100 °C (oil bath) for 1.5 hours. After cooling down, the mixture was diluted in EtOAc (50 mL) and filtered through a Celite pad. The filtrate was concentrated in vacuo and the residual material was purified by silica gel column chromatography (2% MeOH in CH_2Cl_2) to afford compound **1004B** (300 mg, 91% yield).

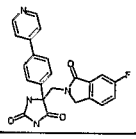
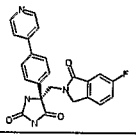
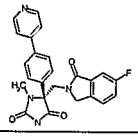
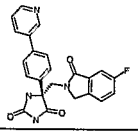
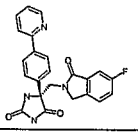
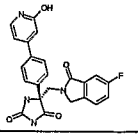
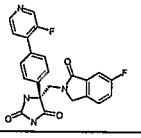
Step 2

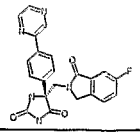
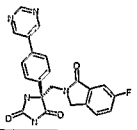
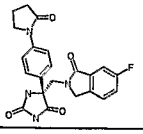
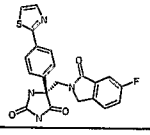
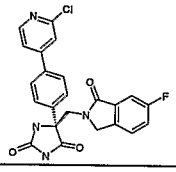
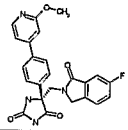
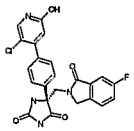
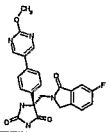
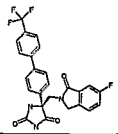
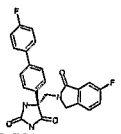
A solution of compound **1004B** (60 mg, 0.10 mmol), 3-bromoimidazo[1,2-a]pyridine (30 mg, 0.15 mmol), and $[PdCl_2(dppf)]CH_2Cl_2$ (8.2 mg, 0.01 mmol) in CH_3CN (3 mL) was treated with potassium carbonate (0.6 mL, 0.6 mmol, 1M in H_2O). The mixture was vacuumed and refilled with argon three times. The reaction mixture was stirred at 90 °C (oil bath) for 17 hours. After cooling, the mixture was diluted in EtOAc (20 mL) and filtered through a Celite pad. The filtrate was concentrated in vacuo and the residual material was purified

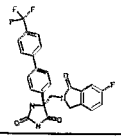
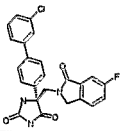
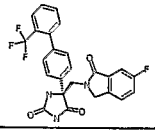
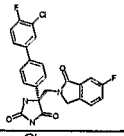
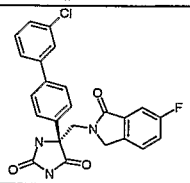
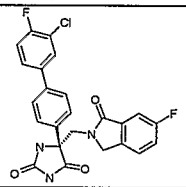
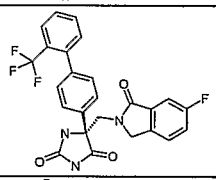
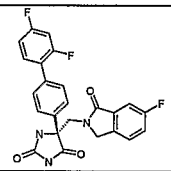
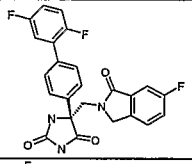
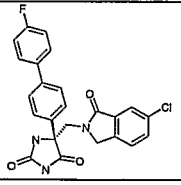
by preparative TLC (10% MeOH in CH_2Cl_2) to afford compound 1004C (42 mg, 71% yield).

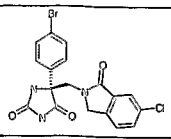
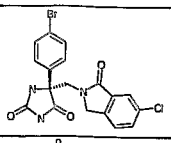
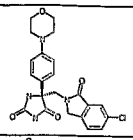
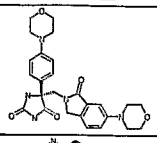
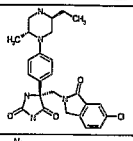
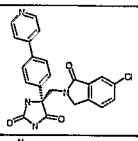
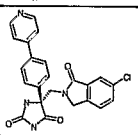
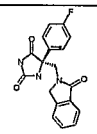
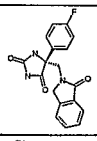
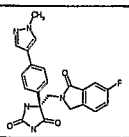
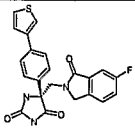
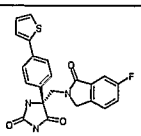
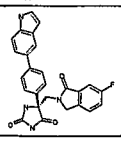
The following compounds were prepared as described in Examples 1001, 1002, 1003, or 1004.

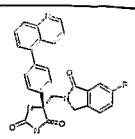
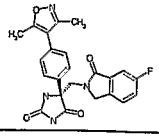
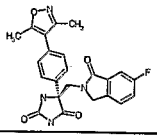
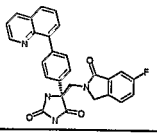
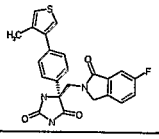
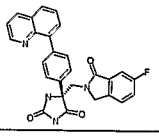
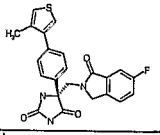
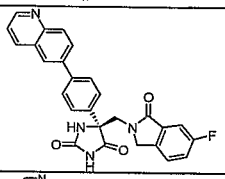
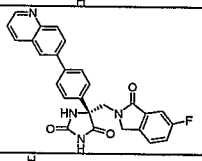
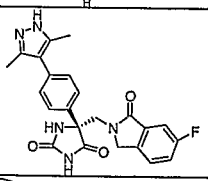
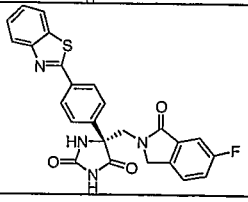
Table 1000

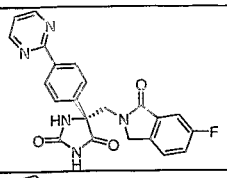
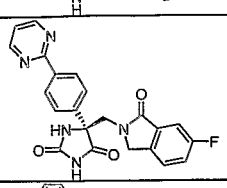
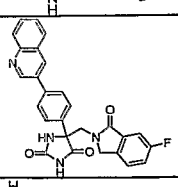
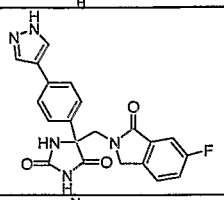
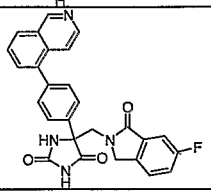
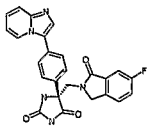
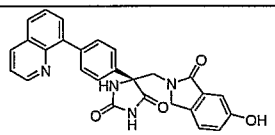
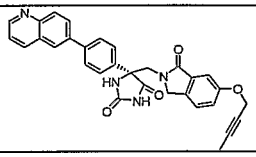
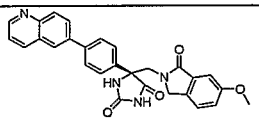
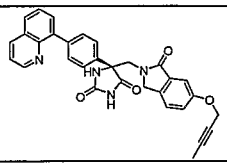
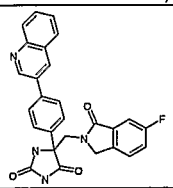
Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
110		416.13	417.1 $[M+H]^+$	A
111		416.13	417.1 $[M+H]^+$	A
112		430.14	431.1 $[M+H]^+$	B
113		416.13	417.1 $[M+H]^+$	A
114		416.13	417.1 $[M+H]^+$	A
115		432.12	433.2 $[M+H]^+$	A
116		434.12	435.2 $[M+H]^+$	A

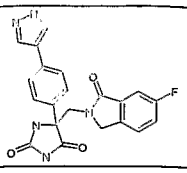
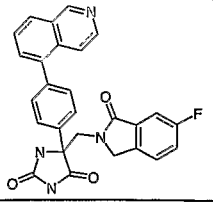
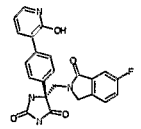
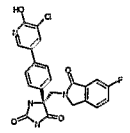
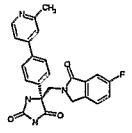
117		417.12	418.1 $[M+H]^+$	A
118		417.12	418.1 $[M+H]^+$	A
119		422.14	423.2 $[M+H]^+$	A
120		422.08	423.1 $[M+H]^+$	A
121		450.09	451.1 $[M+H]^+$	D
122		446.14	447.2 $[M+H]^+$	A
123		466.08	467.3 $[M+H]^+$	A
124		447.13	448.2 $[M+H]^+$	A
125		483.12	484.3 $[M+H]^+$	D
126		433.12	434.2 $[M+H]^+$	A

127		483.12	484.3 $[M+H]^+$	B
128		449.09	450.2 $[M+H]^+$	A
129		483.12	484.3 $[M+H]^+$	C
130		467.08	468.3 $[M+H]^+$	C
131		449.09	450.2 $[M+H]^+$	A
132		467.08	468.3 $[M+H]^+$	A
133		483.12	484.3 $[M+H]^+$	A
134		451.11	452.2 $[M+H]^+$	A
135		451.11	452.2 $[M+H]^+$	A
136		449.09	450.1 $[M+H]^+$	n/a

137		432.98	434.1 $[M+H]^+$	C
138		432.98	434.1 $[M+H]^+$	A
139		440.13	441.1 $[M+H]^+$	A
140		491.2	492.3 $[M+H]^+$	C
141		481.2	482.1 $[M+H]^+$	A
141		432.1	433.2 $[M+H]^+$	D
143		432.1	433.2 $[M+H]^+$	A
144		339.1	340 $[M+H]^+$	C
145		339.1	340 $[M+H]^+$	A
146		419.4	420.2 $[M+H]^+$	A
147		421.44	422.2 $[M+H]^+$	A
148		421.44	422.2 $[M+H]^+$	A
149		454.45	455.3 $[M+H]^+$	A

150		466.46	467.3 $[M+H]^+$	A
151		434.14	435.2$[M+H]^+$	A
152		434.14	435.1$[M+H]^+$	C
153		466.14	467.3$[M+H]^+$	C
154		435.11	436.2$[M+H]^+$	C
155		466.14	467.3$[M+H]^+$	A
156		435.11	436.1$[M+H]^+$	A
157		466.14	467.3$[M+H]^+$	C
158		466.14	467.3$[M+H]^+$	A
159		433.16	434.2$[M+H]^+$	A
160		472.10	473.3$[M+H]^+$	A

161		417.12	418.2[M+H]$^+$	A
162		417.12	440.2[M+Na]$^+$	C
163		466.14	467.3[M+H]$^+$	B
164		405.12	406.2[M+H]$^+$	A
165		466.14	467.3[M+H]$^+$	A
166		455.44	456.3 [M+H]$^+$	n/a
167		464.15	465.3 [M+H]$^+$	A
168		516.18	517.1 [M+H]$^+$	C
169		478.16	479.3 [M+H]$^+$	A
170		516.18	517.3 [M+H]$^+$	n/a
171		466.46	467.3 [M+H]$^+$	B

172		405.38	406.2 $[M+H]^+$	A
173		466.46	467.3 $[M+H]^+$	A
174		432.12	433.1 $[M+H]^+$	A
175		466.08	467.1 $[M+H]^+$	A
176		430.14	431.2 $[M+H]^+$	D

Proton NMR Spectral Data for Selected Compounds in Table 1000.

Compound 111. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.0 (s, 1H), 8.7 9(d, J = 6.0 Hz, 2H), 7.92 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 6.0 Hz, 2H), 7.65 (m, 1H), 7.48 (m, 2H), 4.40 (d, J = 17.3 H, 1H), 4.31 (d, J = 17.3 Hz, 1H), 4.27 (d, J = 14.2 Hz, 1H), 4.14 (d, J = 14.2 Hz, 1H).

Compound 120. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 3.3 Hz, 1H), 7.84 (d, J = 3.3 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.65 (s, 1H), 7.47 (m, 2H), 4.38 (d, J = 17.6 Hz, 1H), 4.28 (d, J = 17.6 Hz, 1H), 4.27 (d, J = 14.3 Hz, 1H), 4.13 (d, J = 14.3 Hz, 1H).

Compound 123. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.84 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.66 (dd, J = 8.5, 4.6 Hz, 1H), 7.54 (d, J = 8.4 Hz,

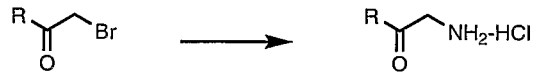
2H), 7.49 (m, 2H), 6.65 (s, 1H), 4.40 (d, J = 17.5 Hz, 1H), 4.31 (d, J = 17.5 Hz, 1H), 4.29 (d, J = 14.2 Hz, 1H), 4.10 9d, J = 14.2 Hz, 1H).

Compound 139. ^{1}H NMR (500 MHz, CD_3OD) δ 3.17-3.21 (m, 4H), 3.83-3.88 (m, 4H), 4.14-4.52 (m, 4H), 7.01 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8 Hz, 1H), 7.46-7.48 (m, 3H), 7.75 (s, 1H).

Compound 143. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21-4.50 (m, 4H), 7.498 (d, J = 0.8 Hz, 1H), 7.52 (d, J = 0.4 Hz, 1H), 7.73-7.76 (m, 3H), 7.76-7.87 (m, 4H), 8.60 (d, J = 6 Hz, 2H).

Compound 155. ^{1}H NMR (500 MHz, CD_3OD) δ 8.84 (dd, J = 1.89, 4.1 Hz, 1H); 8.43 (dd, J = 1.58, 8.2 Hz, 1H); 7.99 (dd, J = 1.58, 8.2 Hz; 1H); 7.85 (m, 3H); 7.8 (dd, J = 1.26 Hz, 6.94 Hz, 1H); 7.75 (m, 3H), 7.70 (dd, J = 7.25 Hz, 0.95 Hz, 1H); 7.59 (dd, J = 4.73 Hz, 7.57 Hz, 1H); 7.58 (dd, J = 4.4Hz, 8.2Hz, 1H); 7.51 (dd, J = 2.5 Hz, 7.8 Hz, 1H); 7.40 (m, 1H); 4.54 (d, J=17.0 Hz, 1H); 4.48 (d, J = 17.0 Hz, 1H); 4.48 (d, J = 14.5 Hz, 1H); 4.32 (1H, d, J = 14.5 Hz, 1H).

Example 1005:

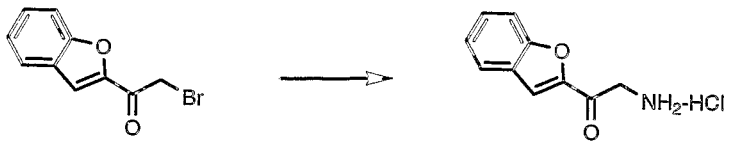


1005A **1005B**

General procedure for example **1005**

Compound **1005A** was treated with one equivalent of hexamethylene tetraamine in chloroform or other suitable solvent for about 5 hours. The product was collected by filtration and then treated with HCl in ethanol for one day to three days. The solid was then collected by filtration to give compound **1005B**.

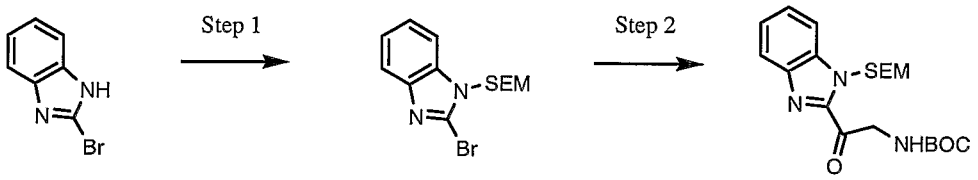
Example 1006



1006A 1006B

1-Benzofuran-2-yl-2-bromo-ethanone (**1006A**, 3.0g, 12.55 mmol), hexamethylene tetraamine (1.94 g, 13.80 mmol), and NaI (350 mg) were stirred in $CHCl_3$ (40 mL) for five hours. The solid was collected by filtration and dried under vacuum. The solid was then suspended in ethanol (30 mL) and HCl (conc, 36% in water,10 mL) was added. The solution was stirred at 25 °C for 4 d. The solid was collected by filtration and washed by ethanol, dried under vacuum to give compound **1006B** (3.05 g, contained NH_4Cl).

Example 1007



1007A 1007B 1007C

Step 1

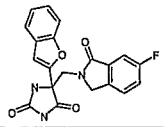
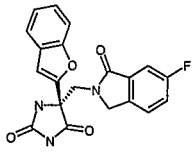
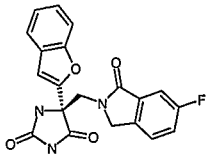
To a flame dried flask was added 2-bromo-1H-benzimidazole (**1007A**, 2.94 g, 14.92 mmol), anhydrous THF (75 mL), and NaH (95%, 490 mg, 19.4 mmol). The solution was stirred at 25 °C for 45 minutes; SEMCl (3.17 mL, 17.9 mmol) was added. The solution was stirred at 25 °C for 2.5 hours. Water (50 mL) and EtOAc (100 mL) were added. The aqueous layer was separated and extracted with EtOAc (100 mL) once. The organic layers were combined and concentrated under vacuum. The product was purified by SGC (Hexane/EtOAc: 3:1) to give compound **1007B** (3.6 g, 74%).

