HYDANTOIN COMPOUNDS 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.

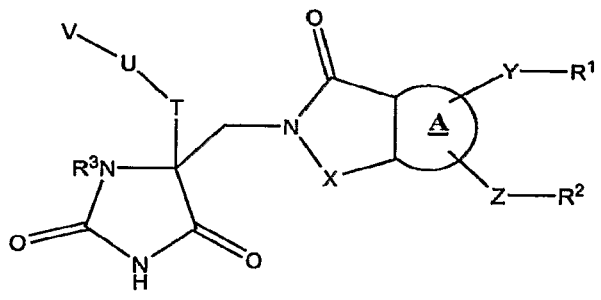
PCT Publication WO2006/019768 refers to hydantoin derivatives that are TACE inhibitors.

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, aggrecanase, 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, aggrecanaseTNF-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 ester thereof, wherein:

ring **A** is selected from the group consisting of aryl and heteroaryl, each of which is substituted with –Y-R^1 and –Z-R^2 as shown;

X is selected from the group consisting of –S-,-O-, -$S(O)_2$, -S(O)-, -$(C(R^3)_2)_m$- and -$N(R^3)$-;

T is absent or present, and if present, T is selected from the group consisting of alkyl, aryl, and heteroaryl, wherein when each of said T aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl or heteroaryl ring, wherein each of the aforementioned T aryl, and heteroaryl, optionally with said five- to eight-membered aryl or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different;

U is absent or present or absent, and if present, U is selected from the group consisting of –O-, -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-;

V is absent or present, and if present V is selected from the group consisting of alkyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and N-oxides of said heterocyclyl and heteroaryl, wherein when each of said V cycloalkyl, heterocyclyl, aryl, heteroaryl, and N-oxides of said heterocycyl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of said V alkyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl heterocyclyl, optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl, or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different;

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 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 -$S(O)_2$-;

m is 1 to 3;

n is 1 to 3;

R^1 is selected from the group consisting of H, cyano, -C(O)OH, -C(O)O-alkyl, -C(O)NH_2, -C(O)NH(alkyl), -C(O)N(alkyl)$_2$, alkynyl, halogen, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, and heterocyclyl, wherein when each of said cycloalkyl, heterocyclyl, aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of the R^1 alkyl, alkynyl, aryl, heteroaryl, and heterocyclyl, optionally with the five or six-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different; with the proviso that when Y is –N(R^4)-, -S -or –O-, then R^1 is not halogen or cyano;

R^2 is selected from the group consisting of H, cyano, -C(O)OH, -C(O)O-alkyl, -C(O)NH_2, -C(O)NH(alkyl), -C(O)N(alkyl)$_2$, alkynyl, halogen, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, and heterocyclyl, wherein when each of said cycloalkyl, heterocyclyl, aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of the R^2 alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, optionally with the five or six-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different; with the proviso that when Y is –N(R^4)-, -S -or –O-, then R^2 is not halogen or cyano;

each R^3 is the same of different and is independently selected from the group consisting of H, alkyl, and aryl;

each R^4 is the same or different and is independently selected from the group consisting of H, alkyl, cycloalkyl, haloalkyl, hydroxy, -alkylcycloalkyl, -alkyl-N(alkyl)$_2$, heterocyclyl, aryl, and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, ayl, and heteroaryl contains two radicals on adjacent

carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring;

R^{10} is selected from the group consisting of hydrogen, cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-N(R^4)-C(O)-N(R^4)_2$, $-N(R^4)-C(O)-OR^4$, $-OC(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-S(O)_2N(R^4)_2$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl, wherein each of the R^{10} alkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{30} moieties which can be the same or different;

or wherein two R^{10} moieties, when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;

R^{20} is selected from the group consisting of cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-N(R^4)-C(O)-N(R^4)_2$, $-N(R^4)-C(O)-OR^4$, $-OC(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-S(O)_2N(R^4)_2$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl; wherein when each of said R^{20} aryl, heteroaryl, heterocyclyl and cycloalkyl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of said R^{20} alkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl, optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or substituted with one to four moieties selected independently from the group consisting of

alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkyl, cyano, nitro, -NH_2, -NH(alkyl), and -$N(alkyl)_2$;

or when two R^{20} moieties when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;

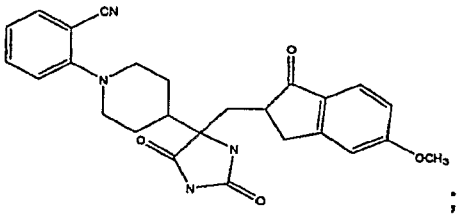
R^{30} is selected from the group consisting of cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-N(R^4)-C(O)-N(R^4)_2$, $-N(R^4)-C(O)-OR^4$, $-OC(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-S(O)_2N(R^4)_2$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl; wherein when each of said R^{30} aryl, heteroaryl, heterocyclyl and cycloalkyl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of said R^{30} alkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl, optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or substituted with one to four moieties selected independently from the group consisting of alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro, -NH_2, -NH(alkyl), and -$N(alkyl)_2$;

or when two R^{30} moieties when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;

with the proviso that at least one of T, U, and V must be present; and further that at least one of conditions (1) – (5) below are satisfied:

(1) at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, -

$OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$,
$-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is
$-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



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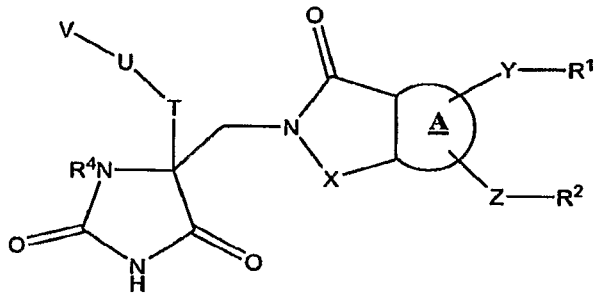
(2) U is present and is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-;

(3) each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, $-(C(R^4)_2)_n-C(O)OH$, $-(C(R^4)_2)_n-C(O)O$-alkyl, $-(C(R^4)_2)_n-C(O)NH_2$, $-(C(R^4)_2)_n-C(O)NH$(alkyl), and $-(C(R^4)_2)_n-C(O)N(alkyl)_2$. wherein each R^4 independently is H or alkyl; and n is 1-3;

(4) T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; and

(5) ring A is heteroaryl, and V is other than alkynyl.

In another 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 (II):



(II)

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

the ring labeled **A** is selected from the group consisting of aryl and heteroaryl, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown;

X is selected from the group consisting of –S-,-O-, $-C(R^3)_2-$ or $-N(R^3)-$;

T is absent or present, and if present, T is selected from the group consisting of H (with U and V being absent), alkyl, alkenyl, alkynyl, 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 alkynyl, –C(O)-, –C(O)O-, and $-C(O)NR^4-$;

V is absent or present, and if present V is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl-, cycloalkyl, alkylaryl-, and arylalkyl-, said aryl, heteroaryl, heterocyclyl, heterocyclylalkyl-, 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 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 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, $-OR^4$, cyano, $-C(O)OR^4$, $-C(O)N(R^4)_2$, 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 or cyano;

R^2 is selected from the group consisting of H, $-OR^4$, cyano, $-C(O)OR^4$, $-C(O)N(R^4)_2$, 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^3 is the same of different and is independently selected from the group consisting of H, alkyl, and aryl;

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

R^{10} is selected from the group consisting of cyano, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4-$, $-S(O)_2R^4-$, $-N(R^4)S(O)_2R^4$, $-S(O)_2N(R^4)_2$, -O(fluoroalkyl), $-C(O)OR^4$, $-C(O)N(R^4)_2$, 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, $-N(R^4)_2$, and $-C(O)N(R^4)_2$; and

R^{30} is selected from the group consisting of halogen, alkyl, fluoroalkyl, $-N(R^4)_2$, and $-C(O)N(R^4)_2$.

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, aggrecanase, 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) or (II) above or a pharmaceutically acceptable salt, solvate, ester 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.

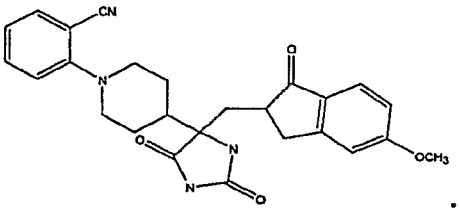
In another embodiment, in formula (I), X is selected from the group consisting of $-(C(R^3)_2)_m-$ and $-N(R^3)-$.

In another embodiment, in formula (I), X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

In another embodiment, in formula (I), X is $-(C(R^3)_2)_m$, wherein m is 1.

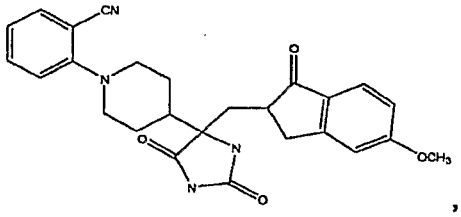
In another embodiment, in formula (I), R^3 is H.

In another embodiment, in formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



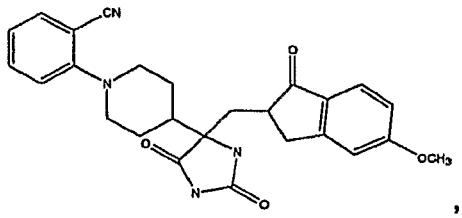
In another embodiment in formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-$

$N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



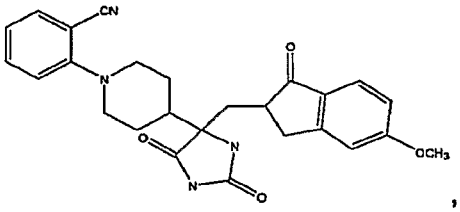
, wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, and $-C(R^4)=N-OR^4$.

In another embodiment in formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



, wherein said T or V is substituted with at least one R^{10} moiety that is cyano.