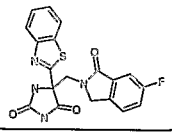
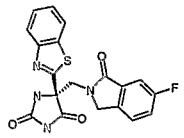
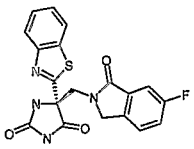
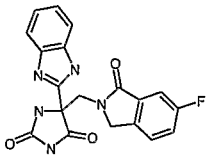
Step 2

To a flame dried flask was added compound **1007B** (1.427 g, 4.35 mmol) and anhydrous ethyl ether/THF (2:1, 15 mL). The solution was cooled to -78°C. n-Butyllithium (1.6 M, 0.46 mL, 0.73 mmol) was added and stirred at -78 °C for 30 minutes. In another flamed dried pear shaped flask was added N-(tert-butoxycarbonyl)glycine-N'-methoxy-N'-methylamide (949 mg, 4.35 mmol) and anhydrous THF (2 mL). Isopropyl magnesium chloride (2 M, 2.5 mL, 5.0 mmol) was added at 0 °C. The solution was stirred at 0 °C for 5 minutes and was added into the compound **1003C** solution via cannula at -78 °C. The solution was then gradually warmed up to -20 °C and stirred between -20 °C and 10 °C for 4 hours. Saturated NH_4Cl solution was added and the aqueous solution was extracted with EtOAc (50 mL) three times. The organic phases were combined and concentrated. The product was purified by SGC (Hexane/EtOAc: 3:1) to give compound **1007C** (1.0 g, 57%).

The following compounds were prepared as described in **Example 1, 14, 1005, 1006, and/or 1007.**

Table 1001

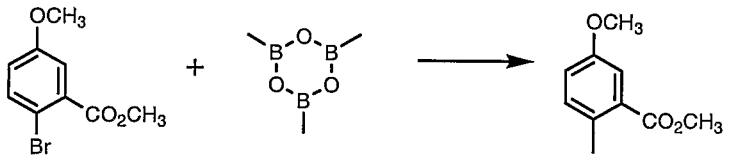
Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
177		379.10	380.1 $[M+H]^+$	A
178		379.10	380.1 $[M+H]^+$	A
179		379.10	380.1 $[M+H]^+$	D

180		396.07	397.1 $[M+H]^+$	B
181		396.07	397.1 $[M+H]^+$	A
182		396.07	397.1 $[M+H]^+$	B
183		379.11	380.1 $[M+H]^+$	A

Proton NMR Spectral Data for Selected Compounds in Table 1003.

Compound 181. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.3 (s, 1H), 9.34 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.67 (m, 1H), 7.61 (m, 1H), 7.50 (m, 3H), 4.65 (d, J = 14.3 Hz, 1H), 4.44 (d, J = 17.3 Hz, 1H), 4.38 (d, J = 17.3 Hz, 1H), 4.34 (d, J = 14.3 Hz, 1H).

Example 1008



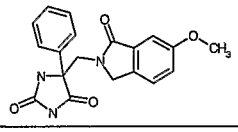
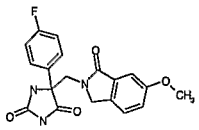
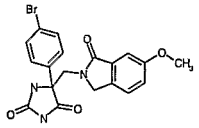
1008A **1008B** **1008C**

Compound **1008A** (20g, 81.61 mmol), **1008B** (13.36 mL, 97.93 mmol), $Pd(dppf)Cl_2$ (1.0g, 1.36 mmol), dioxane (350 mL), water (50 mL), and Cs_2CO_3

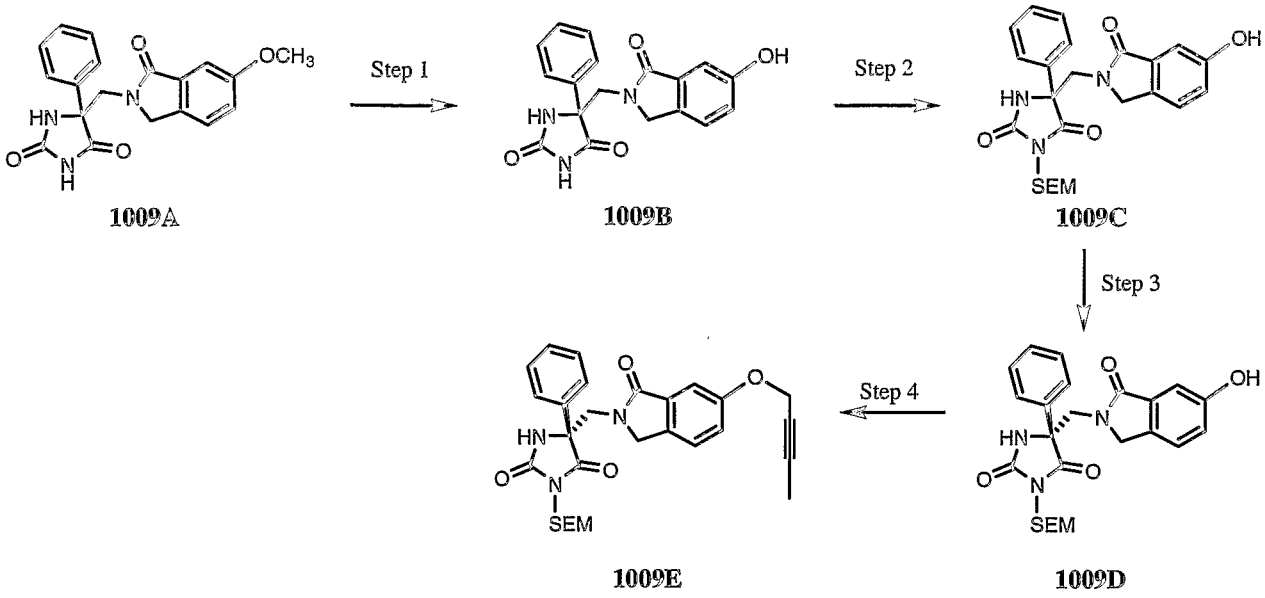
(22.5g, 163 mmol) were stirred at 110 °C (oil bath) under nitrogen for 16 hours. After cooling, the solid was removed by filtration. The solution was concentrated and purified by SGC (Hexane/EtOAc, 10:1) to give **1008C** (12.1g, 80%).

The following compounds were prepared as described in Examples 14 and 1008.

Table 1002

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
184		351.12	352.1 $[M+H]^+$	A
185		369.11	370.1 $[M+H]^+$	A
186		429.03	430.2 $[M+H]^+$ 432.2 $[M+Na]^+$	A

Example 1009



1009A 1009B 1009C 1009E 1009D

Step1

Compound **1009A** (1.18g, 3.36mmol) and pyridine hydrochloride (2.33g, 20.17 mmol) were added into a 20 mL microwave reactor tube and reacted at 200 °C for 1 hour. After cooling down, the solid was dissolved in DMF and purified by C18 chromatography (CH_3CN/water 5% to 90%, with 0.1% HCO_2H) to give compound **1009B** (0.87 g, 77%).

Step 2

Compound **1009B** (0.75 g, 2.22 mmol) was dissolved in DMF (12 mL). SEMCl (0.48 mL, 2.44 mmol) and DIPEA (0.775 mL, 4.44 mmol) were added and the solution was stirred at 25 °C for 4 hours. DMF was removed under vacuum and the product was purified by SGC (Hexane/EtOAc: 3:1 to 1:1) to give compound **1009C** (0.81 g, 78%).

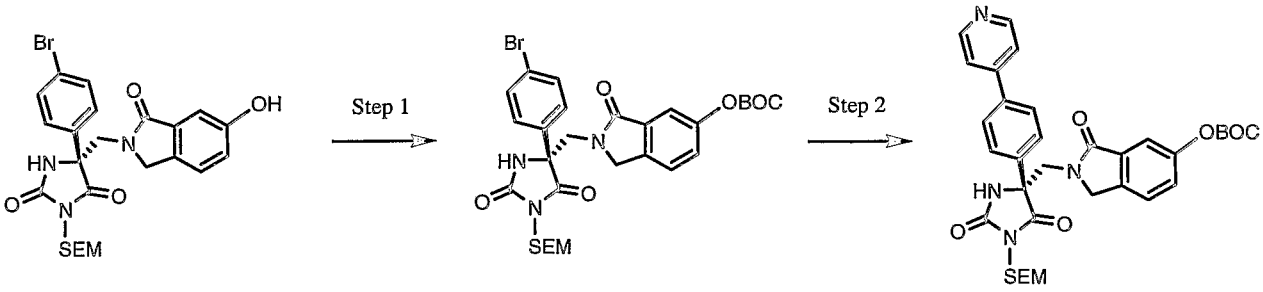
Step 3

Compound **1009C** was resolved on Chiralcel OD column by using Hexane and 2-propanol as mobile phase. The first peak was collected and concentrated to give compound **1009D**.

Step 4

Compound **1009D** (100mg, 0.214 mmol), 1-bromo-2-butyne (34 mg, 0.257 mmol), and Cs_2CO_3 (140 mg, 0.428 mmol) were stirred in DMF (2 mL) at 0 °C for 2 hours, then at 25 °C for overnight. Water (5 mL) was added and the aqueous solution was extracted with EtOAc (10 mL) three times. The organic phases were combined and concentrated. The product was purified by SGC (Hexane/EtOAc: 3:1) to give compound **1009E** (81 mg).

Example 1010



1010A **1010B** **1010C**

1010D

Step 1

Compound **1010A** (1.03g, 1.88 mmol), $(BOC)_2O$ (493 mg, 2.26 mmol), and Cs_2CO_3 (741 mg, 2.26 mmol) were stirred overnight in $CHCl_3$ (20 mL). Water was added. The aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were concentrated and purified by SGC (Hexane/EtOAc 5% to 90%) to give compound **1010B** (1.01 g, 83%).

Step 2

To a dry flask was added compound **1010B** (500 mg, 0.77 mmol) and 4-pyridyl boronic acid (190 mg, 1.55 mmol). The flask was vacuumed and

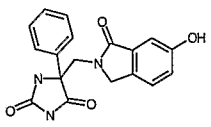
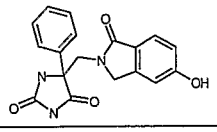
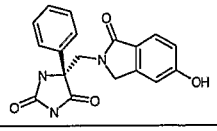
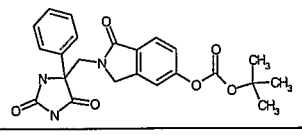
refilled with nitrogen three times. $Pd(dppf)Cl_2$ (28 mg, 0.04 mmol) was added and followed by addition of CH_3CN (5 mL) and K_2CO_3 (1M, 4 mL). The solution was stirred at 80 °C (oil bath) for 16 hours. After cooling down, CH_3CN (100 mL) was added and the solid was removed by filtration. The aqueous layer was separated and extracted once with EtOAc (20 mL). The organic solution was combined and concentrated. The product was purified by SGC (CH_2Cl_2/MeOH/NH_4OH: 20:1:0.1) to give compound **1010C**.

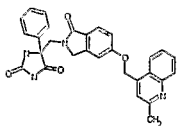
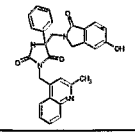
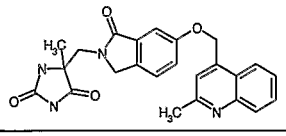
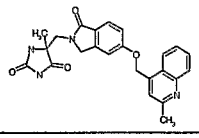
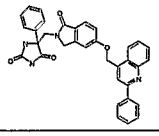
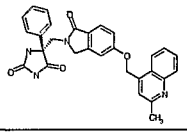
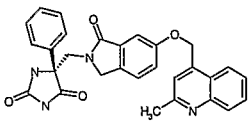
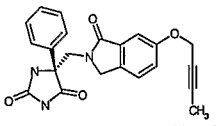
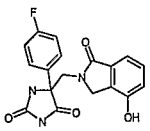
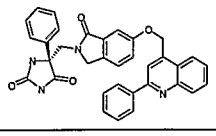
Step 3

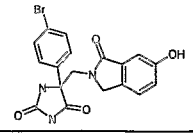
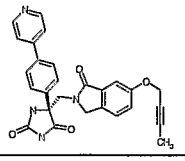
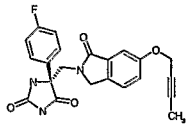
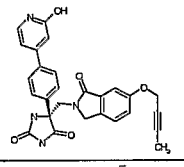
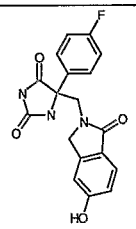
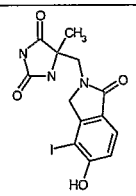
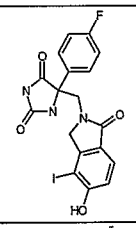
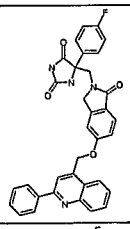
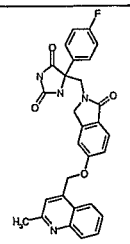
Compound **1010C** obtained in step 2 was dissolved in MeOH (10 mL) and HCl (4M in dioxane, 3 mL) was added and stirred overnight at 25 °C. MeOH was then removed and the product was dried under vacuum to give compound **1010D** (315 mg, 75% from compound **1010B**).

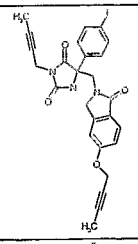
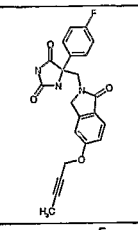
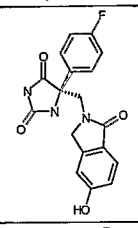
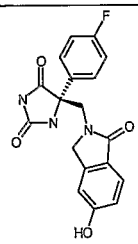
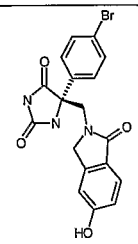
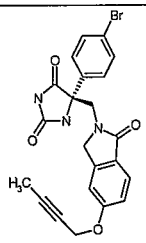
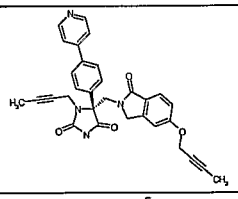
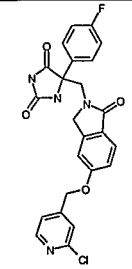
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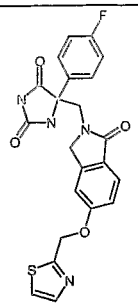
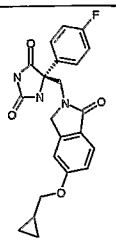
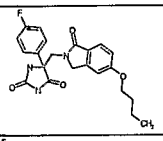
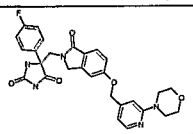
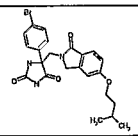
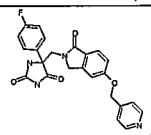
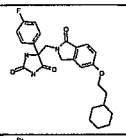
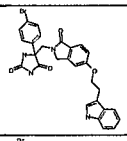
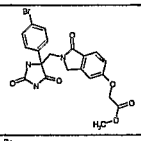
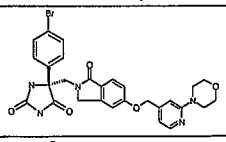
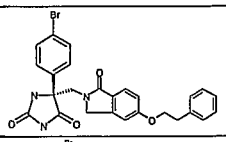
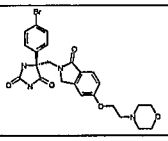
Table 1003

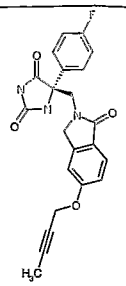
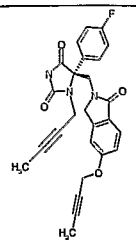
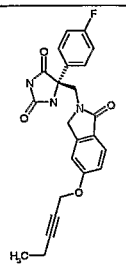
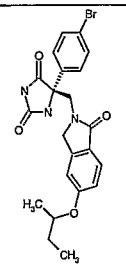
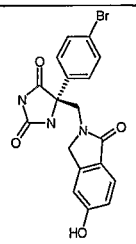
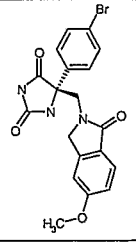
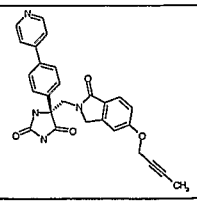
Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
187		337.11	338.1 $[M+H]^+$	B
188		337.11	338.1 $[M+H]^+$ 360.1 $[M+Na]^+$	A
189		337.11	338.2 $[M+H]^+$ 360.2 $[M+Na]^+$	A
190		437.16	438.2 $[M+H]^+$	A

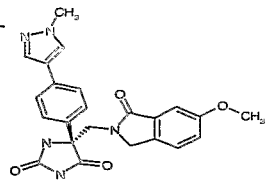
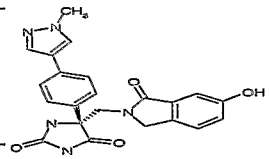
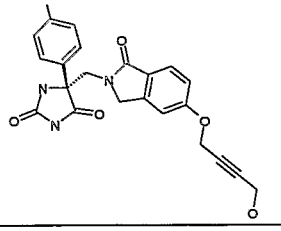
191		492.18	493.3 $[M+H]^+$	A
192		492.18	493.3 $[M+H]^+$	C
193		430.16	431.1 $[M+H]^+$	A
194		430.16	431.1 $[M+H]^+$	A
195		554.20	555.1 $[M+H]^+$	B
196		492.16	493.1 $[M+H]^+$	A
197		492.16	493.1 $[M+H]^+$	A
198		389.14	390.1 $[M+H]^+$	A
199		355.10	356.1 $[M+H]^+$	C
200		554.20	555.1 $[M+H]^+$	B