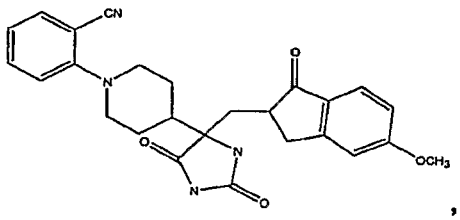
In another embodiment, in formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



, wherein said T or V is substituted with at least one R^{10} moiety that is $-SR^4$.

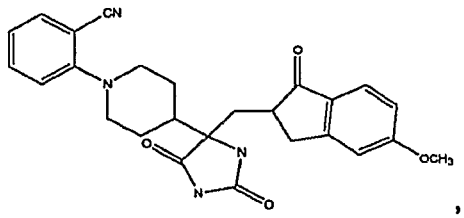
In another embodiment, in formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-$

$N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



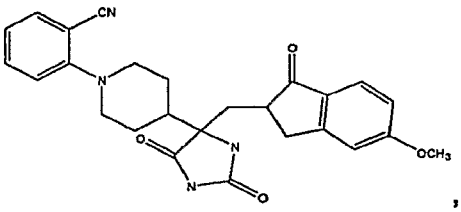
, wherein said T or V is substituted with at least one R^{10} moiety that is $-S(O)_2R^4$.

In another embodiment, in formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than

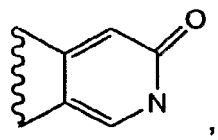


, wherein said T or V is substituted with at least one R^{10} moiety that $-S(O)_2N(R^4)_2$.

In another embodiment, in formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



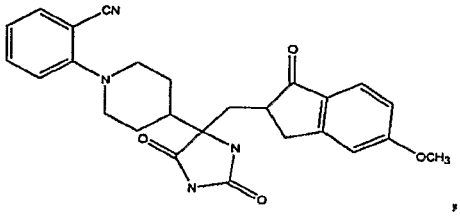
, wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and



, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

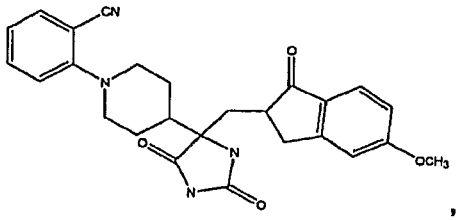
In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, -

$C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



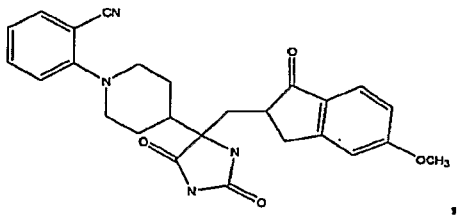
, wherein ring **A** is phenyl.

In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than

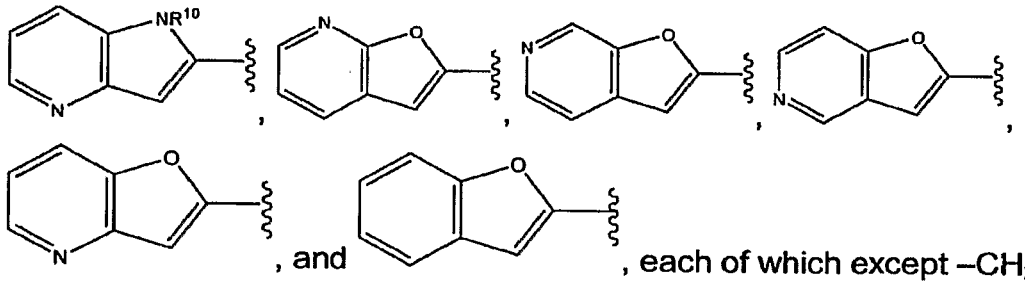


, wherein T is selected from the group consisting of alkyl, aryl, heteroaryl, wherein when each of said T aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl or heteroaryl ring; wherein each of the aforementioned T aryl, and heteroaryl, optionally with said five- to eight-membered aryl or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different.

In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than

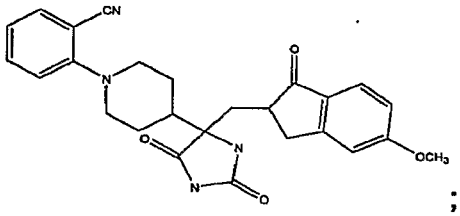


, wherein T is selected from the group consisting of $-CH_2-$, phenyl,



, each of which except $-CH_2-$ is optionally substituted with one to four R^{10} moieties such that the number of R^{10} moieties per each T does not exceed four.

In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than

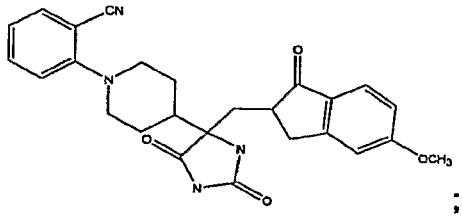


;

wherein U is absent or present, and if present is selected from the group consisting of –C(O)-, and -C(O)O-.

In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, -

$C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than

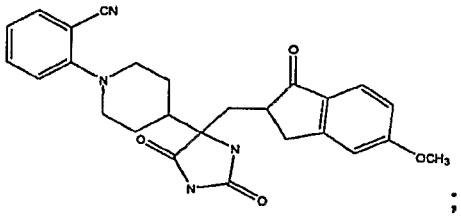


;

wherein V is absent or present, and if present is selected from the group consisting of aryl, and heteroaryl, wherein when each of said V aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl or heteroaryl ring; wherein each of the aforementioned V aryl, and heteroaryl, optionally with said five- to eight-membered aryl or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different.

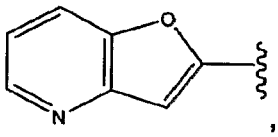
In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl,

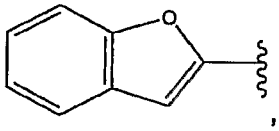
wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



;

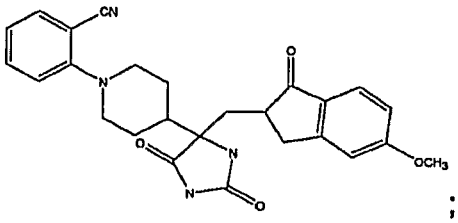
wherein V is selected from the group consisting of phenyl, pyridyl, pyrazinyl, indazolyl,



, and 

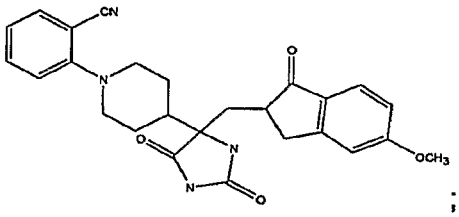
, each of which is optionally substituted with one to four R^{10} moieties which can be the same or different.

In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



; wherein each of Y and Z is independently selected from the group consisting of a covalent bond and –O- .

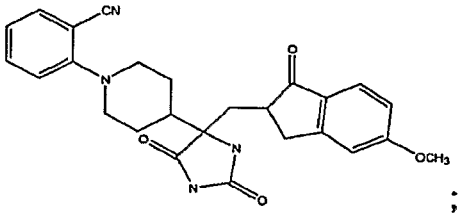
In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



; wherein Y is –O- and Z is a covalent bond.

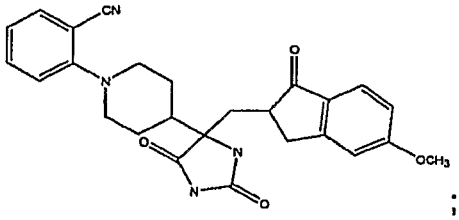
In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, -

$S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



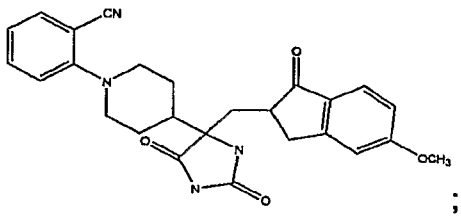
; wherein each of R^1 and R^2 is independently selected form the group consisting of H and alkyl.

In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



; wherein R^1 is alkyl and R^2 is H.

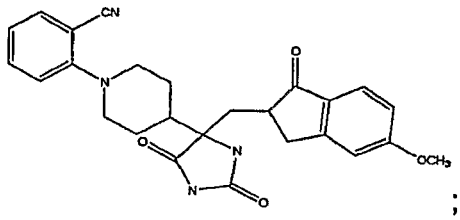
In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



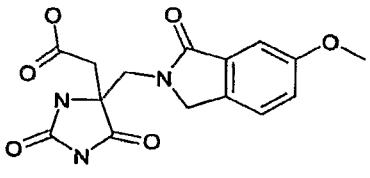
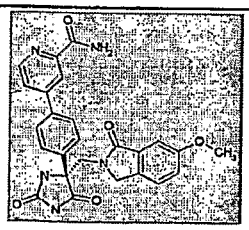
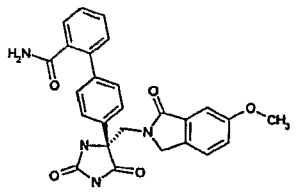
; wherein R^1 is methyl.

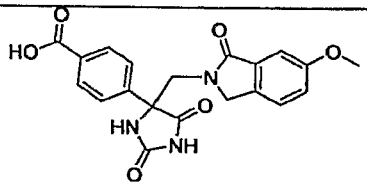
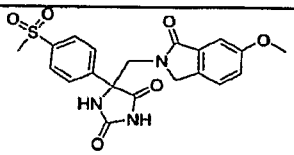
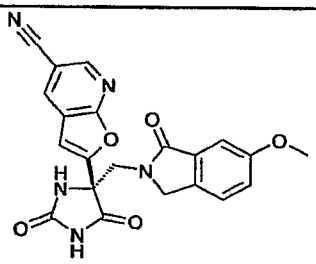
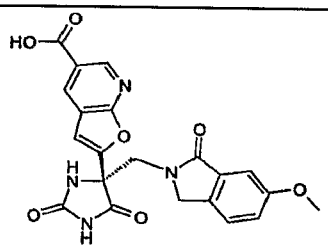
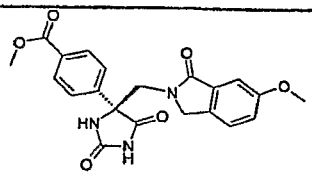
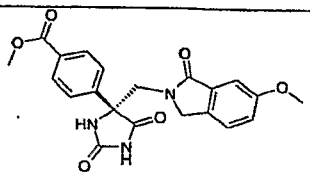
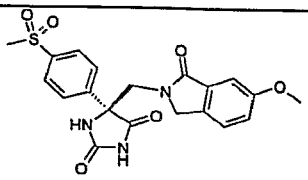
In another embodiment, in Formula (I), at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl,

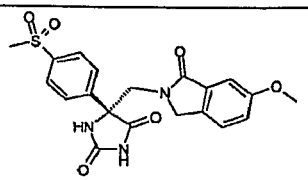
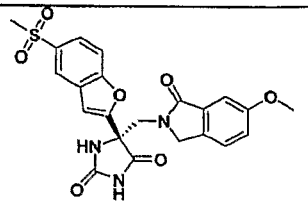
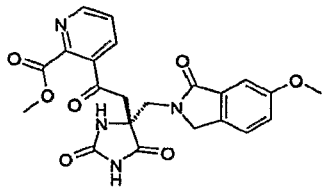
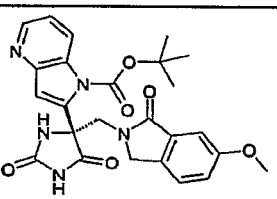
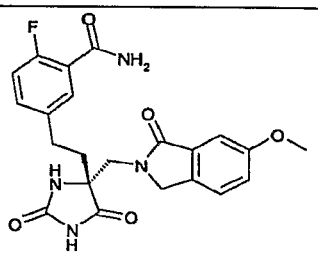
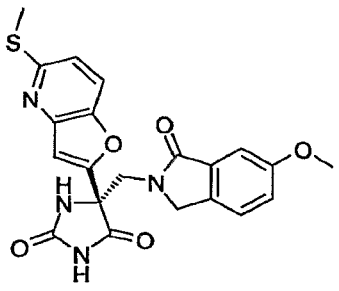
wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than

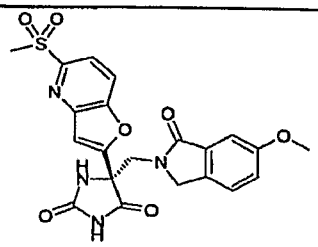
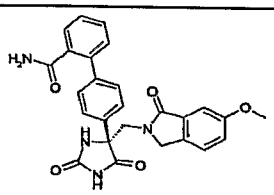
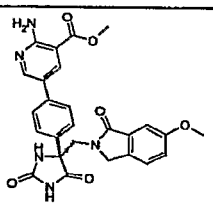
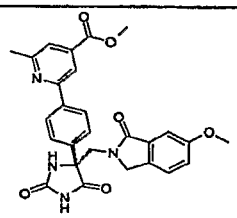
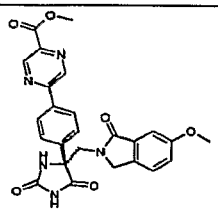
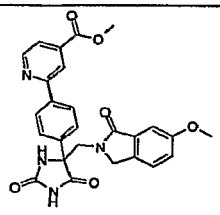


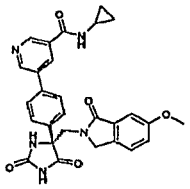
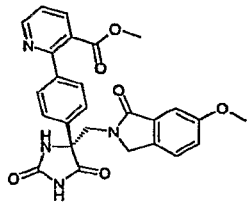
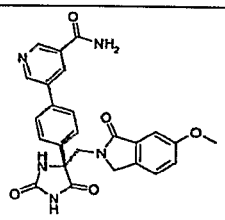
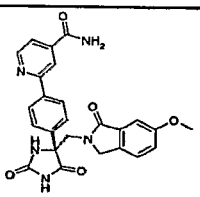
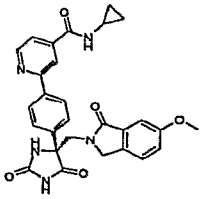
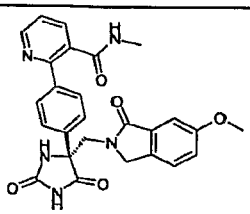
; wherein the compound of Formula (I) is selected from the group consisting of:

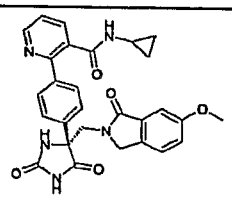
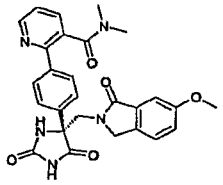
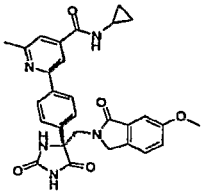
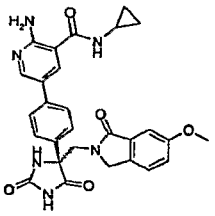
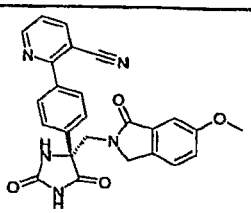
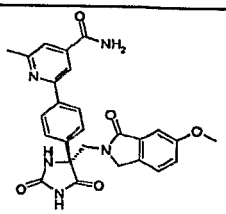
Compound ID	Structures
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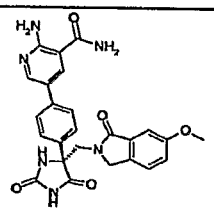
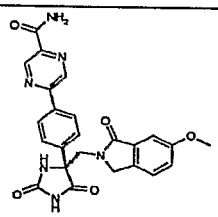
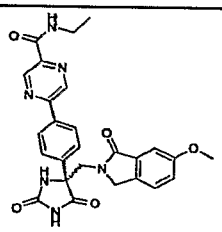
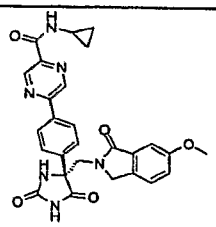
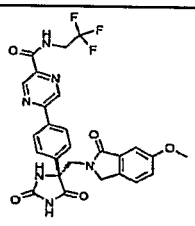
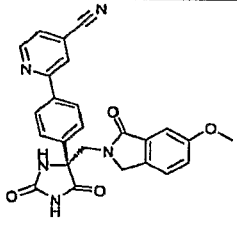
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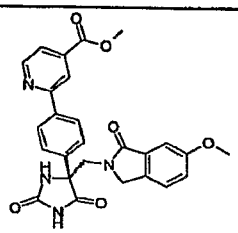
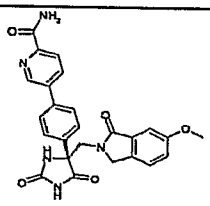
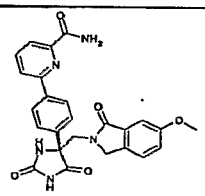
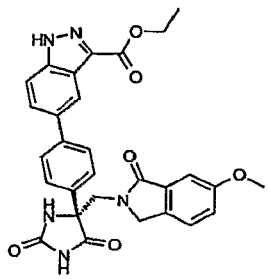
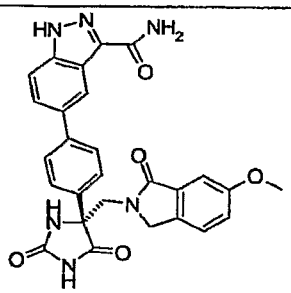
Compound ID	Structures
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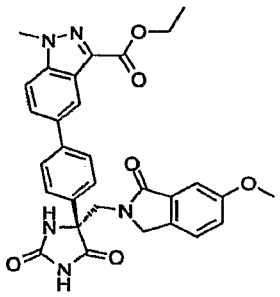
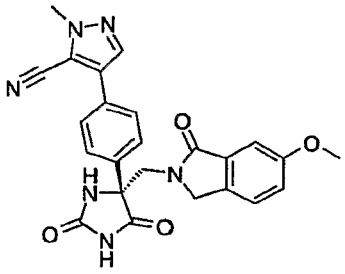
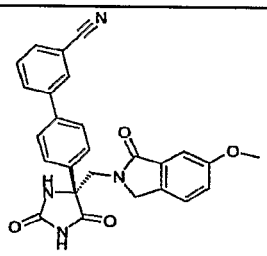
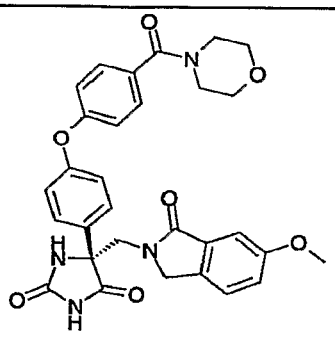
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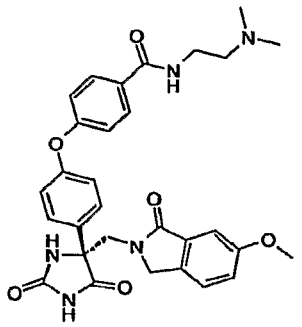
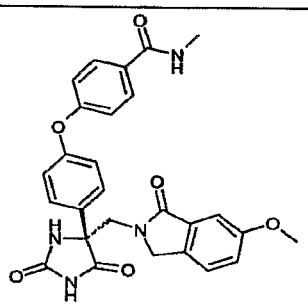
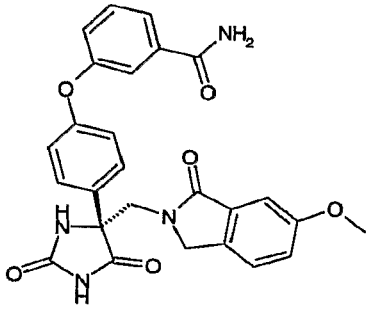
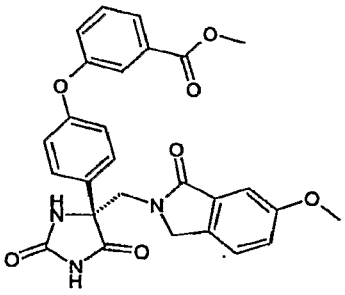
Compound ID	Structures
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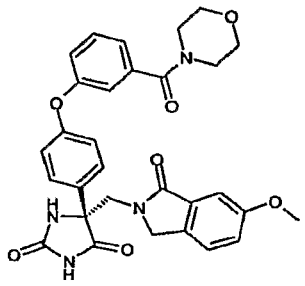
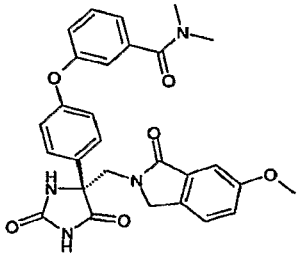
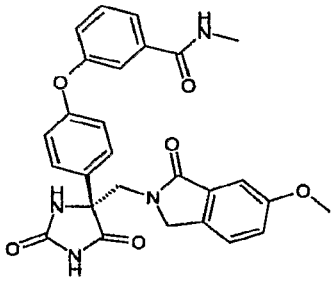
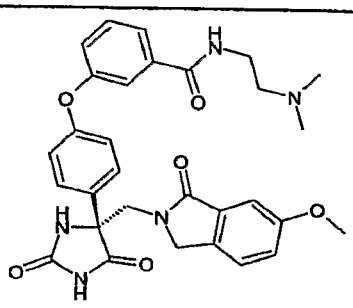
Compound ID	Structures
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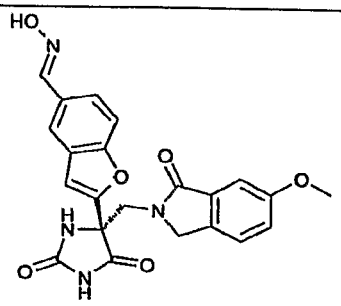
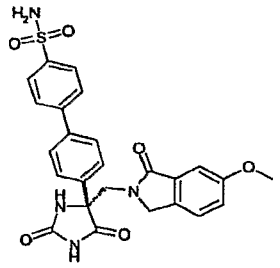
Compound ID	Structures
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Compound ID	Structures
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Compound ID	Structures
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Compound ID	Structures
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Compound ID	Structures
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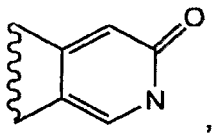
Compound ID	Structures
97	 and
105	 ;