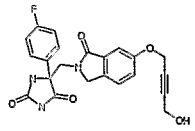
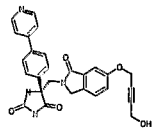
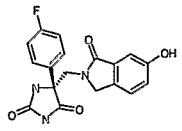
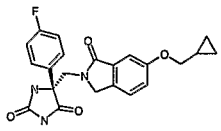
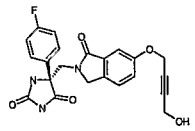
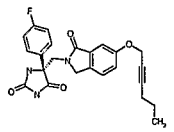
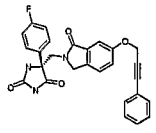
201		415.02	416.2 $[M+H]^+$	B
202		466.16	467.1 $[M+H]^+$	A
203		407.13	408.2 $[M+H]^+$	A
204		482.16	483.3 $[M+H]^+$	A
205		355.1	356 $[M+H]^+$	A
206		400.99	402 $[M+H]^+$	C
207		480.99	482 $[M+H]^+$	D
208		572.19	573 $[M+H]^+$	B
209		510.17	511 $[M+H]^+$	A

210		459.16	460 $[M+H]^+$	D
211		407.13	408 $[M+H]^+$	A
212		355.1	356 $[M+H]^+$	C
213		355.1	356 $[M+H]^+$	A
214		415.02	416.418 $[M+H]^+$	A
215		467.05	468.470 $[M+H]^+$	A
216		518.2	519 $[M+H]^+$	C
217		480.1	481 $[M+H]^+$	A

218		452.1	453 $[M+H]^+$	B
219		409.14	410 $[M+H]^+$	A
220		411.16	412 $[M+H]^+$	A
221		531.19	532 $[M+H]^+$	B
222		485.1	486.488 $[M+H]^+$	A
223		446.14	447 $[M+H]^+$	A
224		465.21	466 $[M+H]^+$	C
225		558.09	559.561 $[M+H]^+$	A
226		487.04	488.490 $[M+H]^+$	A
227		591.11	592.1 $[M+H]^+$	B
228		519.1	520.1 $[M+H]^+$	C
229		528.1	529.4 $[M+H]^+$	B

230		407.13	408 $[M+H]^+$	A
231		459.16	460 $[M+H]^+$	C
232		421.14	422 $[M+H]^+$	A
233		471.08	472.474 $[M+H]^+$	C
234		415.02	416.418 $[M+H]^+$	A
235		429.03	430.432 $[M+H]^+$	A
236		466.16	467 $[M+H]^+$	A

237		431.44	432.2 $[M+H]^+$	A
238		417.41	418.2 $[M+H]^+$	n/a
239		423.12	424.2 $[M+H]^+$	A

240		423.12	424.2 $[M+H]^+$	A
241		482.16	483.3 $[M+H]^+$	A
242		355.10	356.2 $[M+H]^+$	A
243		409.14	410.2 $[M+H]^+$	A
244		423.12	424.1 $[M+H]^+$	n/a
245		435.16	436.2 $[M+H]^+$	n/a
246		469.14	470.3 $[M+H]^+$	n/a

Proton NMR Spectral Data for Selected Compounds in Table 1003.

Compound 198. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 7.64 (m,2H). 7.43 (m, 4H), 7.22 (t, J = 2.2 Hz, 1H), 7.16 (dd, J = 9.6, 1.2 Hz, 1H). 4.82 (d, J = 2.0 Hz, 2H), 4.16 (m, 4H), 3.33 (s, 3H).

Compound 203. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.63 (dd, J = 8.8, 5.6 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.13 (m, 4H), 4.80 (d, J = 0.8 Hz, 1H), 4.39 (d, J = 17.6 Hz, 1H), 4.17 (d, J = 17.6 Hz, 1H), 4.13 (d, J = 13.6 Hz, 1H), 3.71 (d, J = 13.6 Hz, 1H) 3.34 (s, 3H).

Compound 213. ^{1}H NMR (500 Hz, CD_3OD) δ 4.11 (d, J = 15Hz, 1H), 4.27 (d, J = 15Hz,1H), 4.29 (d, J = 17Hz, 1H), 4.38 (d, J = 17Hz, 1H), 6.84-6.89 (m,2H), 7.16-7.21 (m,2H), 7.56-7.60 (m, 1H), 7.71-7.76 (m,2H)

Compound 219. ^{1}H NMR (500 Hz, CD_3OD) δ 0.36-0.40 (m,2H), 0.61-0.68 (m, 2H), 1.25-1.35 (m,1H), 3.91 (d, J = 7Hz, 2H), 4.14 (d, J = 15Hz,1H), 4.30 (d, J = 15Hz,1H), 4.34 (d, J = 17Hz,1H), 4.43 (d, J = 17Hz,1H), 7.01-7.05 (m,2H), 7.17-7.23 (m,2H), 7.65-7.69 (m,1H), 7.72-7.77 (m,2H)

Compound 232. ^{1}H NMR (500 Hz, CD_3OD) δ 1.13 (t, J = 8Hz, 3H), 2.21-2.27 (m, 2H), 4.15 (d, J = 14Hz,1H), 4.31 (d, J = 14Hz, 1H), 4.36 (d, J = 17Hz, 1H), 4.45 (d, J = 17Hz,1H), 4.79 (t, J = 2Hz, 2H), 7.04-7.14 (m, 2H), 7.16-7.25 (m,2H), 7.64-7.79 (m, 3H).

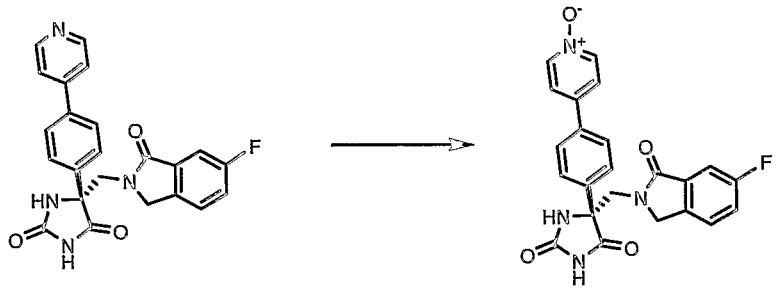
Compound 233. ^{1}H NMR (500 Hz, CD_3OD) δ 7.678 (d, J = 8.5Hz, 1H); 7.455 (d, J = 4.1Hz, 1H), 7.817 (d, J = 4.1Hz, 1H); 7.099 (s, 1H); 7.052 (dd, J = 2.207, 6.305Hz, 1H); 4.515 (d, J = 17.3 Hz, 1H), 4.450 (d, J = 17.3 Hz, 1H); 4.065 (d, J = 14.5 Hz, 1H); 3.89 (s, 3H); 3.87(d, J = 14.5 Hz, 1H); 3.85 (m, 1H); 2.46 (m. 2H); 2.09 (m, 1H)1.89 (m, 1H); 1.76 (m, 1H); 1.67(m, 1H); 1.54 (m, 1H); 1.32 (m, 1H).

Compound 239. ^{1}H NMR (500 Hz, DMSO-d_6) δ 4.11 (d, J = 15 Hz, 1H), 4.27 (d, J = 15 Hz,1H), 4.29 (d, J = 17 Hz, 1H), 4.38 (d, J = 17 Hz, 1H), 6.84-6.89 (m,2H), 7.16-7.21 (m,2H), 7.56-7.60 (m, 1H), 7.71-7.76 (m,2H)

Compound 243. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.53 (s, 1H), 7.67 (dd, J = 8.5, 5 Hz, 2H), 7.46 (d, J = 8 Hz, 1H), 7.27 (t, J = 8.5 Hz, 2H), 7.15 (m, 2H), 4.31 9d, J = 17.0 Hz, 1H), 4.22 (d, J = 17 Hz, 1H), 4.13 (d, J = 14.2 Hz, 1H),

4.06 (d, J = 14.2 Hz, 1H), 3.88 9d, J = 6.5 Hz, 2H), 3.35 9m, 2H), 1.22 (m, 1H), 0.57 (d, J = 8 Hz, 1H), 0.33 (d, J = 5 Hz, 1H).

Example 1011

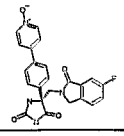


1011A 1011B

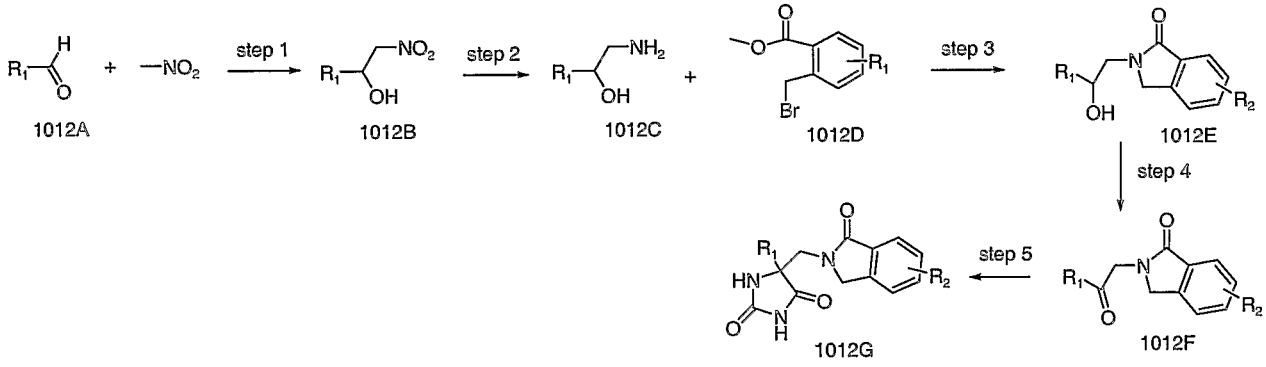
To a solution of compound **1011A** (100mg) in DMF (5 mL) was added m-chlorobenzoyl peroxide (MCPBA, 100mg). The solution was stirred overnight at 25 °C. The product was purified by C18 reverse phase chromatography (CH_3CN/water 5% to 90%, with 0.1% HCO_2H) to give compound **1011B** (73 mg).

The following compounds were prepared as described in **Examples 1010 and 1011.**

Table 1004

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
247		432.12	433.1 $[M+H]^+$	A

Example 1012.



In step 1, Compound **1012A** was treated with nitromethane and KO^{t}Bu in a mixture of THF and *t*-BuOH for 2 to 12 h. Alternatively, compound **1012A** was treated with nitromethane and TBAF in a suitable solvent such as THF for 2 to 12 h. Compound **1012B** was purified by silica gel chromatography.

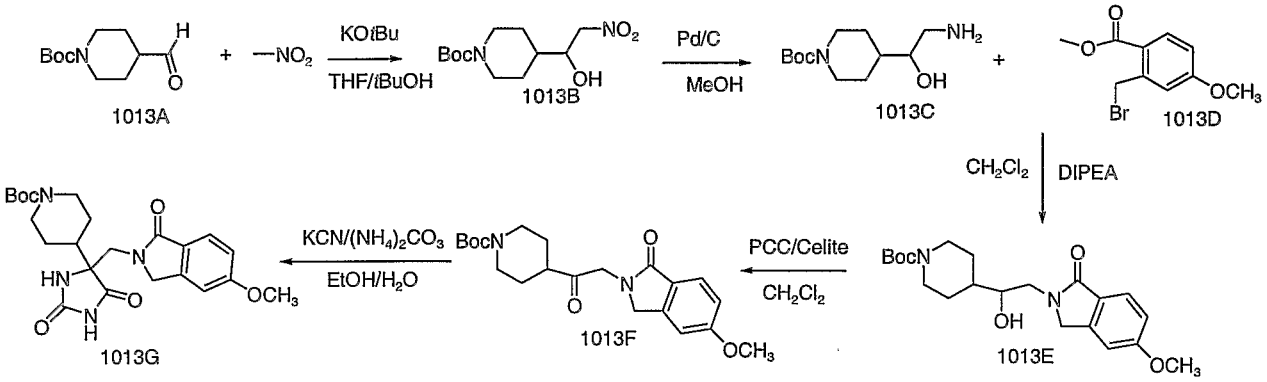
In step 2, Compound **1012B** was treated with Pd/C in a suitable solvent such as methanol, in a Parr shaker under H_2 atmosphere. After filtering off the catalyst and concentration of solvent, the product was used without further purification.

In step 3, the benzyl bromide (compound **1012D**) was mixed with compound **1012C**, DIPEA, and DMF. The solution was stirred at 0 °C to room temperature for 12 to 24 hours. The product was either removed by filtration or purified by silica gel chromatography.

In step 4, compound **1012E** was treated with PCC and Celite in a suitable solvent such as dichloromethane for 2 to 12 h. Compound **1012F** was purified by silica gel chromatography.

In step 5, compound **1012F** was reacted with potassium cyanide and ammonium carbonate in an appropriate alcohol and water solution, at 50 °C to 90 °C, for 5 to 48 hours. After cooling, water was added and compound **1012G** was collected by filtration.

Example 1013.



Compound **1013B**: To a solution of THF (15 mL) and t-BuOH (15 mL) was added compound **1013A** (1.2 g, 5.6 mmol) and nitromethane (0.61 mL, 11.2 mmol) followed by addition of KO^{t}Bu (0.63 g, 5.6 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH 6 using HOAc. The reaction mixture was diluted with EtOAc (30 mL), and was extracted with brine. The aqueous layer was extracted with EtOAc (30 mL × 2) The combined organic layers were washed with brine, dried, and concentrated to dryness. The crude material was purified via PTLC (25% EtOAc/Hexanes) to give 1.24 g (81%) of compound **1013B.**

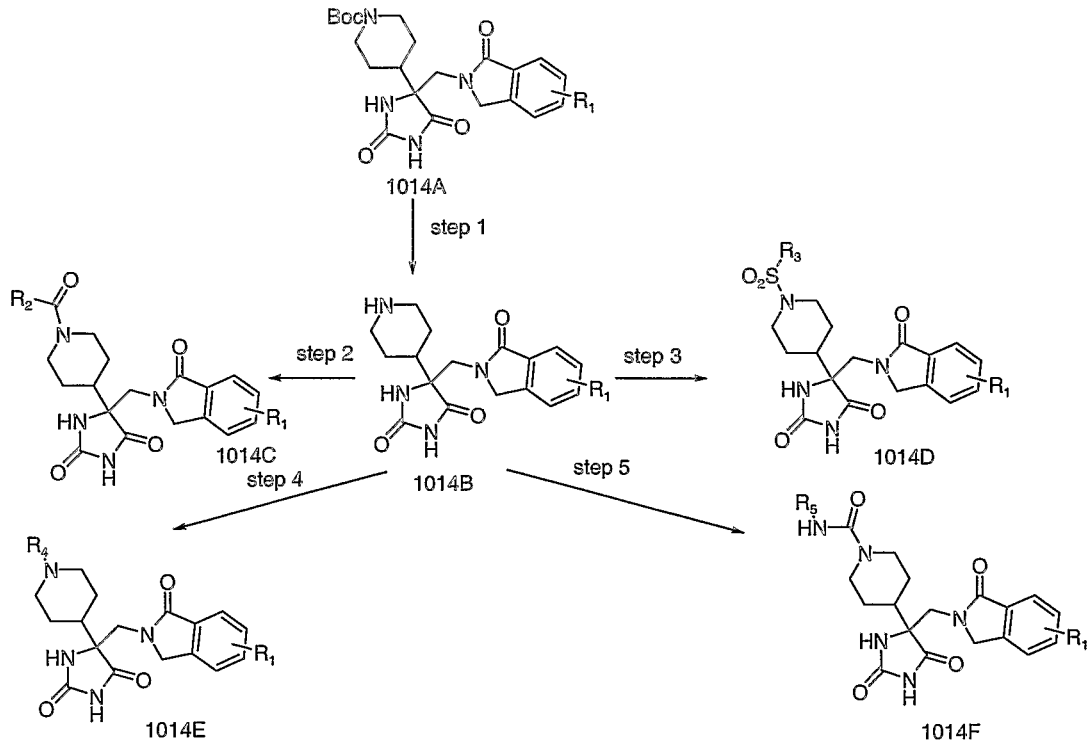
Compound **1013C**: Compound **1013B** (1.24 g, 4.5 mmol) was treated with Pd/C in methanol in a Parr shaker under H_2 atmosphere (50 psi) overnight. After filtering off the catalyst and concentration of solvent, compound **1013C** (1.1 g, 99%) was used without further purification.