or a pharmaceutically acceptable salt, solvate or ester thereof.

In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-.

In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-;

wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and

 , each of which is substituted with –Y-R^1 and –Z-R^2 as shown.

In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; wherein ring **A** is phenyl.

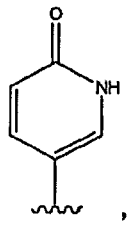
In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein T is absent or present, and when present, is selected from the group consisting of alkyl, and aryl, each of which is unsubstitued or substituted with one to four R^{10} moieties which can be the same or different.

In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein wherein T is absent or present, and when present is selected from the group consisting of $–CH_2-$, and phenyl.

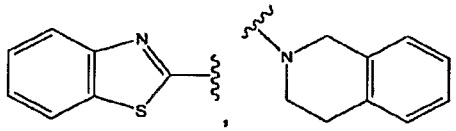
In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein V is selected from the group consisting of alkyl, heterocyclyl, and cycloalkyl, wherein when each of said V heterocyclyl or cycloalkyl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; wherein each of aforementioned V alkyl, heterocyclyl, and cycloalkyl, optionally with said five- to eight-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring is is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different.

In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein V is selected from the group consisting of methyl, ethyl,

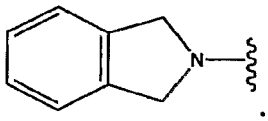
isopropyl, morpholinyl, cyclohexyl, piperidinyl optionally substituted with cyano or phenyl, -CH_2- substituted with tetrahydrofuranyl and



, -$CH(CH_3)$- substituted with phenyl, piperazinyl substituted wth methyl, pyrrolidinyl substituted wth -CH_2-phenyl,



substituted with cyclopropyl, and



.

In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein each of Y and Z is independently selected from the group consisting of a covalent bond and –O-.

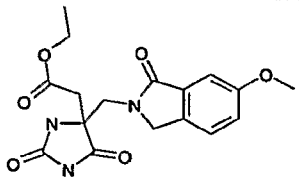
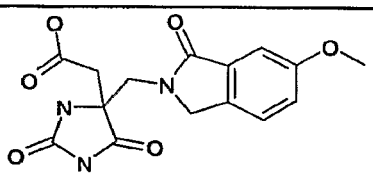
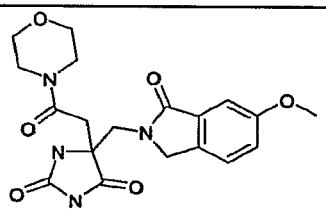
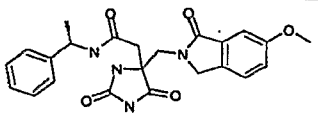
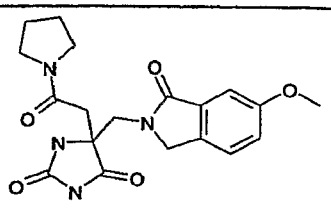
In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein Y is –O- and Z is a covalent bond.

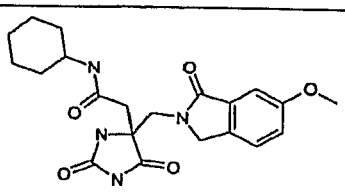
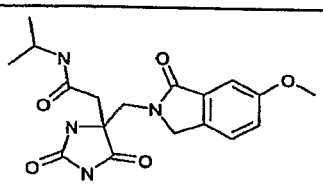
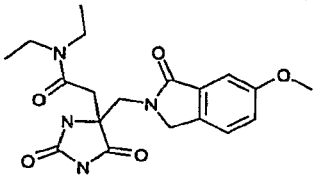
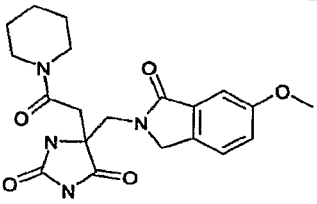
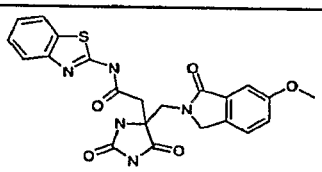
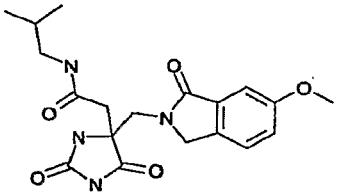
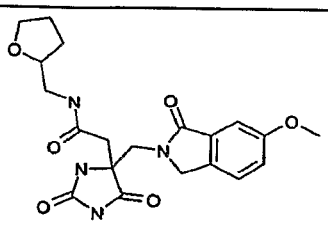
In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein each of R^1 and R^2 is independently selected form the group consisting of H and alkyl.

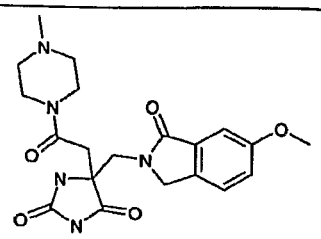
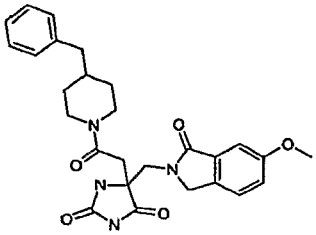
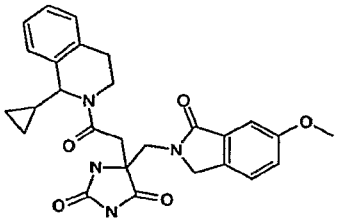
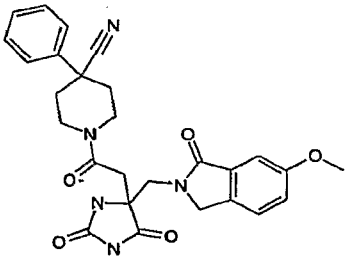
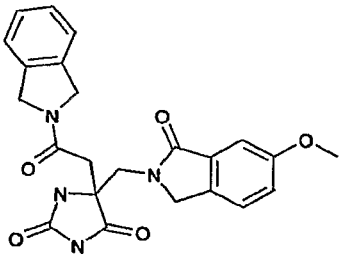
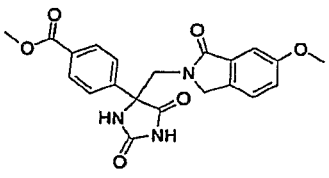
In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein R^1 is alkyl and R^2 is H.

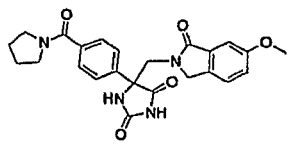
In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein R^1 is methyl.

In another embodiment, in Formula (I), U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-; and wherein the compound of Formula (I) is selected from the group consisting of:

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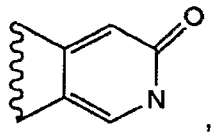
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or a pharmaceutically acceptable salt, solvate or ester thereof.

In another embodiment, in Formula (I), at least one T and V is present, and each of $-Y-R^1$ and $-Z-R^2$ is independently selected from the group consisting of cyano, $-(C(R^4)_2)_n-C(O)OH$, $-(C(R^4)_2)_n-C(O)O$-alkyl, $-(C(R^4)_2)_n-C(O)NH_2$, $-(C(R^4)_2)_n-C(O)NH$(alkyl), and $-(C(R^4)_2)_n-C(O)N(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3.

In another embodiment, in Formula (I), at least one T and V is present, and each of $-Y-R^1$ and $-Z-R^2$ is independently selected from the group consisting of cyano, $-(C(R^4)_2)_n-C(O)OH$, $-(C(R^4)_2)_n-C(O)O$-alkyl, $-(C(R^4)_2)_n-C(O)NH_2$, $-(C(R^4)_2)_n-C(O)NH$(alkyl), and $-(C(R^4)_2)_n-C(O)N(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and



, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

In another embodiment, in Formula (I), at least one T and V is present, and each of $-Y-R^1$ and $-Z-R^2$ is independently selected from the group consisting of cyano, $-(C(R^4)_2)_n-C(O)OH$, $-(C(R^4)_2)_n-C(O)O$-alkyl, $-(C(R^4)_2)_n-C(O)NH_2$, $-(C(R^4)_2)_n-C(O)NH$(alkyl), and $-(C(R^4)_2)_n-C(O)N(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein said ring **A** is phenyl.

In another embodiment, in Formula (I), at least one T and V is present, and each of $-Y-R^1$ and $-Z-R^2$ is independently selected from the group consisting of cyano, $-(C(R^4)_2)_n-C(O)OH$, $-(C(R^4)_2)_n-C(O)O$-alkyl, $-(C(R^4)_2)_n-C(O)NH_2$, $-(C(R^4)_2)_n-C(O)NH$(alkyl), and $-(C(R^4)_2)_n-C(O)N(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein T or V is aryl which is unsubstituted or substituted with one to four R^{10} moieties.

In another embodiment, in Formula (I), at least one T and V is present, and each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein said T or V is phenyl which is unsubstituted or substituted with one to four R^{10} moieties.

In another embodiment, in Formula (I), at least one T and V is present, and each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein R^{10} is fluoro.

In another embodiment, in Formula (I), at least one T and V is present, and each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein only one of T and V is present.

In another embodiment, in Formula (I), at least one T and V is present; each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein U is absent.

In another embodiment, in Formula (I), at least one T and V is present; each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3, wherein n is 1.

In another embodiment, in Formula (I), at least one T and V is present; each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein each of Y and Z is

independently selected from the group consisting of a covalent bond and -CH_2-, and each of R^1 and R^2 is independently selected from the group consisting of cyano, -C(O)OH or -$C(O)NH_2$.

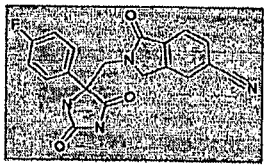
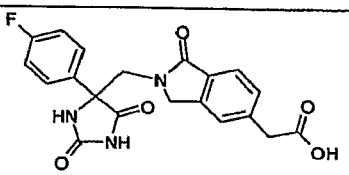
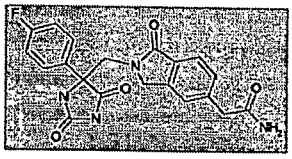
In another embodiment, in Formula (I), at least one T and V is present, each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein Y is a covalent bond, and R^1 is H.

In another embodiment, in Formula (I), at least one T and V is present; each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein Z is a covalent bond, and R^2 is cyano.

In another embodiment, in Formula (I), at least one T and V is present; each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein Z is –CH_2-, and R^2 is -C(O)OH or -$C(O)NH_2$.

In another embodiment, in Formula (I), at least one T and V is present; each of –Y-R^1 and –Z-R^2 is independently selected from the group consisting of cyano, –$(C(R^4)_2)_n$-C(O)OH, –$(C(R^4)_2)_n$-C(O)O-alkyl, –$(C(R^4)_2)_n$-$C(O)NH_2$, –$(C(R^4)_2)_n$-C(O)NH(alkyl), and –$(C(R^4)_2)_n$-C(O)N$(alkyl)_2$, wherein each R^4 independently is H or alkyl; and n is 1-3; wherein the compound of Formula (I) is selected from the group consisting of:

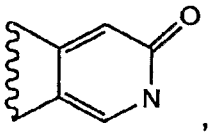
Compound ID	Structures

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or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties.

In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and



, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; wherein said ring **A** is phenyl.

In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10}

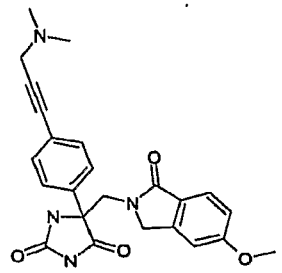
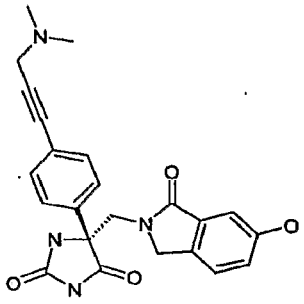
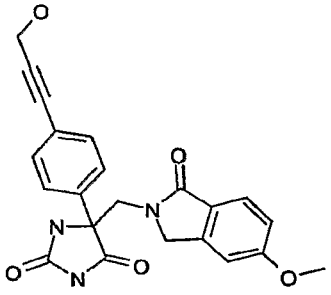
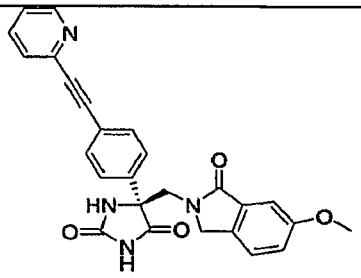
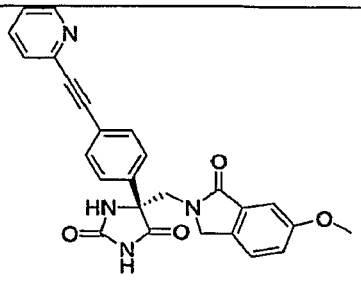
moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; wherein T is aryl, U is –O- or absent, and V is alkynyl which is unsubstituted or substituted with one or two R^{10} moieties selected from the group consisting of $-OR^4$, $-N(R^4)_2$, and heteroaryl; wherein when said heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; wherein each R^4 independently is H or alkyl, and said R^{10} heteroaryl is optionally independently substituted with one to four R^{30} moieties which can be the same or different.

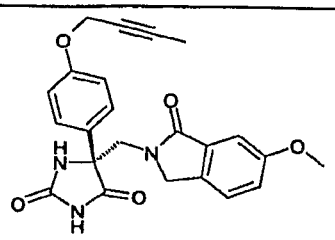
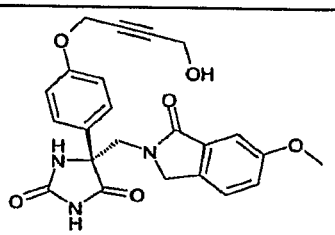
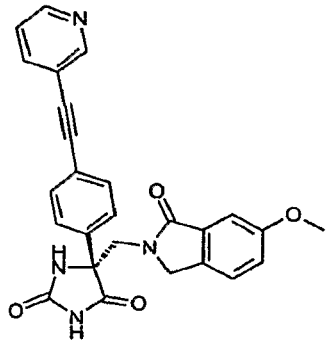
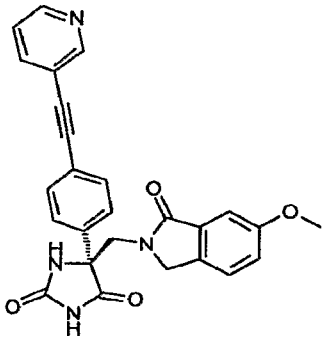
In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; wherein T is phenyl.

In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; wherein said V alkynyl is selected from the group consisting of $-CH_2-C\equiv C-CH_3$, and R^{10} substituted $-C\equiv C-$, and $-CH_2-C\equiv C-CH_2-$.

In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; wherein said R^{10} substituents are selected from the group consisting of $-N(alkyl)_2$, -OH, $-OCH_3$, and pyridyl.

In another embodiment, in Formula (I), T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; wherein the compound of Formula (I) is selected from the group consisting of:

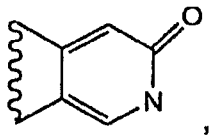
Compound ID	Structures
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or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein ring A is selected from the group consisting of thiophenyl, pyridyl, pyrimidyl, and



, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein T is selected from the group consisting of alkyl, and halo-substituted aryl.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein U and V are absent.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein Y is selected from the group consisting of a covalent bond and –O-, and Z is a covalent bond.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein R^1 is selected from the group consisting of H and $-CH_3$; and R^2 is H.

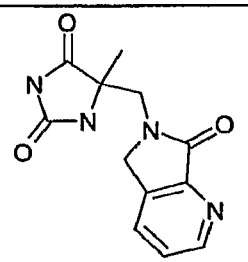
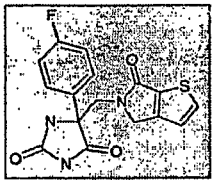
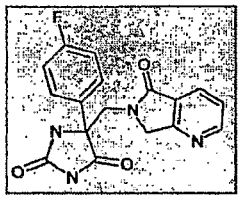
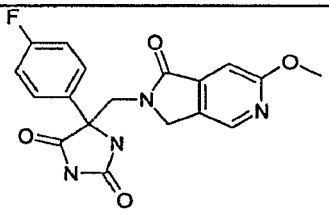
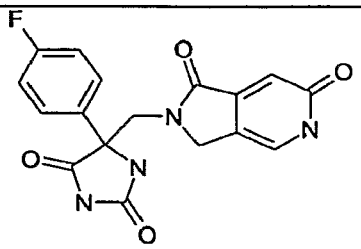
In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein Y is a covalent bond R^1 is H.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein Y is is –O- and R^1 is $-CH_3$.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein Z is a covalent bond and R^2 is H.