Compound **1013E**: Compound **1013C** (1.02 g, 4.2 mmol) was dissolved in dichloromethane (30 mL) at 0 °C. Compound **1013D** (1.13 g, 4.2 mmol) and DIPEA (0.73 mL, 4.2 mmol) were added and the reaction was stirred at 0 °C and slowly warmed up to rt overnight. The reaction mixture was washed with HCl (1N, 50 mL) and brine (50 mL). The organic layer was dried and concentrated to dryness. The crude material was purified via PTLC (50% EtOAc/Hexanes) to give 0.88 g (54%) of compound **1013E.**

Compound **1013F**: Compound **1013E** (0.88 g, 2.25 mmol) was dissolved in methylene chloride (30 mL). PCC (1.22 g, 5.63 mmol) and Celite (1.22 g) were added and the reaction mixture was stirred at 25 °C overnight. The solid was filtered off and the resulting solution was concentrated and purified via sgc (90% EtOAc/Hexanes) to give 0.62 g (71%) of compound **1013F.**

Compound **1013G**: Compound **1013F** (1.01 g, 2.6 mmol), KCN (0.25 g, 3.9 mmol), and $(NH_4)_2CO_3$ (0.75 g, 7.8 mmol) were suspended in a mixture of NH_3 in Methanol (7 N, 10 mL) and water (10 mL). The solution was stirred at 90 °C overnight. After cooling, water (20 mL) was added. The solid was filtered and washed with water three times. The solid was dried under vacuum to give compound **1013G** (0.86 g, 72%).

Example 1014.



Step 1.

Compound **1014A** was stirred with 2 to 20 equivalents of hydrogen chloride in methanol for 5 to 48 hours. The solvent was removed and the compound **1014B** could be used without further purification.

Step 2.

Compound **1014B** was treated with carboxylic anhydride and DIPEA to give compound **1014C** which was purified by silica gel chromatography.

Step 3.

Compound **1014B** was coupled with sulphonyl chloride compound to give compound **1014D**, which was purified by silica gel chromatography.

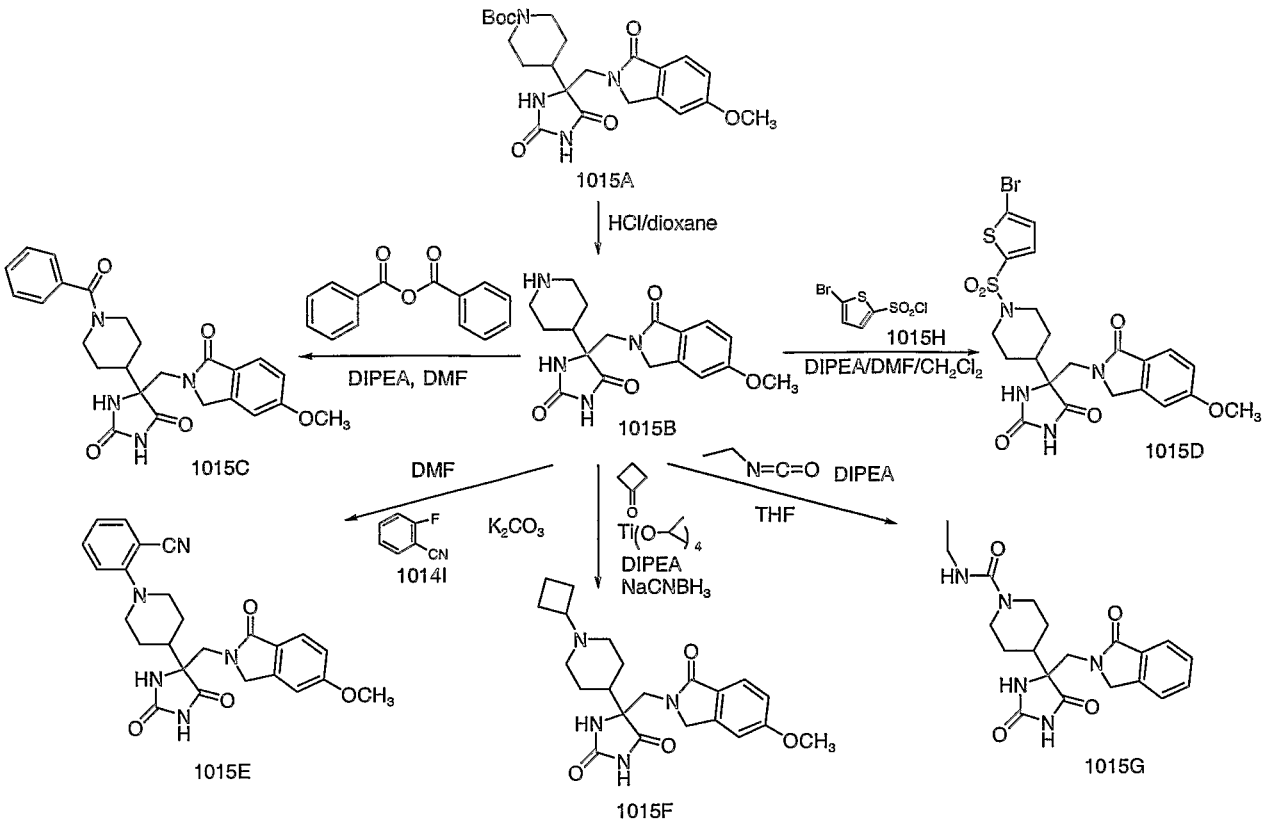
Step 4.

Compound **1014B** was reacted with carbonyl compound under reductive amination conditions to give compound **1014E**. Alternatively, compound **1014B** was treated with a suitable electrophile and a base to give compound **1014E**, which was purified by silica gel chromatography.

Step 5.

Compound **1014B** was reacted with isocyanate compound and DIPEA to give compound **1014F**, which was purified by silica gel chromatography.

Example 1015.



Compound **1015B**: Compound **1015A**(0.86 g) was suspended in methanol (10 mL) and HCl (4M in dioxane, 10 mL) was added. The solution was stirred at 25 °C for 3 hours. Solvent was removed and the material was dried under vacuum to give compound **1015B** (0.74 g, 99%).

Compound **1015C**: Compound **1015B** (40 mg, 0.11 mmol) and benzoic acid anhydride (25 mg, 0.11 mmol) were dissolved in DMF (1 mL). DIPEA (0.06 mL, 0.33 mmol) was added and the reaction mixture was stirred at room temperature overnight. Solvent was removed and the crude material was purified via sgc (5% NH_3•MeOH/CH_2Cl_2) to give 3.7 mg (7%) of compound **1015C**.

Compound **1015D**: Compound **1015B** (40 mg, 0.11 mmol) and compound **1015H** (30 mg, 0.11 mmol) were dissolved in DMF (1 mL). DIPEA (0.25 mL, 1.4 mmol) was added and the reaction mixture was stirred at room

temperature overnight. Solvent was removed and the crude material was purified via sgc (5% NH_3•MeOH/CH_2Cl_2) to give 2.2 mg (3%) of compound **1015D**.

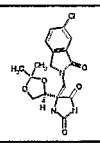
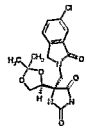
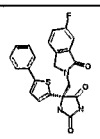
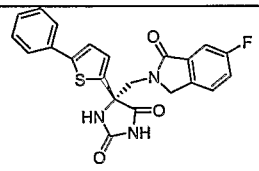
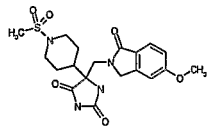
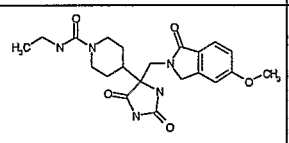
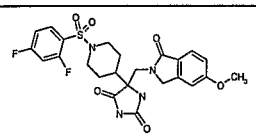
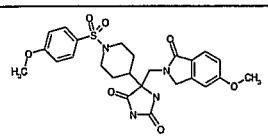
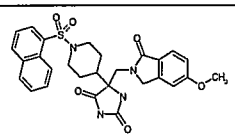
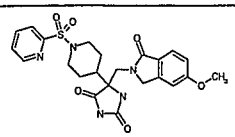
Compound **1015E**: Compound **1015B** (40 mg, 0.11 mmol) and compound **1015I** (0.024 mL, 0.22 mmol) were dissolved in DMF (1 mL). K_2CO_3 (46 mg, 0.33 mmol) was added and the reaction mixture was stirred at 90 °C overnight. Solvent was removed and the crude material was purified via sgc (5% NH_3•MeOH/CH_2Cl_2) to give 2.6 mg (5%) of compound **1015E**.

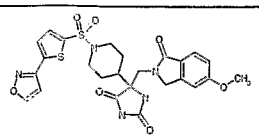
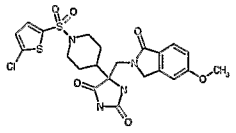
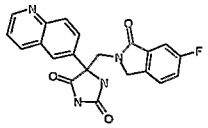
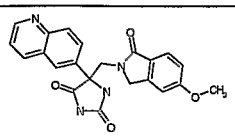
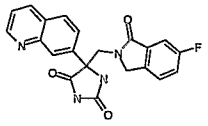
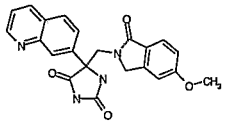
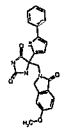
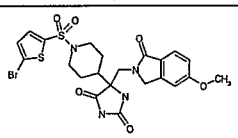
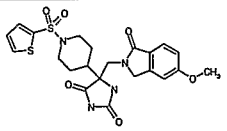
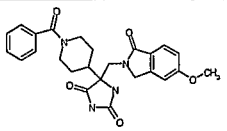
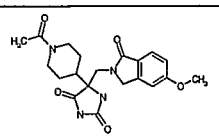
Compound **1015F**: Compound **1015B** (46 mg, 0.13 mmol) and cyclobutanone (0.2 mL) were stirred in methylene chloride (1 mL). Titanium tetraisopropoxide (0.045 mL, 0.15 mmol) was added followed by addition of DIPEA (0.027 mL, 0.16 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, $NaCNBH_3$ (41 mg, 0.65 mmol) was added and the mixture was stirred at rt overnight. The solvent was removed. The crude material was purified via PTLC (10% NH_3•MeOH/CH_2Cl_2) to give 3.1 mg (6%) of compound **1015F.**

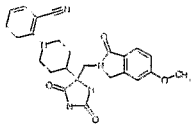
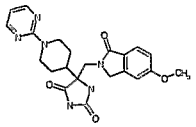
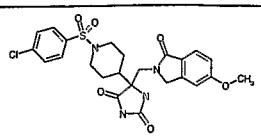
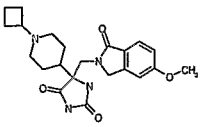
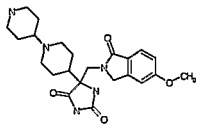
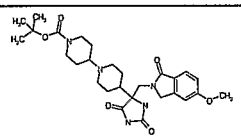
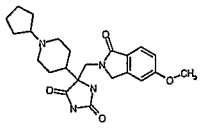
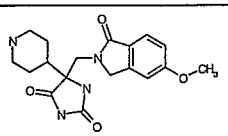
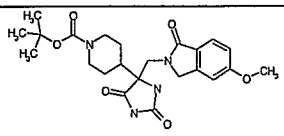
Compound **1015G**: Compound **1015B** (80 mg, 0.24 mmol) and ethyl isocyanate (0.018 mL, 0.24 mmol) were dissolved in DMF (1 mL). DIPEA (0.17 mL, 0.97 mmol) was added and the reaction mixture was stirred at room temperature overnight. Solvent was removed and the crude material was purified via sgc (9% NH_3•MeOH/CH_2Cl_2) to give 11 mg (11%) of compound **1015G**.

The following compounds were prepared as described in **Examples 1012 to 1015.**

Table 1005

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
248		379.09	380.1[M+H]$^+$	C
249		379.09	380.1[M+H]$^+$	C
250		421.09	422.1[M+H]$^+$	B
251		421.09	422.1[M+H]$^+$	A
252		436.14	437.1[M+H]$^+$	B
253		429.2	430.1[M+H]$^+$	B
254		534.14	535.1[M+H]$^+$	B
255		528.17	529.3[M+H]$^+$	B
256		548.17	549.3[M+H]$^+$	A
257		499.15	500.3[M+H]$^+$	B

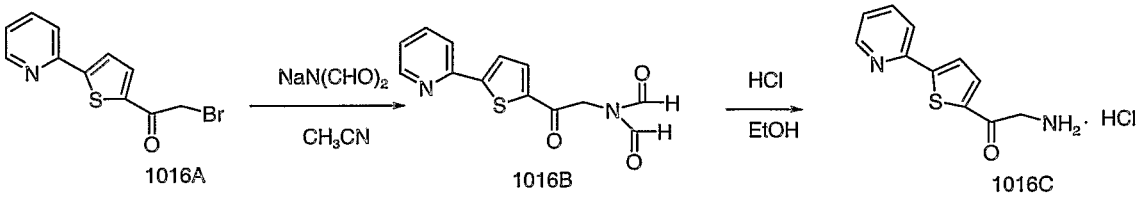
258		571.12	572.1[M+H]$^+$	A
259		538.07	539.1[M+H]$^+$	A
260		390.11	391.1[M+H]$^+$	A
261		402.13	403.2[M+H]$^+$	A
262		390.11	391.1[M+H]$^+$	A
263		402.13	403.1[M+H]$^+$	A
264		433.11	434.1[M+H]$^+$	A
265		582.02	585.1[M+H]$^+$	A
266		504.11	505.1[M+H]$^+$	A
267		462.19	463.1[M+H]$^+$	B
268		400.17	401.1[M+H]$^+$	A

269		459.19	460.1[M+H]$^+$	B
270		436.19	437.2[M+H]$^+$	B
271		532.12	533.3[M+H]$^+$	B
272		412.21	413.2[M+H]$^+$	C
273		441.24	442.1[M+H]$^+$	C
274		541.29	542.3[M+H]$^+$	C
275		426.23	427.2[M+H]$^+$	C
276		358.16	359.1[M+H]$^+$	C
277		458.22	459.1[M+H]$^+$	B

Proton NMR Spectral Data for Selected Compounds in Table 1005.

Compound 262. ^{1}H NMR (500 Hz, CD_3OD) δ 8.921 (m, 1H); 8.433 (d, J = 8.6 Hz, 1H); 8.357 (s, 1H); 8.072 (m, 4H); 7.622 (m, 1H); 7.545 (m, 1H); 7.476 (m, 1H); 7.369 (m, 1H); 4.522 (d, J = 17 Hz, 1H); 4.510 (d, J = 14.5 Hz, 1H); 4.425 (d, J = 17 Hz, 1H), 4.350 (d, J = 14.5 Hz, 1H).

Example 1016.



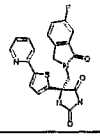
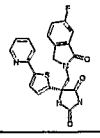
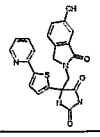
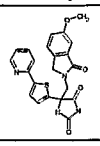
1016A 1016B 1016C

Compound **1016B**: Compound **1016A** (500 mg, 1.77 mmol) was suspended in CH_3CN (5 mL) followed by addition of $NaN(CHO)_2$ (202 mg, 2.12 mmol). The reaction mixture was stirred at rt for 30 min before warmed up to 70 °C and stirred for 2 h. Solid was collected by suction filtration and washed with acetonitrile to give **1016B** (380 mg, 78%) as brown solid.

Compound **1016C**: Compound **1016B** (380 mg, 1.38 mmol) was stirred with HCl (36% aq., 1 mL) and EtOH (10 mL) at rt for 2 days. It was then heated to 60 °C for 2 hr. Solvent was removed and it was dried under vacuum to give **1016C** (345 mg, 98%). The material was used without further purification.

The following compounds were prepared as described in **Example 1016, Example 2** and **Example 8**.

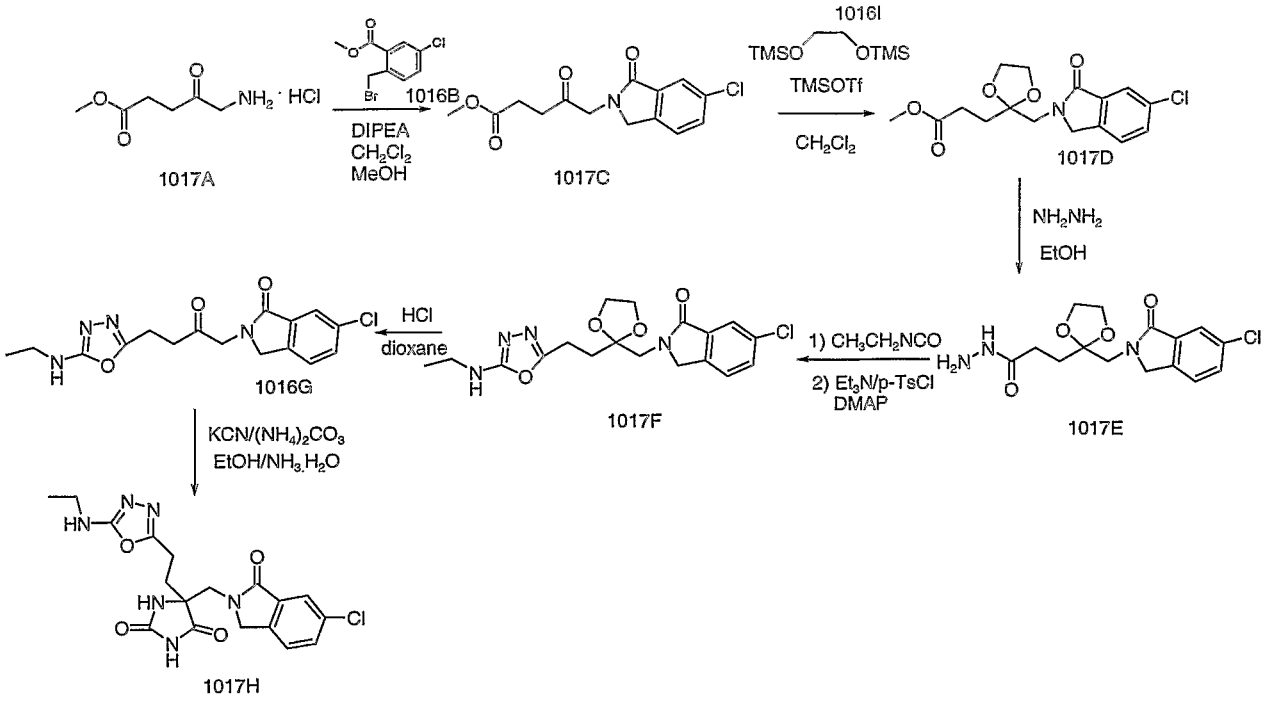
Table 1006

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
278		422.08	423.1[M+H]$^+$	A
279		422.08	423.1[M+H]$^+$	C
280		420.9	421.1[M+H]$^+$	A
281		434.1	435.2[M+H]$^+$	A

Proton NMR Spectral Data for Selected Compounds in Table 1006.