In another embodiment, in Formula (I), at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl; wherein the compound of Formula (I) is selected from the group consisting of:

Compound ID	Structures

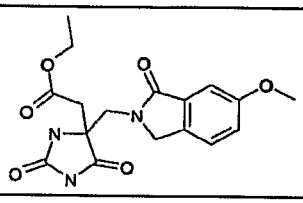
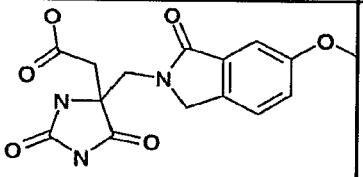
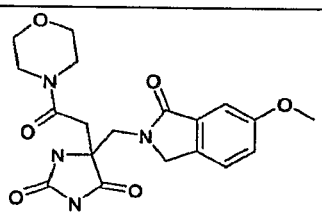
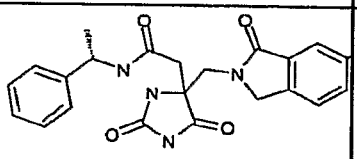
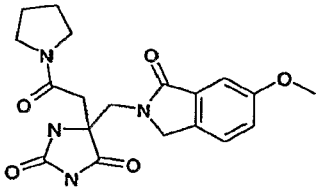
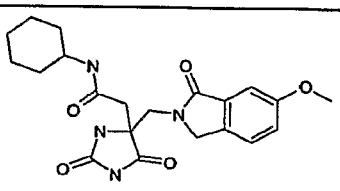
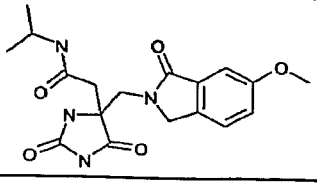
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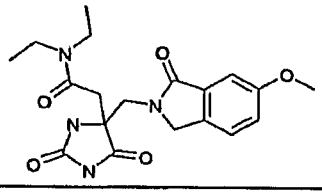
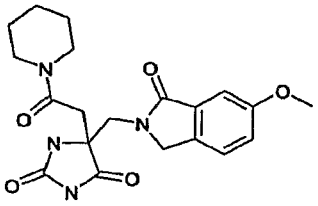
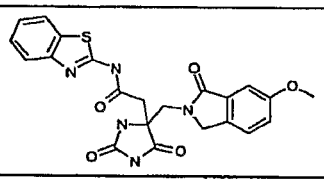
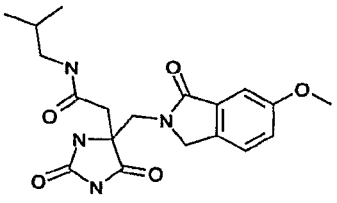
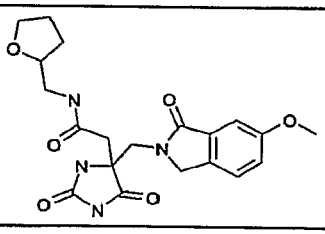
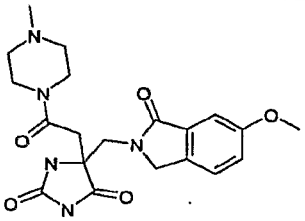
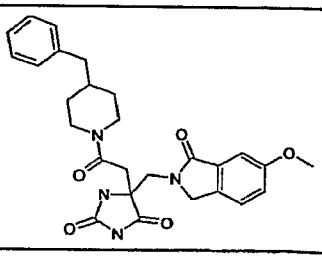
or a pharmaceutically acceptable salt or solvate thereof.

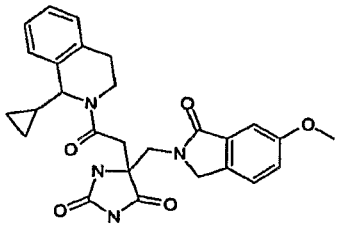
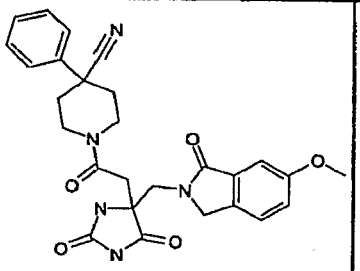
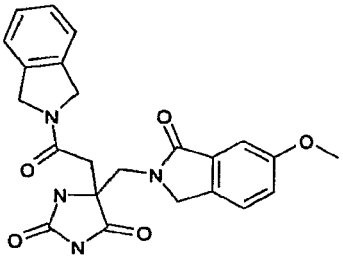
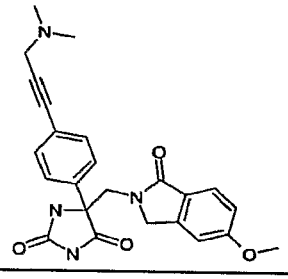
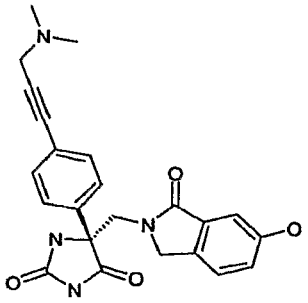
In another embodiment, the compound of Formula (I) is selected from the group consisting of compounds listed in the table below (Table 1), or a pharmaceutically acceptable salt, solvate, ester or isomer thereof. This table also lists the mass spectroscopy data and the Ki rating for each compound. Those 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

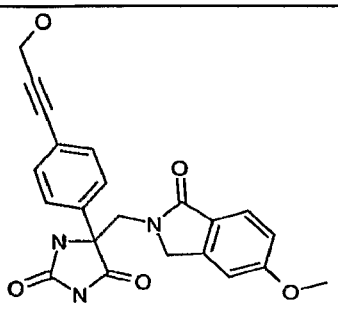
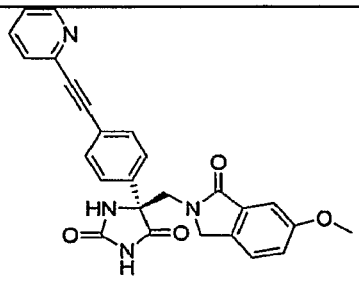
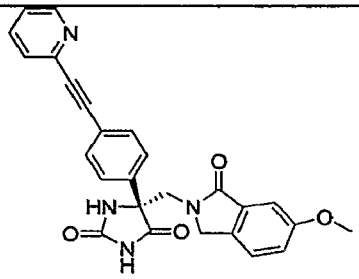
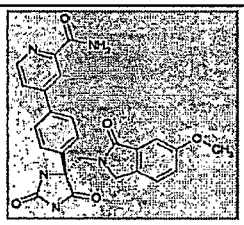
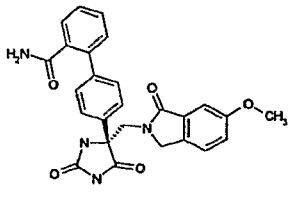
100 to 1000 nM are designated with letter "C"; and those with a Ki value of more than 1000 nM (>1000 nM) are designated with letter "D". The syntheis and characterization of these compounds is described hereinbelow in the "EXAMPLES" section of the present application.

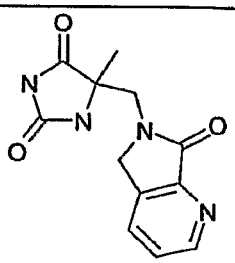
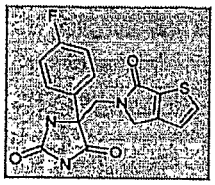
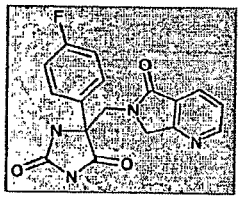
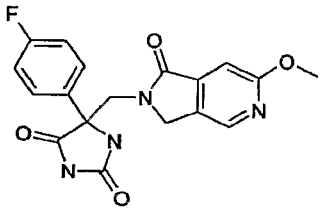
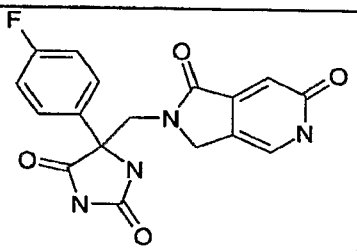
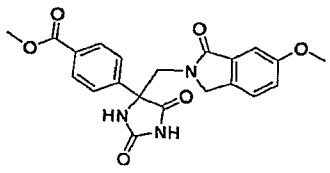
Table 1

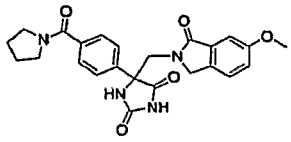
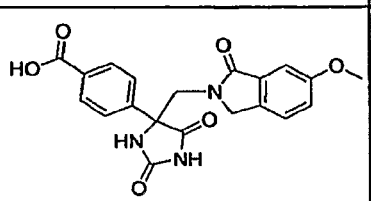
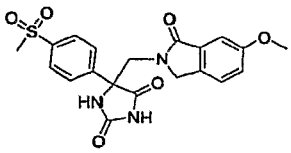
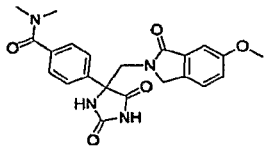
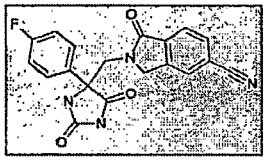
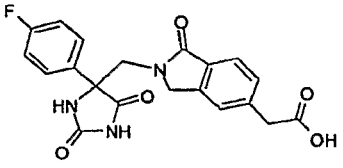
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
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2		333.10	334.2[M+H]$^+$	C
3		402.15	403.2[M+H]$^+$	B
4		436.2	437.2[M+H]$^+$	B
5		386.2	387.2[M+H]$^+$	A
6		414.19	415.2[M+H]$^+$	B
7		374.16	375.2[M+H]$^+$	B