Compound 278. ^{1}H NMR (500 Hz, CD_3OD) δ 8.503 (d, J = 4.73 Hz, 1H); 7.84 (m, 2H); 7.67 (d, J = 3.8 Hz, 1H); 7.56 (dd, J = 4.4 Hz, 8.5 Hz, 1H); 7.50 (dd, J = 2.5 Hz,7.8 Hz, 1H); 7.38 (m, 1H); 7.33 (d, J = 4.1 Hz, 2H); 7.3 (m, 1H); 4.52 (d, J = 17 Hz, 1H); 4.45 (d, J = 17 Hz, 1H); 4.43 (d, J = 14.2 Hz, 1H); 4.28 (d, J = 14.2 Hz, 1H).

Example 1017.



Compound **1017C**: Compound **1017A** (1.5 g, 8.26 mmol) was dissolved in dichloromethane (20 mL) and methanol (10 mL) at 0 °C. Compound **1017B** (2.64 g, 10 mmol) and DIPEA (2.9 mL, 16.5 mmol) were added and the reaction was stirred at 0 °C and slowly warmed up to rt overnight. The reaction mixture was then heated to 50 °C and stirred for 2 h. The reaction mixture was washed with brine (50 mL). The organic layer was dried and concentrated to dryness. The crude material was purified via PTLC (50% EtOAc/hexanes) to give 0.7g (29%) of compound **1017C.**

Compound **1017D:** Compound **1017C** (200 mg, 0.68 mmol) was stirred in CH_2Cl_2 (15 mL) at 0 °C followed by addition of compound **1017I** (0.5 mL, 2.04 mmol) and TMS-OTf (13 μL, 0.07 mmol). The reaction mixture was stirred at 0 °C to 5 °C for 6 hr before warmed up to rt and stirred overnight. The solvent was removed and the crude material was purified via PTLC (EtOAc) to give 0.21g (91%) of compound **1017D.**

Compound **1017E:** Compound **1017D** (210 mg, 0.62 mmol) was heated in a sealed tube with NH_2NH_2 (0.2 mL, 6.2 mmol) and EtOH (2 mL) at 60 °C overnight. Solvent was removed and gave crude material **1017E** (210 mg, 99%) which was used without further purification.

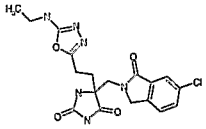
Compound **1017F:** Compound **1017E** (210 mg, 0.62 mmol) and ethyl isocyanate (59 μL, 0.74 mmol) were dissolved in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight. To this mixture was added Et_3N (0.43 mL, 3.1 mmol), DMAP (15 mg, cat.) and *p*-TsCl (141 mg, 0.74 mmol). The reaction was stirred at rt overnight. Solvent was removed and the crude material was purified via sgc (10% NH_3◦MeOH/CH_2Cl_2) to give 60 mg (25%) of compound **1017F**.

Compound **1017G:** Compound **1017F** (60 mg, 0.15 mmol) was heated in a sealed tube with HCl (3 mL, 4N in dioxane) at 65 °C for 48 hr. Solvent was removed and the crude material was purified via sgc (5% NH_3•MeOH/CH_2Cl_2) to give 35 mg (66%) of compound **1017G**.

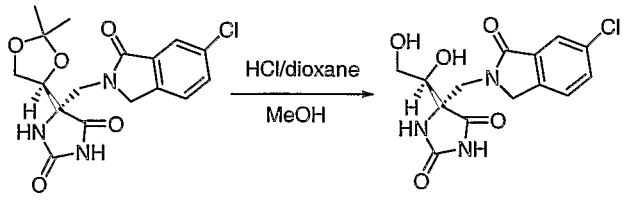
Compound **1017H**: Compound **1017G** (34 mg, 0.1 mmol), KCN (10 mg, 0.15 mmol), and $(NH_4)_2CO_3$ (30 mg, 0.3 mmol) were suspended in a mixture of NH_3•H_2O (1 mL) and ethanol (1mL). The solution was stirred at 90 °C overnight. Solvent was removed and the crude material was purified via sgc (10% NH_3•MeOH/CH_2Cl_2) to give 6 mg (15%) of compound **1017H**.

The following compounds were prepared as described in **Example 1017**

Table 1007

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
282		418.12	419.1[M+H]$^+$	B

Example 1018.

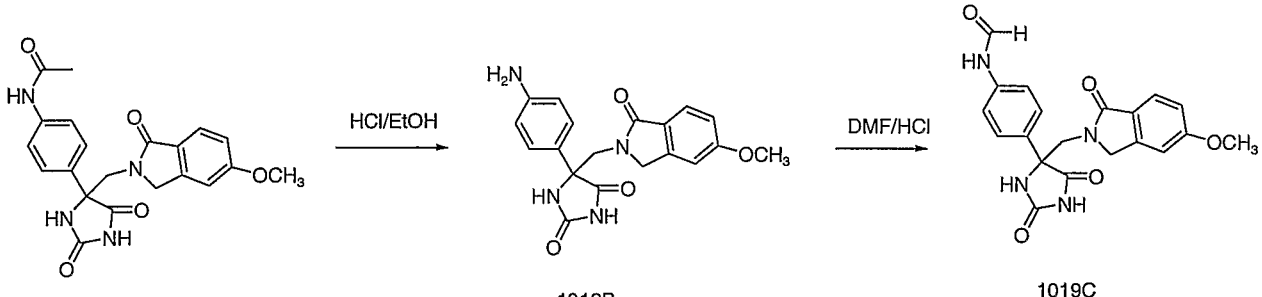


1018A 1018B

Compound **1018A**: Compound **1018A** was synthesized following procedures in **Example 1012**.

Compound **1018B**: Compound **1018A** (180 mg, 047 mmol) was stirred in MeOH (1 mL) at rt. HCl (3 mL, 4N in dioxane) was added and the reaction mixture was heated to 70 °C overnight. Solvent was evaporated. The crude material was taken up in water and the solid was collected by suction filtration to give **1018B** (115 mg, 71%).

Example 1019.



1019A 1019B 1019C

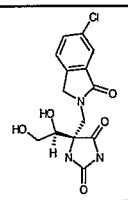
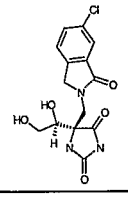
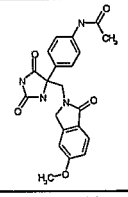
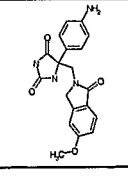
Compound **1019A**: Compound **1019A** was synthesized following procedures described in Example **1012**.

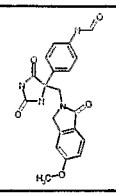
Compound **1019B**: Compound **1019A** (74 mg, 0.18 mmol) was dissolved in EtOH (2 mL) and HCl (0.4 mL, aq. 36%) was added and the reaction mixture was heated to 70 °C overnight. Solvent was removed and gave **1019B** as a light yellow solid (74 mg, 99%).

Compound **1019C**: Compound **1019B** (20 mg, 0.05 mmol) was stirred in DMF (1 mL) and HCl (cat., 4 N in dioxane) at 120 °C overnight. Solvent was removed and the crude material was purified via PTLC (9% NH_3•MeOH/CH_2Cl_2) to give 8 mg (37%) of Compound **1019C**.

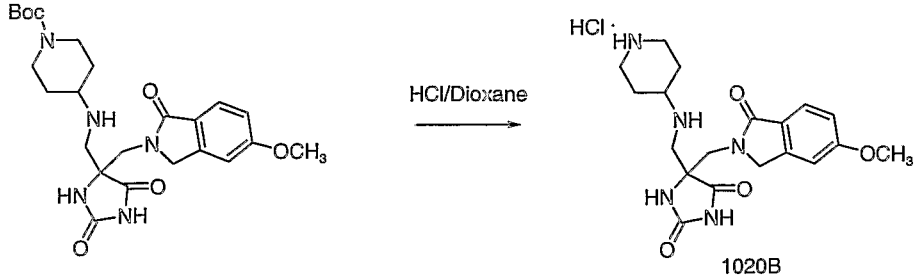
The following compounds were prepared as described in **Example 1012, 1018 and 1019.**

Table 1008

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
283		**339.06**	**340.2[M+H]$^+$**	**B**
284		**339.06**	**340.2[M+H]$^+$**	**D**
285		**408.14**	**409.2[M+H]$^+$**	**A**
286		**366.13**	**367.1[M+H]$^+$**	**A**

287		394.13	395.2[M+H]$^+$	B

Example 1020.

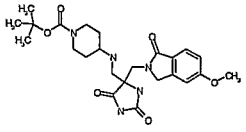
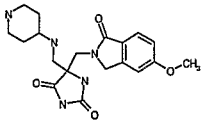


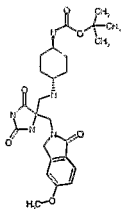
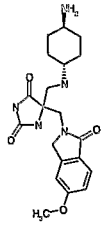
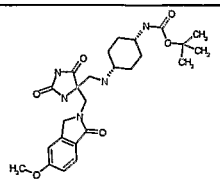
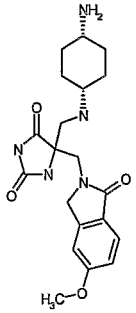
Compound **1020A**: Compound **1020A** was synthesized following the procedures described in Example 22.

Compound **1020B**: Compound **1020A** (855 mg, 1.86 mmol) was stirred in MeOH (10 mL) and HCl (10 mL, 4N in dioxane) at rt for 2 hr. Solvent was removed and the material was dried to give **1020B** (735 mg, 99%).

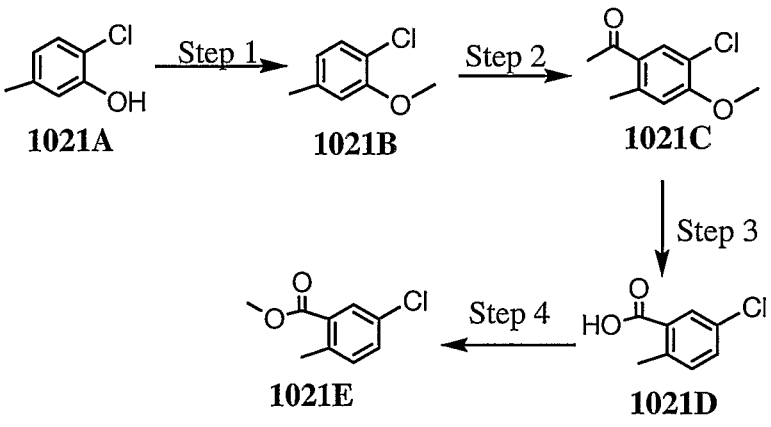
The following compounds were prepared as described in **Example 22** and **Example 1020.**

Table 1009

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
288		487.24	488.3[M+H]$^+$	B
289		387.19	388.1[M+H]$^+$	C

290		501.26	502.3[M+H]$^+$	B
291		401.21	402.2[M+H]$^+$	C
292		501.26	502.3[M+H]$^+$	B
293		401.21	402.1[M+H]$^+$	B

Example 1021



Step 1

DMF (100 mL), cesium carbonate (41.13 g, 126 mmol), and 2-chloro-5-methylphenol (**1021A**) (15.0 g, 105 mmol) were added to a flask. Methyl iodide (17.92 g, 126 mmol) was added dropwise via addition funnel. The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc, washed with water and brine, and dried with Na_2SO_4. The resulting material was filtered, and concentrated to dryness. The crude product was purified via flash sgc using 1:4 EtOAc:hexanes as the mobile phase to give 15.93 g of **1021B**.

Step 2

A flask containing $AlCl_3$ (2.55 g, 19.1 mmol), and LiCl (0.41 g, 9.6 mmol) was placed in a -30 °C cold bath. A solution of **1021B** (1.0 g, 6.38 mmol) and acetyl chloride (0.75 g, 9.5 mmol) in 20 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 1 h at -30 °C, then allowed to warm to rt and stirred overnight at rt. The reaction mixture was poured into a mixture of ice and EtOAc. The organic layer was washed with water, saturated aq $NaHCO_3$, and water, then dried with Na_2SO_4, and concentrated to dryness to give 1.18 g of Compound **1021C**.

Step 3

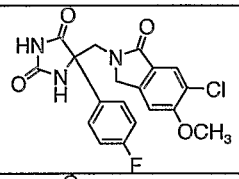
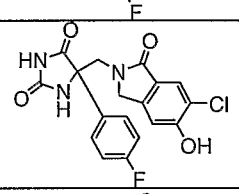
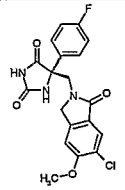
Sodium hydroxide (58 g, 1.45 mol) was dissolved in water (260 mL) and the flask was cooled in an ice-water bath. Bromine (19 mL) was added dropwise to the flask with stirring. The reaction mixture was stirred for 0.5 h after the addition was complete. The resulting solution was added dropwise to an ice-water cooled flask containing Compound **1021C** (18.5 g, 93.1 mmol). After the addition was complete, the reaction mixture was allowed to warm to rt and left stirring overnight. The reaction mixture was heated at 40 °C for 2 h. $NaHSO_3$ (55 g) was added. The reaction mixture was stirred for 1 h. The resulting material was diluted with 10% aq NaOH and extracted with EtOAc to remove starting material. The aqueous layer was adjusted to pH 1 and extracted with additional EtOAc. The organic layer was dried with Na_2SO_4, filtered, and concentrated to dryness to give 12.31 g of **1021D**.

Step 4

DMF (10 mL), Compound **1021D** (0.50 g, 2.49 mmol), and K_2CO_3 (0.41 g, 2.96 mmol) were added to a flask. Methyl iodide (0.42 g, 2.96 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated to dryness to give 0.52 g of **1021E**.

The following compounds were prepared as described in step 1 in **Example 14** and **Example 1021**.

Table 1010

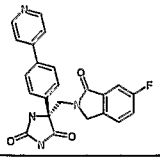
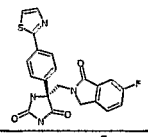
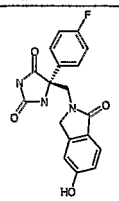
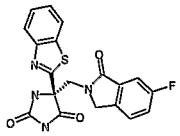
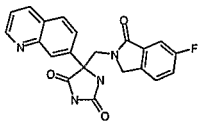
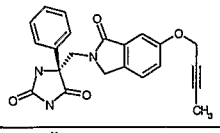
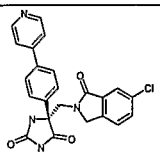
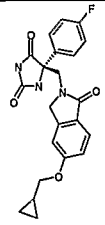
Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
296		**403.07**	**404.2 $[M+H]^+$**	**A**
297		**389.06**	**390.2 $[M+H]^+$**	**A**
298		**403.07**	**404.1 $[M+H]^+$**	**n/a**

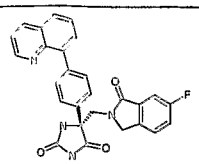
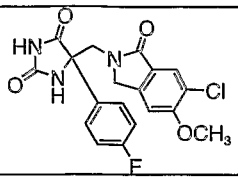
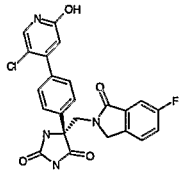
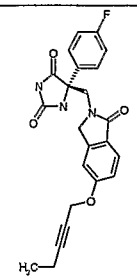
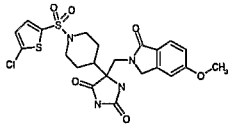
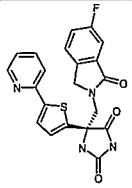
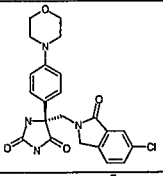
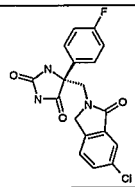
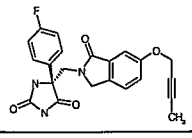
Proton NMR Spectral Data for Selected Compounds in Table 1010.