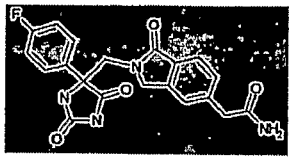
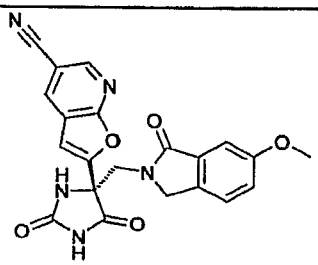
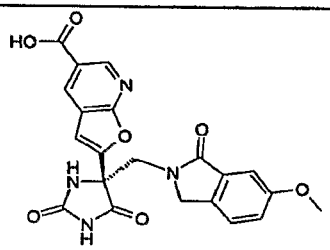
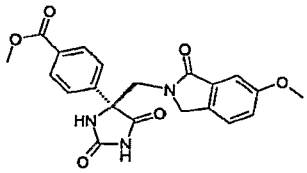
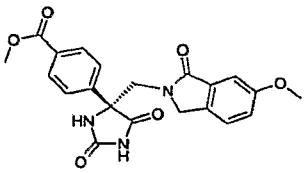
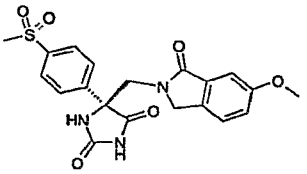
8		388.17	389.2[M+H]$^+$	B
9		400.17	401.2[M+H]$^+$	A
10		465.11	466.3[M+H]$^+$	A
11		388.17	389.2[M+H]$^+$	B
12		416.17	417.2[M+H]$^+$	B
13		415.19	416.2[M+H]$^+$	B
14		490.22	491.3[M+H]$^+$	A

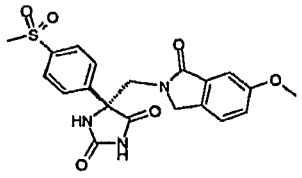
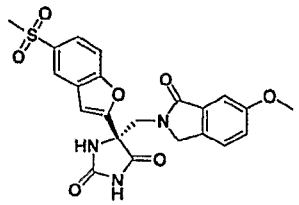
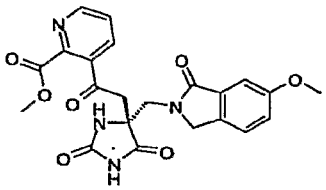
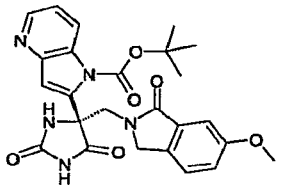
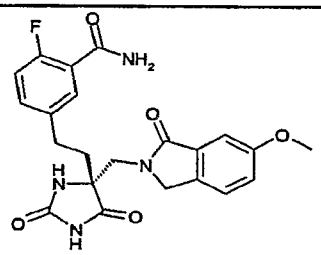
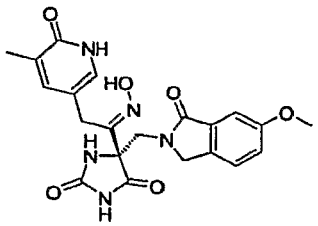
15		488.21	489.3[M+H]$^+$	A
16		501.20	502.3[M+H]$^+$	B
17		434.16	435.07[M+H]$^+$	B
18		432.18	433.2[M+H]$^+$	A
19		418.16	419.2[M+H]$^+$	B

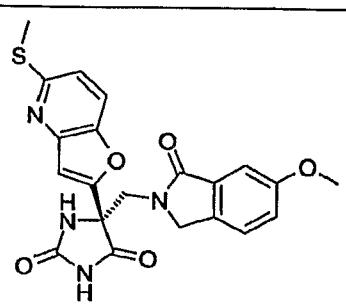
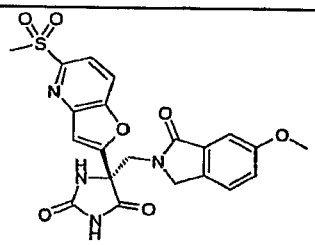
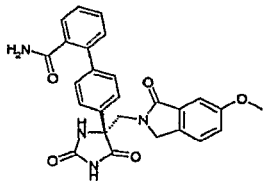
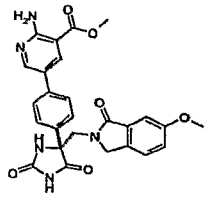
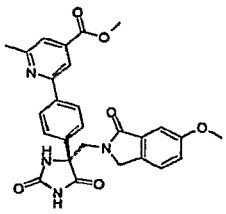
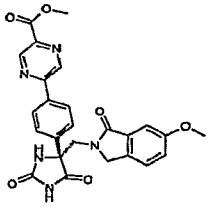
20		405.13	406.2[M+H]$^+$	A
21		452.15	453.2[M+H]$^+$	B
22		452.15	453.2[M+H]$^+$	A
23		471.15	472.3[M+H]$^+$	A
24		470.16	471.3[M+H]$^+$	A

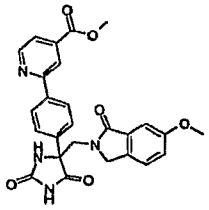
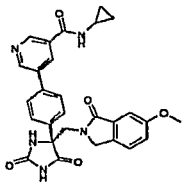
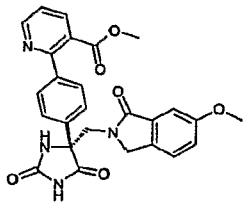
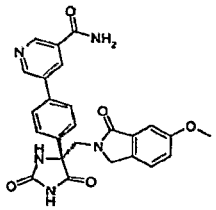
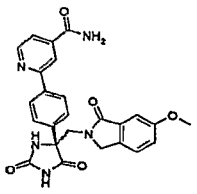
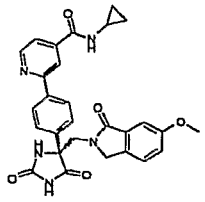
25		260.09	261.1[M+H]$^+$	D
26		345.35	346.2[M+H]$^+$	B
27		340.31	341.2[M+H]$^+$	D
28		370.11	371.1 [M+H]	A
29		356.09	357.1 [M+H]	B
30		409.13	410.1[M+H]$^+$	A

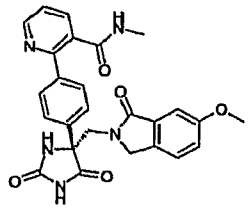
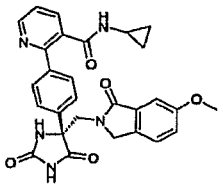
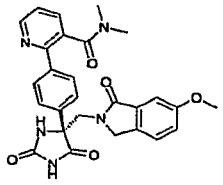
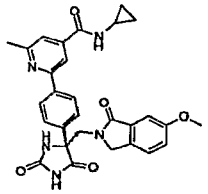
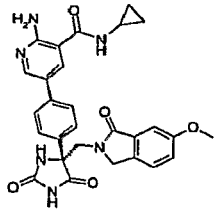
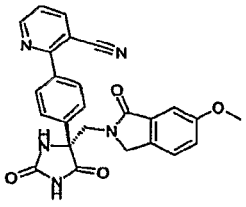
31		448.17	449.2[M+H]$^+$	A
32		395.11	396.1[M+H]$^+$	A
33		429.10	430.0[M+H]$^+$	A
34		422.16	423.0[M+H]$^+$	B
35		364.10	365.0[M+H]$^+$	B
36		397. 11	398.0[M+H]$^+$	C

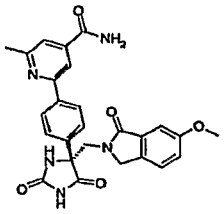
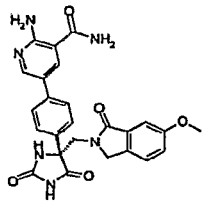
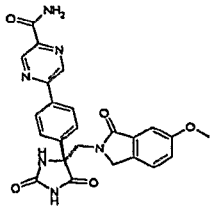
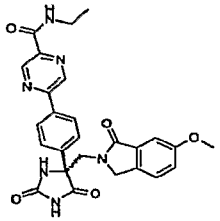
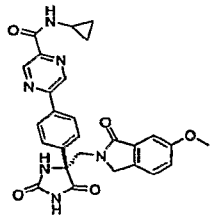
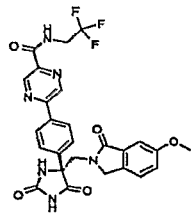
37		396.12	397.1[M+H]$^+$	B
38		417.11	418.1[M+H]$^+$	A
39		436.10	437.0[M+H]$^+$	A
40		409.13	410.1[M+H]$^+$	B
41		409.13	410.1[M+H]$^+$	A
42		429.10	430.1[M+H]$^+$	C

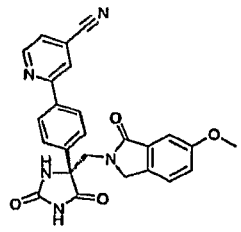
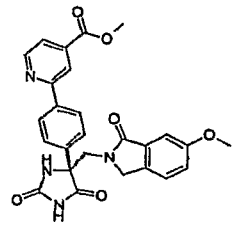
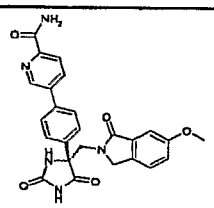
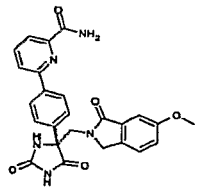
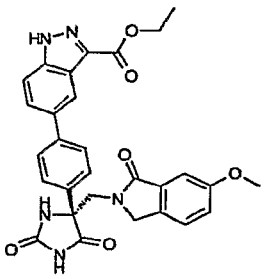
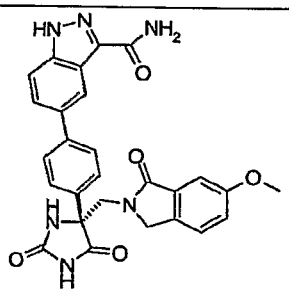
43		429.10	430.1[M+H]$^+$	A
44		469.09	470.0[M+H]$^+$	A
45		452.13	453.2[M+H]$^+$	B
46		491.184	492.3[M+H]$^+$	A
47		440.1	441.2[M+H]$^+$	B
48		439.15	440.4[M+H]$^+$	B