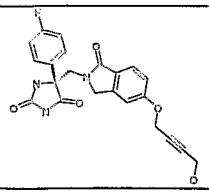
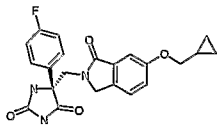
Compound 296. ^{1}H NMR (500 Hz, DMSO-d_6) δ 3.93 (s, 3H), 4.00 (d, J = 14 Hz, 1H), 4.19 (d, J = 14 Hz, 1H), 4.23 (d, J = 18 Hz,1H), 4.34 (d, J = 18 Hz, 1H), 7.24-7.34 (m, 2H), 7.42 (s, 1H), 7.62-7.73 (m, 3H), 8.92 (s, 1H), 10.95 (s, 1H).

Specific TACE inhibitory activity (Ki values) of some representative compounds of the present invention are set forth below.

Table 1011

Compound #	Structure	Ki (nM)
111		0.48
120		4
213		0.8
181		3.17
262		4.91
198		1.29
143		1.87
219		2.4

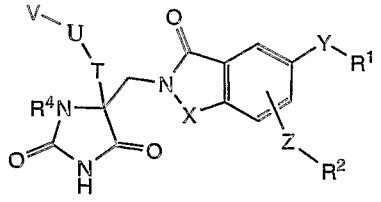
155		1.05
296		1.01
123		1.2
232		1.0
233		2.35
278		2.2
139		2.8
25		0.43
203		0.23

239		0.11
243		3.00

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

THEREFORE, WE CLAIM:

1. A compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein:

X is selected from the group consisting of –S-, $-C(R^4)_2-$ or $-N(R^4)-$;

T is selected from the group consisting of H (with U and V being absent), alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl, and arylalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of T is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

U is absent or present, and if present U is selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(R^4)_2-$, $-N(R^4)C(O)-$, $-O-$, $-N(R^4)S(O)_2-$, $-N(R^4)C(O)N(R^4)-$, and $-N(R^4)C(S)N(R^4)-$;

V is absent or present, and if present V is selected from the group consisting of alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2$, -O-,–S-, -C(O)-, -S(O)-, and $-S(O)_2-$;

Z is absent or present, and if present Z is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, -O-,–S-, -C(O)-, -S(O)-, and $-S(O)_2-$;

n is 1 to 3;

R^1 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^1 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Y is present and Y is N, S or O, then R^1 is not halogen;

R^2 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^2 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Z is present and Z is N, S or O, then R^2 is not halogen;

each R^4 is the same or different and is independently selected from the group consisting of H and alkyl;

R^{10} is selected from the group consisting of $-OR^4$, $-N(R^4)_2$, -S(O)-, $-S(O)_2-$, $-N(R^4)S(O)_2-$, $-S(O)_2N(R^4)-$, -O(fluoroalkyl), halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of R^{10} is unsubstituted or optionally independently substituted

with one to four R^{30} moieties which can be the same or different, each R^{30} moiety being independently selected from the group of R^{30} moieties below;

R^{20} is selected from the group consisting of halogen, alkyl, fluoroalkyl; and

R^{30} is selected from the group consisting of halogen, alkyl, and fluoroalkyl.

2. The compound of claim 1, wherein said isomer is a stereoisomer.

3. The compound of claim 1 wherein T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is -O-.

4. The compound of claim 1 wherein T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present, and if present Z is -O-; and R^2 is selected from the group consisting of alkylaryl and alkylheteroaryl.

5. The compound of claim 1 wherein T is alkyl or aryl; X is $-N(R^4)-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is -O-.

6. The compound of claim 1 wherein X is $-CH_2-$ or $-N(R^4)-$.

7. The compound of claim 6 wherein X is $-CH_2-$.

8. The compound of claim 6 wherein X is $-N(R^4)-$.

9. The compound of claim 8 wherein R^4 is H.

10. The compound of claim 1 wherein T is alkyl.

11. The compound of claim 10 wherein T is $-CH_3$.

12. The compound of claim 1 wherein T is aryl and said aryl is unsubstituted or optionally independently substituted with one to five R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.

13. The compound of claim 12 wherein R^{10} is halogen.

14. The compound of claim 12 wherein R^{10} is heteroaryl.

15. The compound of claim 12 wherein R^{10} is aryl.

16. The compound of claim 1 wherein U selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(O)-$, and $-N(R^4)S(O)_2-$.

17. The compound of claim 16 wherein U is a covalent bond.

18. The compound of claim 16 wherein U is -N(R^4)-.

19. The compound of claim 16 wherein U is -N(R^4)C(O)-.

20. The compound of claim 1 wherein V is selected from the group consisting of aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, and cycloalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of any of said aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.

21. The compound of claim 1 wherein Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n$-, -C(O)- and –O-.

22. The compound of claim 21 wherein Y is –O-.

23. The compound of claim 21 wherein Y is $-(C(R^4)_2)_n$-.

24. The compound of claim 21 wherein Y is –C(O)-.

25. The compound of claim 21 wherein Y is a covalent bond.

26. The compound of claim 1 wherein R^1 is selected from the group consisting of $-OR^4$, H, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.

27. The compound of claim 26 wherein R^1 is H.

28. The compound of claim 26 wherein R^1 is alkylaryl.

29. The compound of claim 26 wherein R^1 is alkyl.

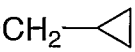
30. The compound of claim 26 wherein R^1 is fluoroalkyl.

31. The compound of claim 26 wherein R^1 is halogen.

32. The compound of claim 26 wherein R^1 is $-OR^4$.

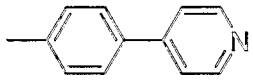
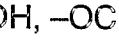
33. The compound of claim 32 wherein R^4 is $-CH_2C{\equiv}CCH_3$.

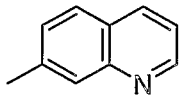
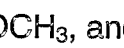
34. The compound of claim 32 wherein R^4 is $-CH_2C{\equiv}CCH_2OH$.

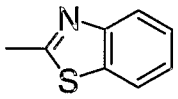
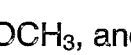
35. The compound of claim 32 wherein R^4 is .

36. The compound of claim 29 wherein said alkyl is $-CH_3$.

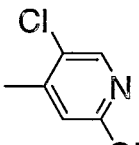
37. The compound of claim 29 wherein said alkyl is $-CH_2CH_3$.

38. The compound of claim 1 wherein T, U, and V when taken together form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

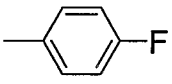
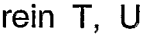
39. The compound of claim 1 wherein T, U, and V when taken together form  and R^1 is selected from the group consisting of F, Cl, OH,$-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

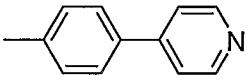
40. The compound of claim 1 wherein T, U, and V when taken together form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

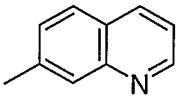
41. The compound of claim 1 wherein T, U, and V when taken together

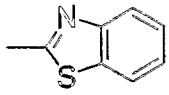
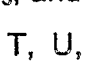


form OH and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

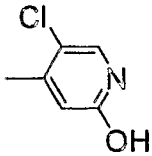
42. The compound of claim 1 wherein T, U, and V when taken together form  and R^1 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

43. The compound of claim 1 wherein T, U, and V when taken together form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

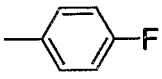
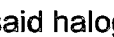
44. The compound of claim 1 wherein T, U, and V when taken together form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

45. The compound of claim 1 wherein T, U, and V when taken together form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

46. The compound of claim 1 wherein T, U, and V when taken together



form OH and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

47. The compound of claim 1 wherein T, U, and V when taken together form  and R^2 is selected from the group consisting of F, Cl, OH, $-OCH_2C{\equiv}CCH_3$, $-OCH_2C{\equiv}CCH_2OH$, $-OCH_3$, and .

48. The compound of claim 30 wherein said fluoroalkyl is $-CH_2CF_3$.

49. The compound of claim 31 wherein said halogen is selected from the group consisting of –Br, -Cl and -F.

50. The compound of claim 32 wherein R^4 is $-CH_3$.

51. The compound of claim 29 wherein said alkyl is substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties.

52. The compound of claim 51 wherein R^{20} is aryl.

53. The compound of claim 1 wherein Z is selected from the group consisting of a covalent bond, $-N(R^4)-$, $-(C(R^4)_2)_n-$, -C(O)- and –O-.

54. The compound of claim 53 wherein Z is –O-.

55. The compound of claim 53 wherein Z is a covalent bond.

56. The compound of claim 53 wherein Z is $-N(R^4)-$.

57. The compound of claim 53 wherein Z is -C(O)-.

58. The compound of claim 53 wherein R^4 is alkyl.

59. The compound of claim 58 wherein said alkyl is $-CH_3$.

60. The compound of claim 53 wherein R^2 is selected from the group consisting of $-OR^4$, hydrogen, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.

61. The compound of claim 60 wherein R^2 is hydrogen.

62. The compound of claim 60 wherein R^2 is alkyl.

63. The compound of claim 60 wherein R^2 is alkylaryl.

64. The compound of claim 60 wherein R^2 is fluoroalkyl.

65. The compound of claim 64 wherein said fluoroalkyl is $-CH_2CF_3$.

66. The compound of claim 60 wherein R^2 is halogen.

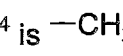
67. The compound of claim 66 wherein said halogen is selected from the group consisting of –Br, -Cl and -F.

68. The compound of claim 60 wherein R^2 is heteroaryl.

69. The compound of claim 60 wherein R^4 is $-CH_3$.

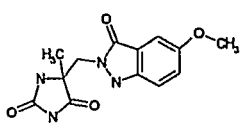
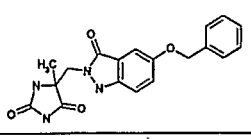
70. The compound of claim 60 wherein R^4 is $-CH_2C{\equiv}CCH_3$.

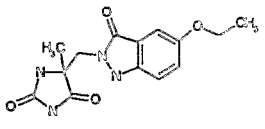
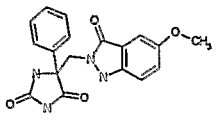
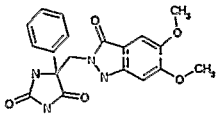
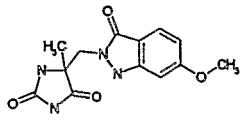
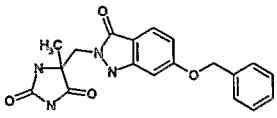
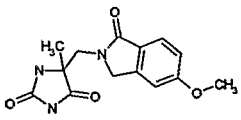
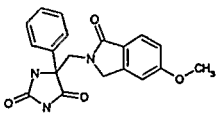
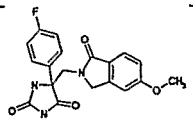
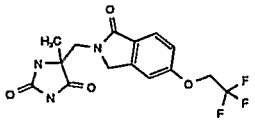
71. The compound of claim 60 wherein R^4 is $-CH_2C{\equiv}CCH_2OH$.

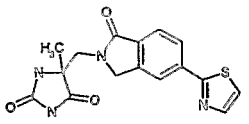
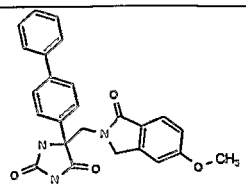
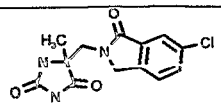
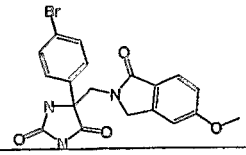
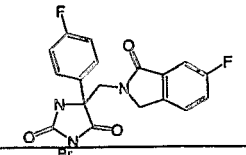
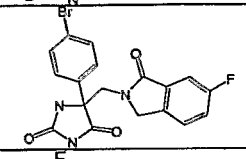
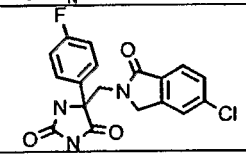
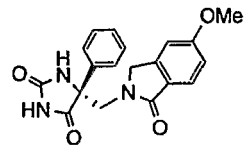
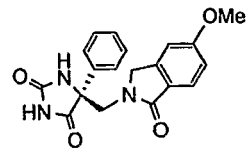
72. The compound of claim 60 wherein R^4 is .

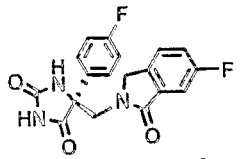
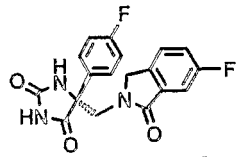
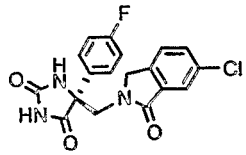
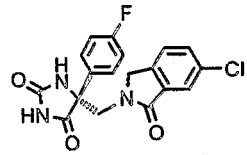
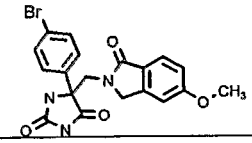
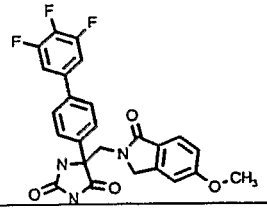
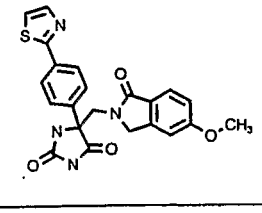
73. The compound of claim 60 wherein said alkyl is $-CH_3$.

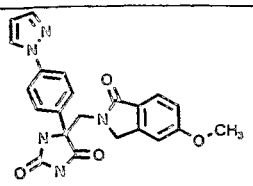
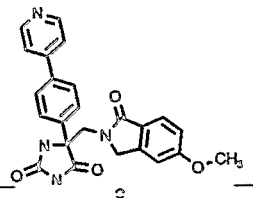
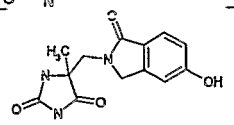
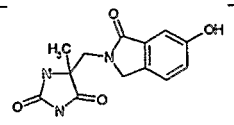
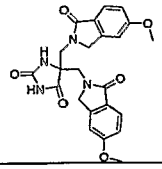
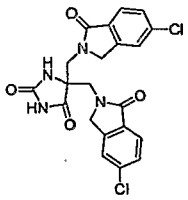
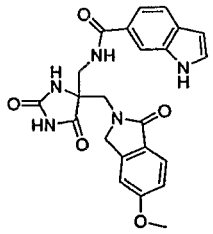
74. A compound exhibiting inhibitory activity of a tumor necrosis factor-alpha-converting enzyme (TACE), tumor necrosis factor-alpha (TNF-α), matrix metalloproteinases (MMPs), a disintegrin and metalloproteases (ADAMs) or any combination thereof, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

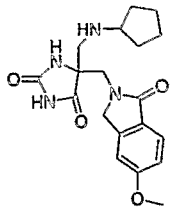
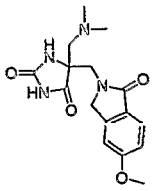
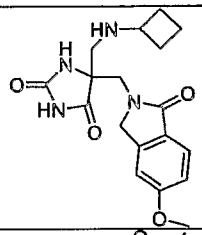
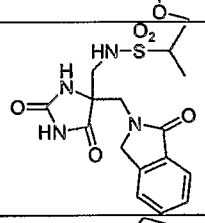
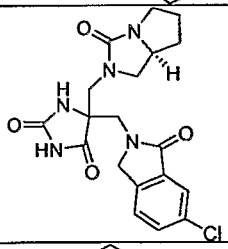
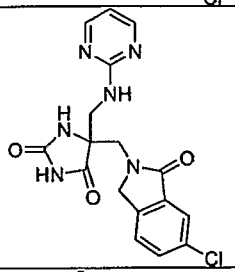
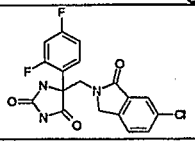
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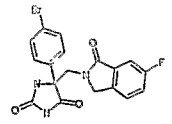
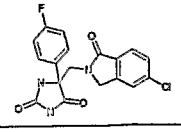
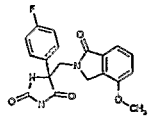
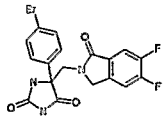
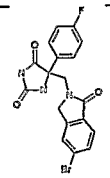
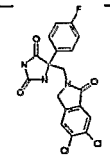
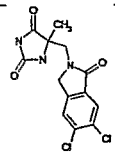
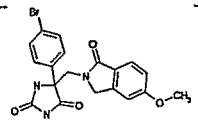
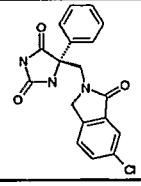
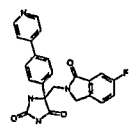
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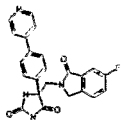
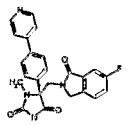
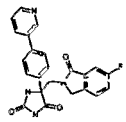
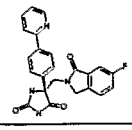
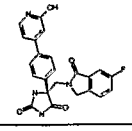
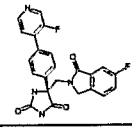
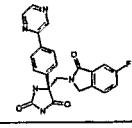
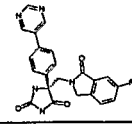
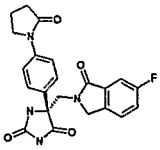
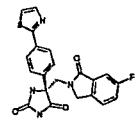
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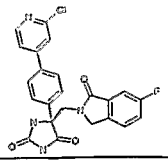
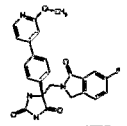
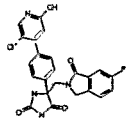
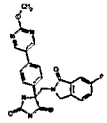
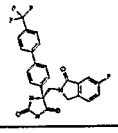
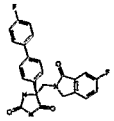
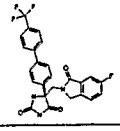
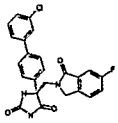
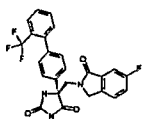
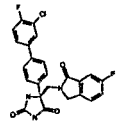
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24	 Enantiomer A
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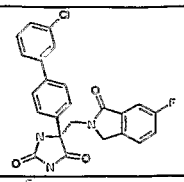
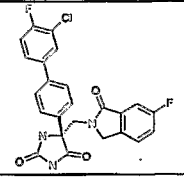
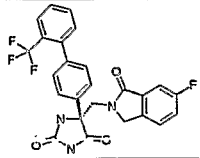
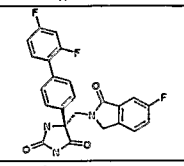
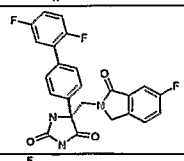
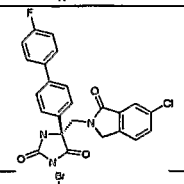
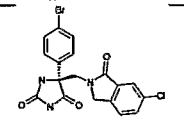
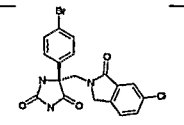
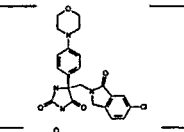
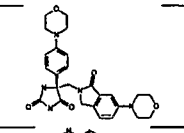
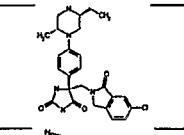
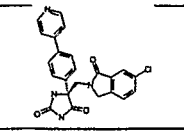
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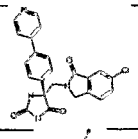
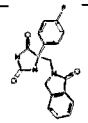
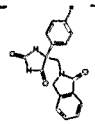
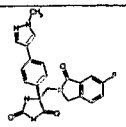
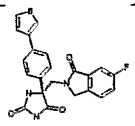
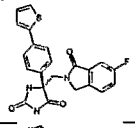
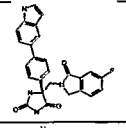
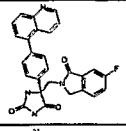
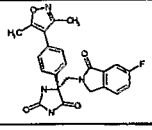
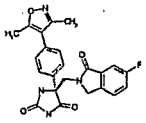
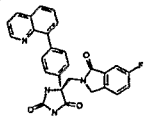
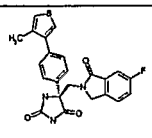
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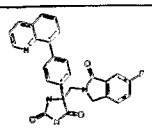
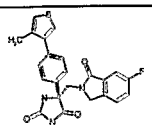
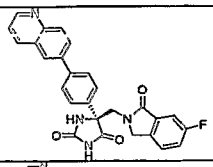
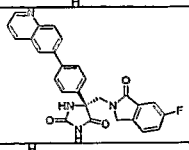
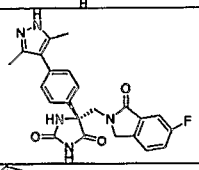
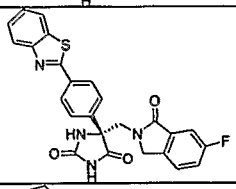
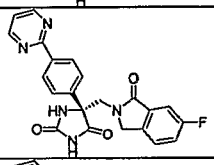
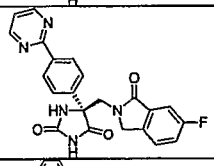
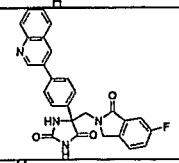
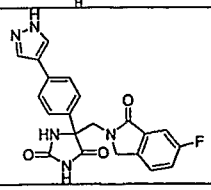
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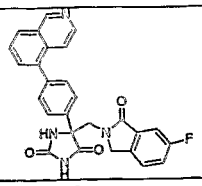
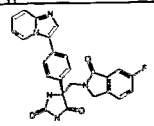
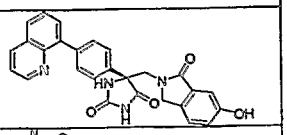
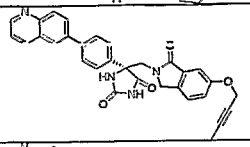
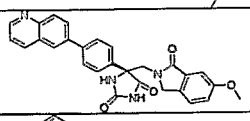
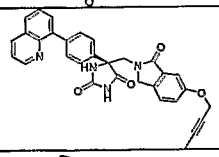
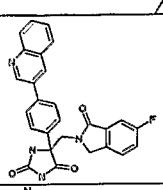
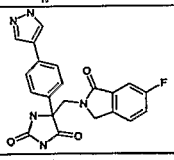
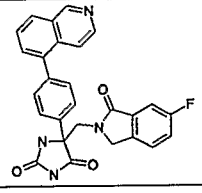
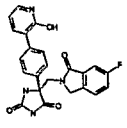
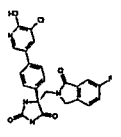
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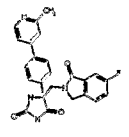
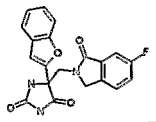
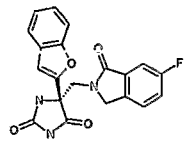
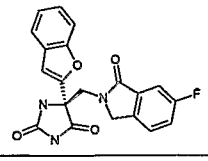
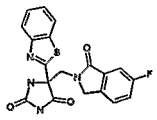
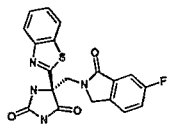
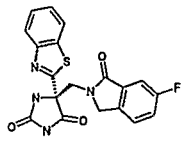
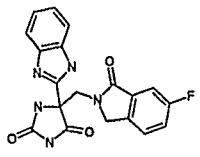
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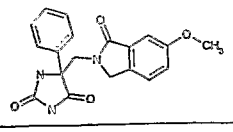
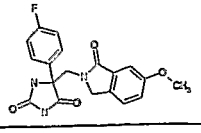
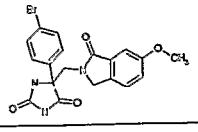
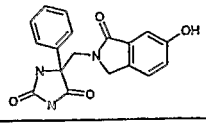
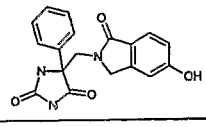
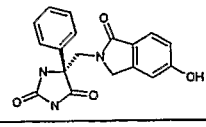
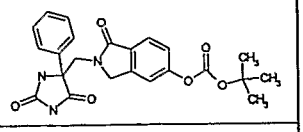
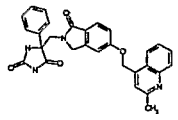
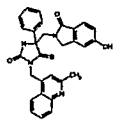
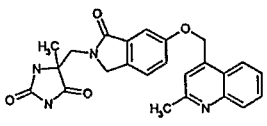
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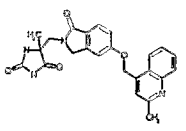
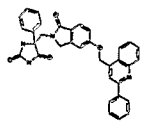
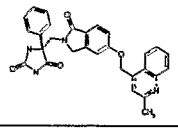
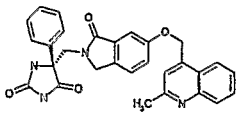
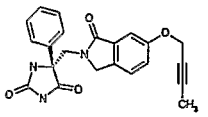
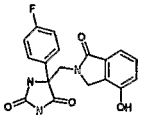
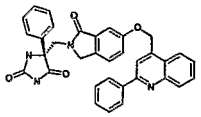
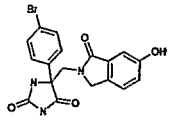
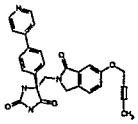
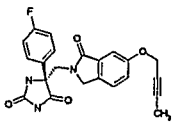
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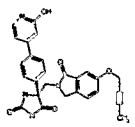
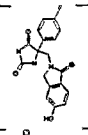
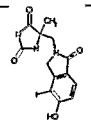
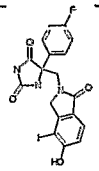
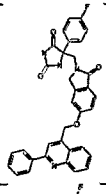
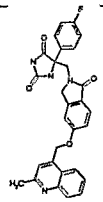
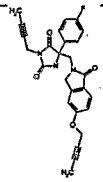
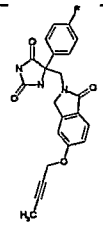
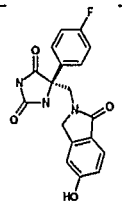
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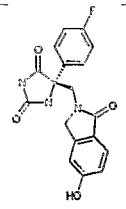
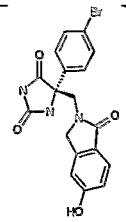
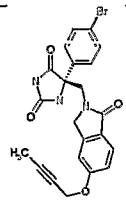
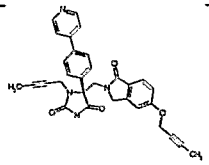
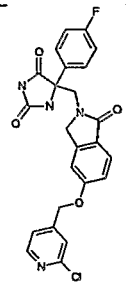
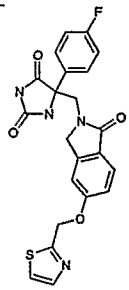
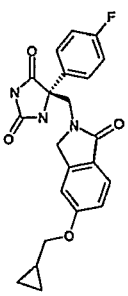
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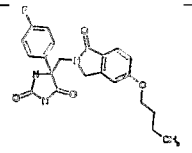
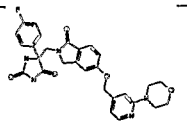
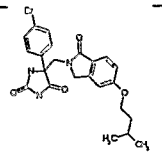
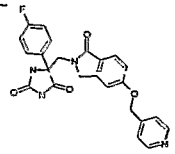
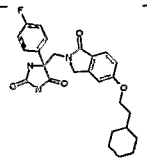
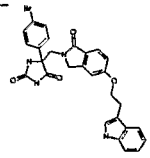
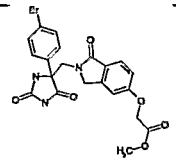
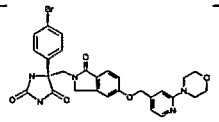
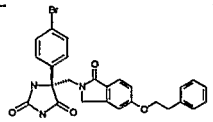
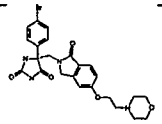
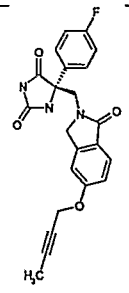
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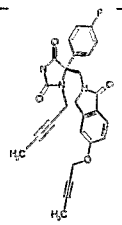
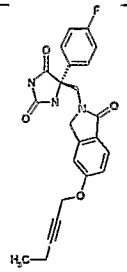
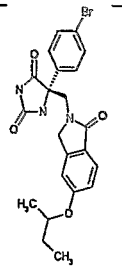
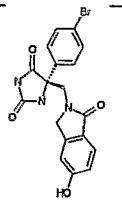
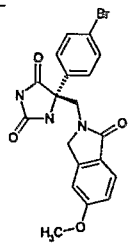
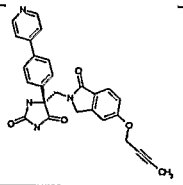
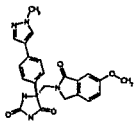
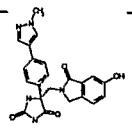
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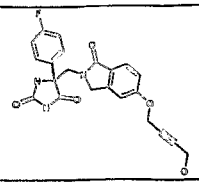
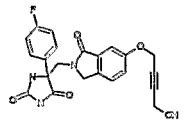
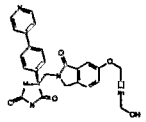
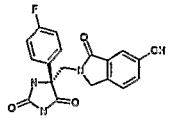
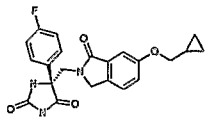
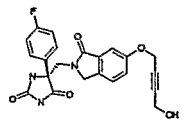
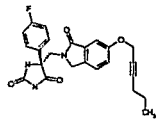
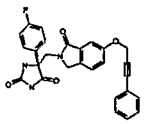
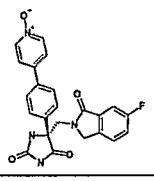
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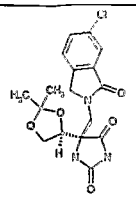
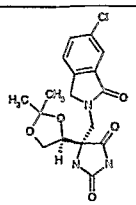
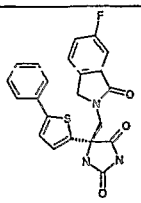
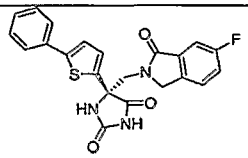
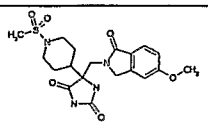
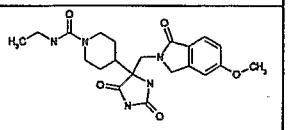
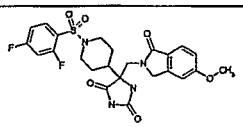
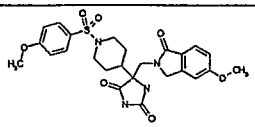
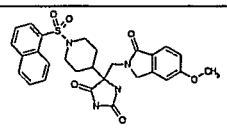
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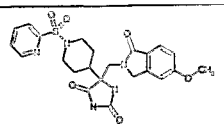
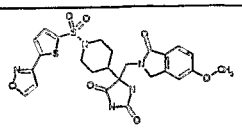
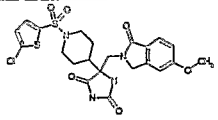
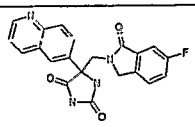
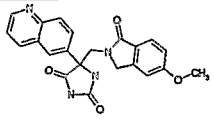
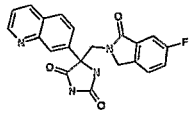
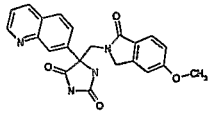
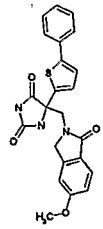
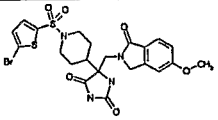
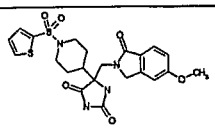
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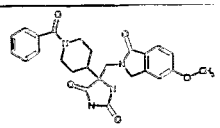
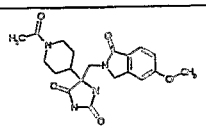
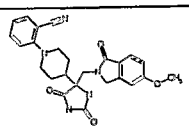
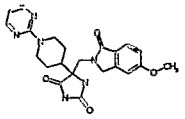
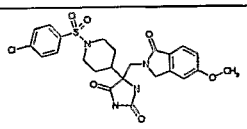
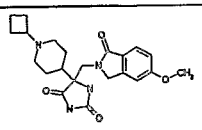
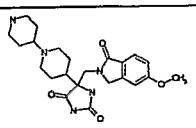
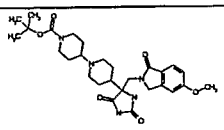
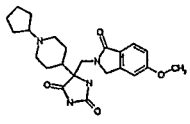
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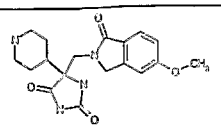
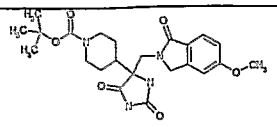
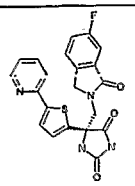
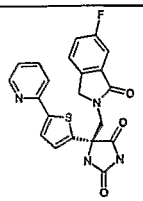
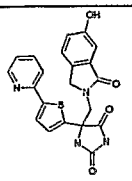
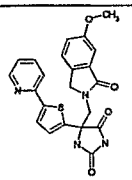
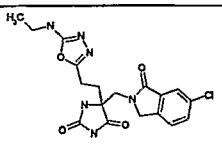
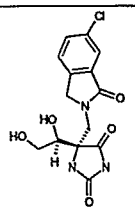
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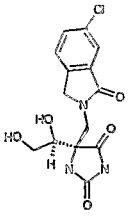
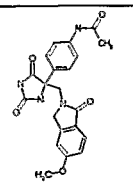
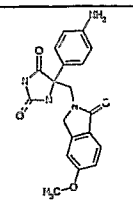
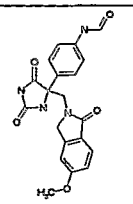
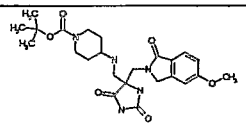
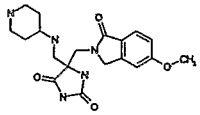
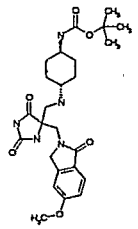
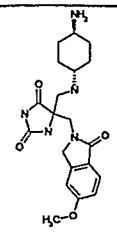
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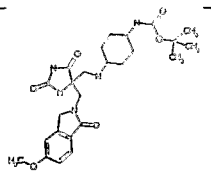
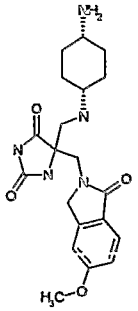
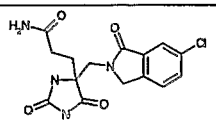
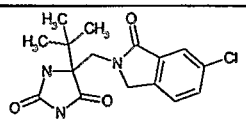
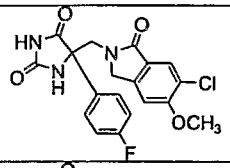
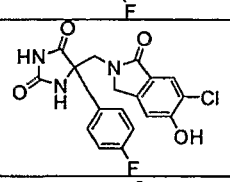
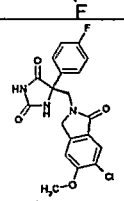
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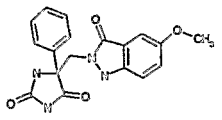
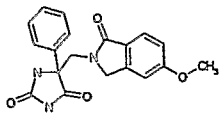
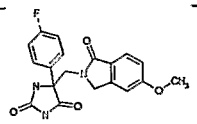
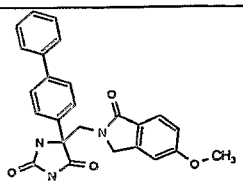
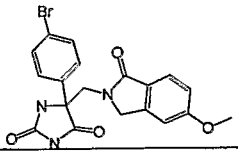
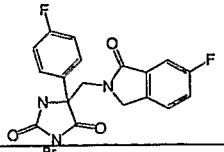
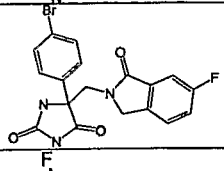
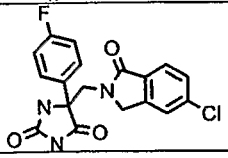
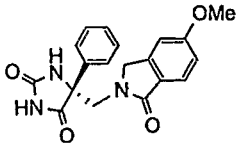
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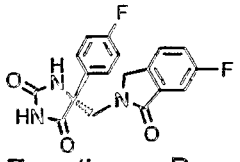
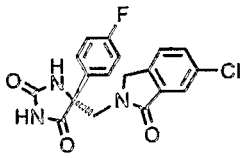
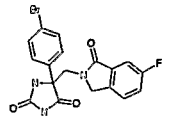
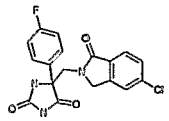
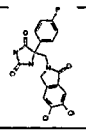
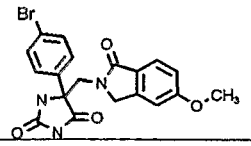
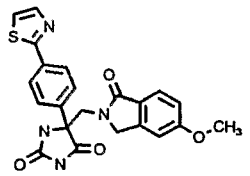
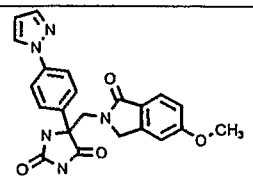
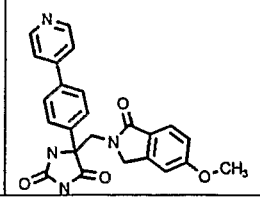
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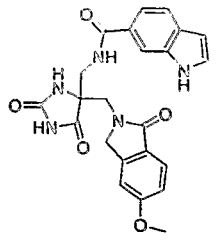
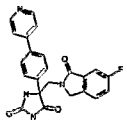
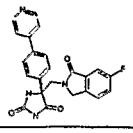
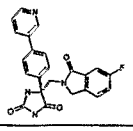
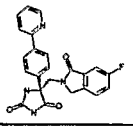
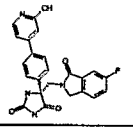
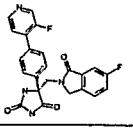
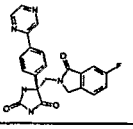
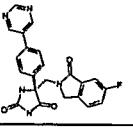
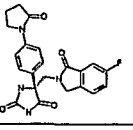
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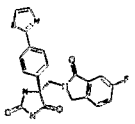
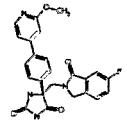
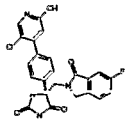
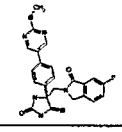
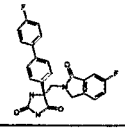
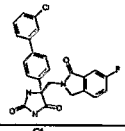
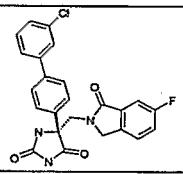
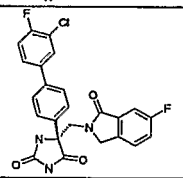
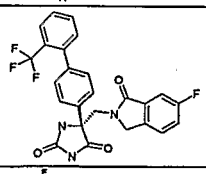
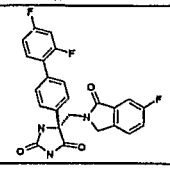
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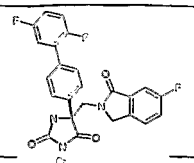
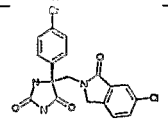
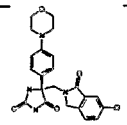
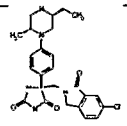
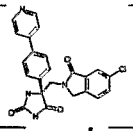
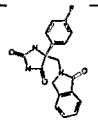
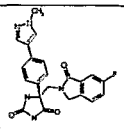
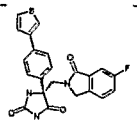
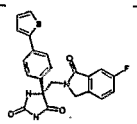
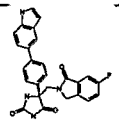
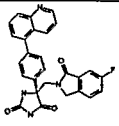
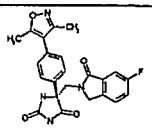
75. The compound of claim 74, wherein said compound is selected from the compounds of structures listed below:

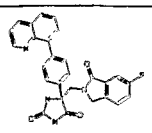
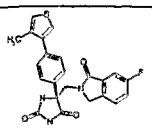
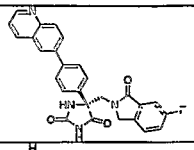
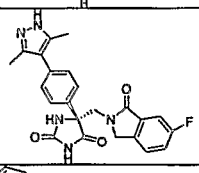
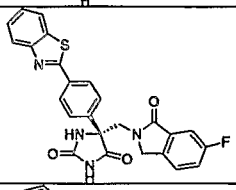
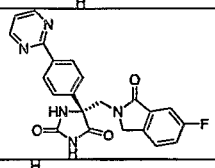
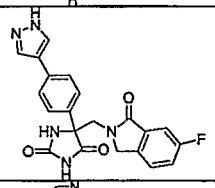
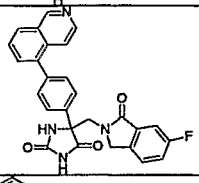
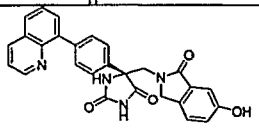
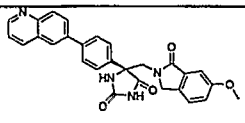
Compound #	Structure
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20	 Enantiomer A

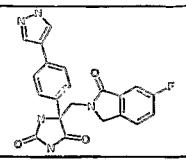
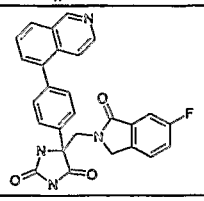
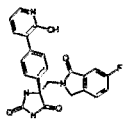
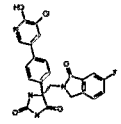
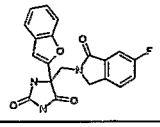
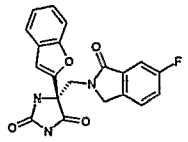
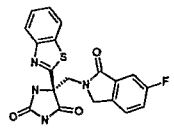
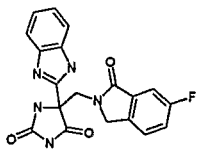
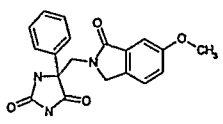
23	 Enantiomer B
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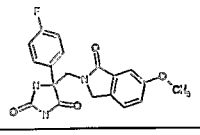
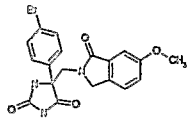
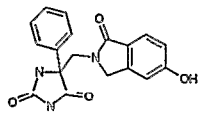
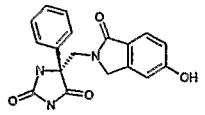
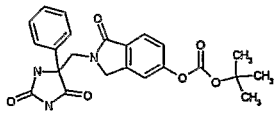
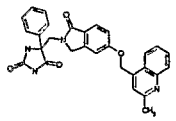
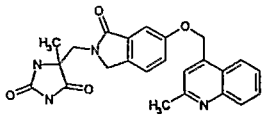
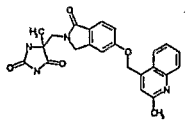
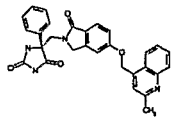
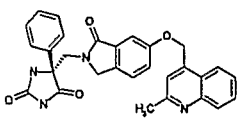
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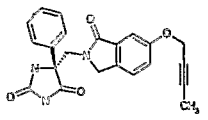
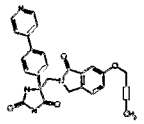
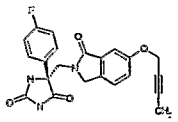
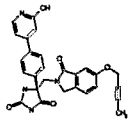
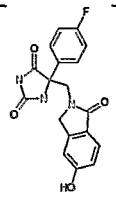
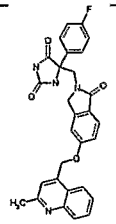
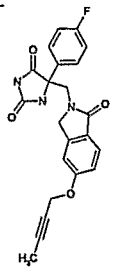
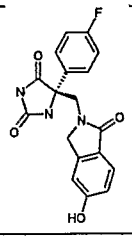
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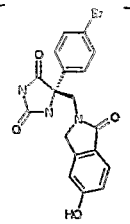
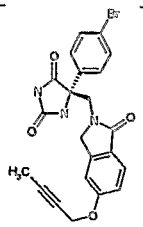
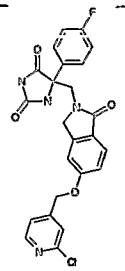
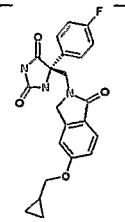
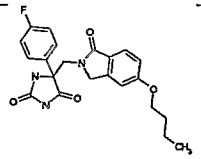
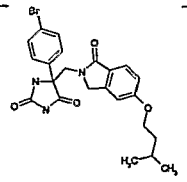
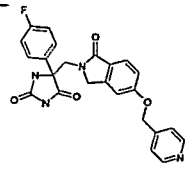
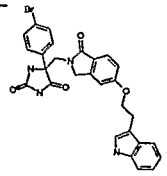
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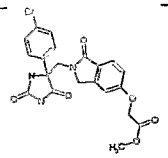
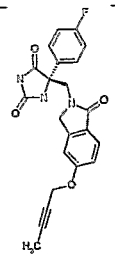
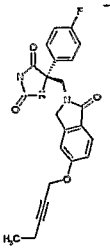
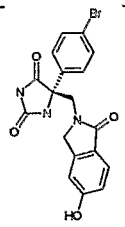
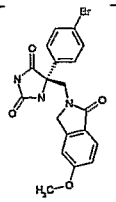
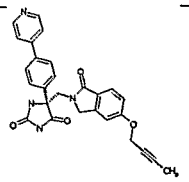
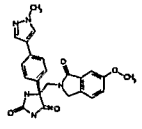
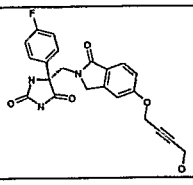
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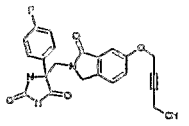
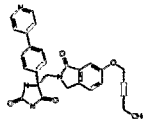
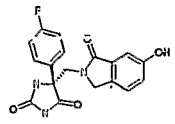
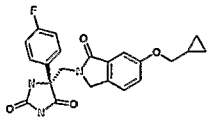
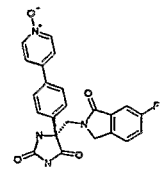
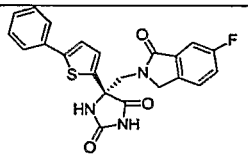
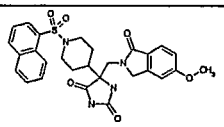
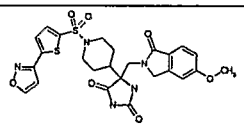
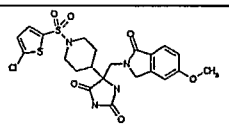
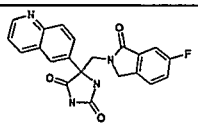
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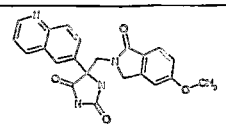
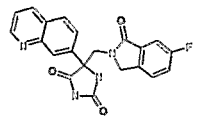
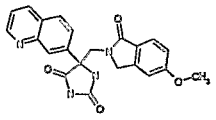
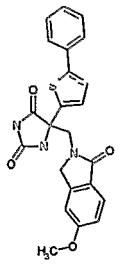
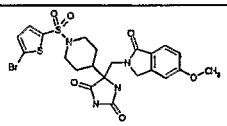
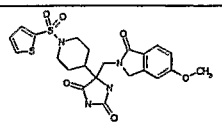
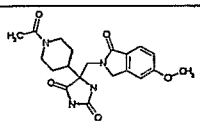
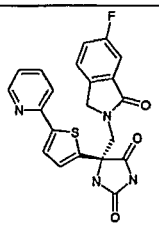
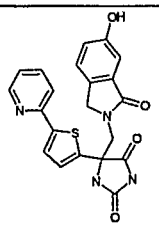
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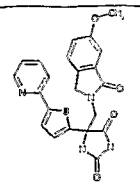
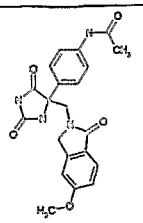
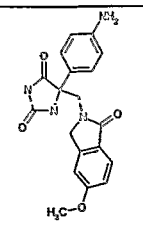
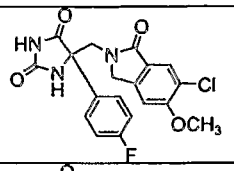
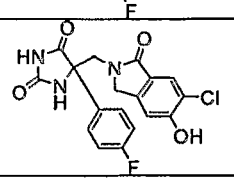
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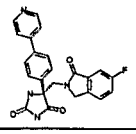
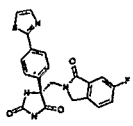
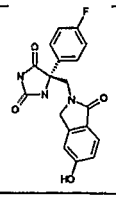
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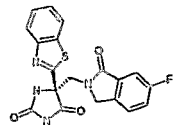
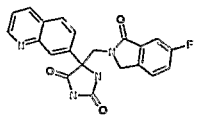
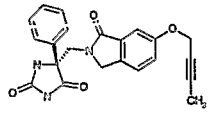
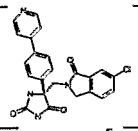
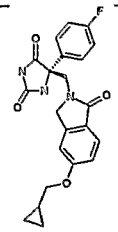
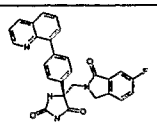
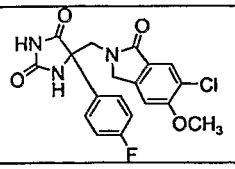
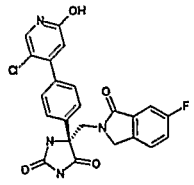
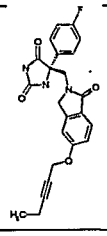
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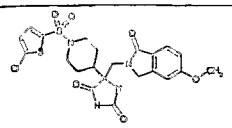
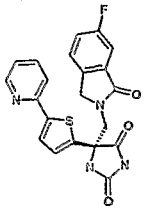
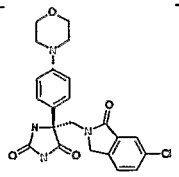
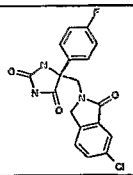
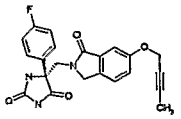
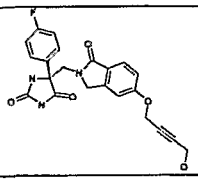
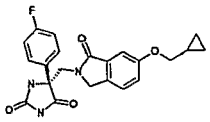
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76. The compound of claim 75, wherein said compound is selected from the compounds of structures listed below:

Compound #	Structure
111	
120	
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181	
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77. The pharmaceutical composition of claim 1 additionally comprising at least one pharmaceutically acceptable carrier.

78. A method of treating disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

79. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF-α, MMPs, ADAMs, or any combination thereof.

80. A method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

81. A pharmaceutical composition for treating disorders associated with TACE, TNF-α, MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

82. A compound of claim 1 in purified form.

83. A method of treating a condition or disease mediated by TACE, MMPs, TNF-α, aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

84. A method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

85. A method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a

therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

86. A method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

87. A method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

88. A method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

89. A method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

90. A method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

91. A method of treating a condition or disease associated with ankylosing spondyiitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

92. A method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

93. A method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

94. A method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

95. A method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof, in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

96. The method of claim 83 further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of disease modifying anti-rheumatic drugs (DMARDS), non-steroidal anti-inflammatory drugs (NSAIDs), cycloxygenase-2 selective (COX-2) inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-inflammatory agents and H1 antagonists.

97. A method of claim 84, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

98. A method of claim 85, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.