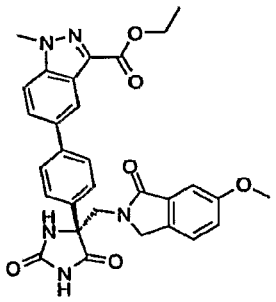
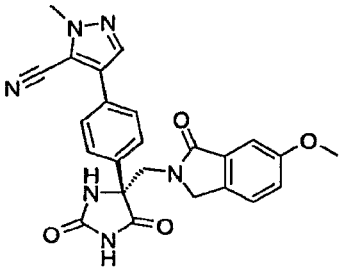
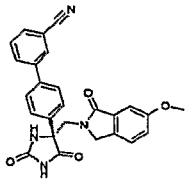
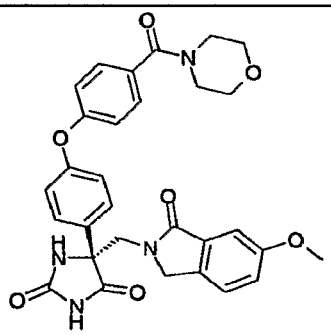
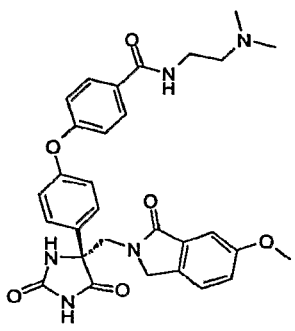
49		438.10	439.5[M+H]$^+$	A
50		470.09	471.5[M+H]$^+$	A
51		470.47	471.3 [M+H]$^+$	A
52		501.49	502.7 [M+H]$^+$	A
53		500.50	501.3 [M+H]$^+$	A
54		487.46	488.3 [M+H]$^+$	A

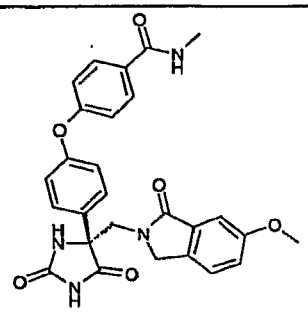
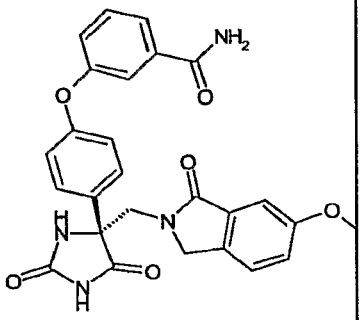
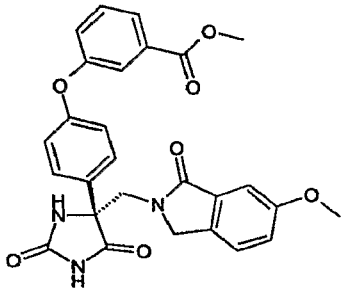
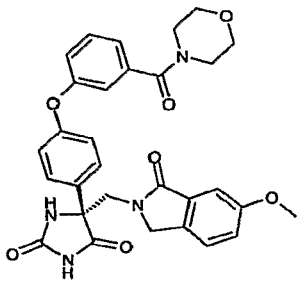
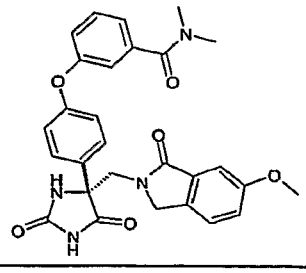
55		486.48	487.3 $[M+H]^+$	A
56		511.53	512.3 $[M+H]^+$	A
57		486.48	487.3 $[M+H]^+$	A
58		471.46	472.3 $[M+H]^+$	A
59		471.46	472.3 $[M+H]^+$	A
60		511.53	512.3 $[M+H]^+$	A

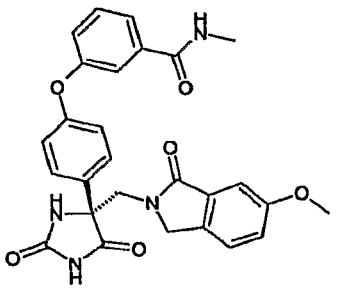
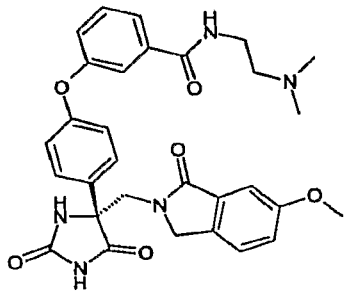
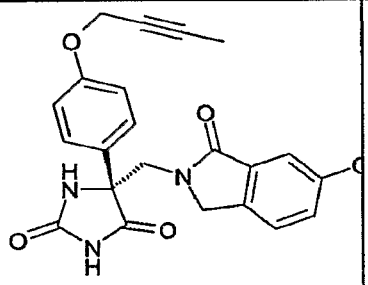
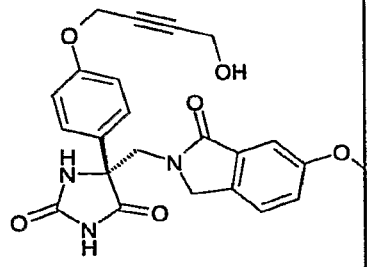
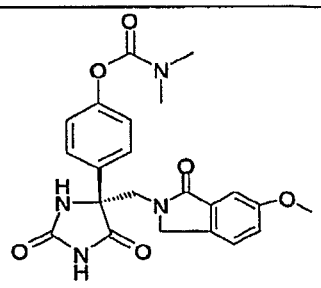
61		485.49	486.3 $[M+H]^+$	A
62		511.53	512.3 $[M+H]^+$	A
63		499.52	500.3 $[M+H]^+$	A
64		525.56	526.3 $[M+H]^+$	A
65		526.54	527.3 $[M+H]^+$	A
66		453.45	454.2 $[M+H]^+$	A

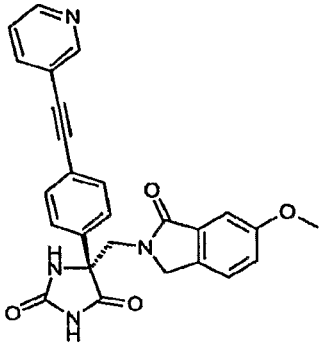
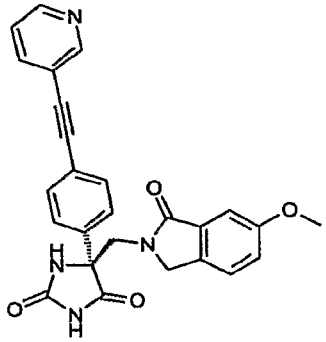
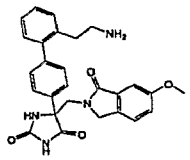
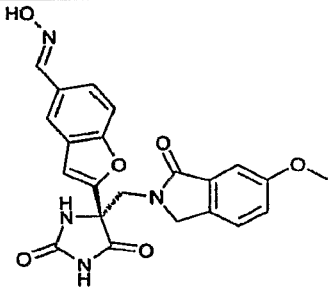
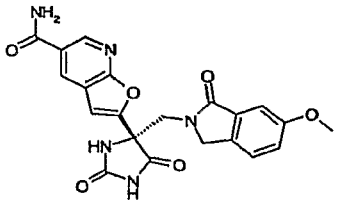
67		485.49	486.3 $[M+H]^+$	A
68		486.48	487.3 $[M+H]^+$	A
68		472.45	473.1 $[M+H]^+$	A
70		500.51	501.3 $[M+H]^+$	A
71		512.52	513.3 $[M+H]^+$	A
72		554.48	555.3 $[M+H]^+$	A

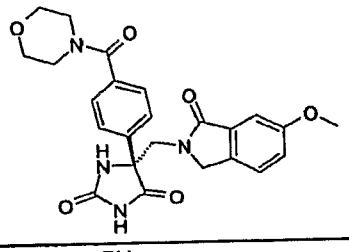
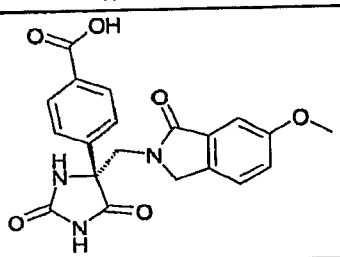
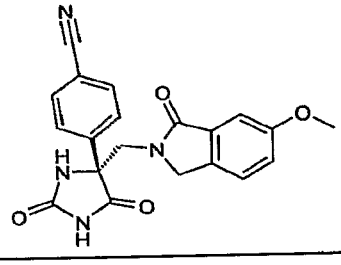
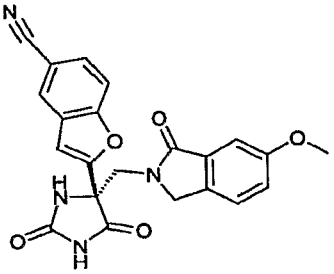
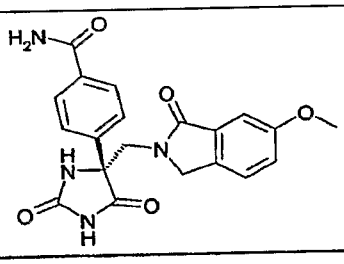
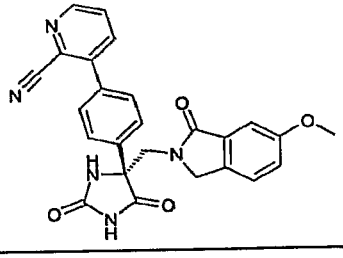
73		453.45	454.2 $[M+H]^+$	A
74		486.48	487.3 $[M+H]^+$	A
75		471.15	472.3 $[M+H]^+$	A
76		471.15	472.3 $[M+H]^+$	A
77		539.18	540.5$[M+H]^+$	A
78		510.17	511.5$[M+H]^+$	A

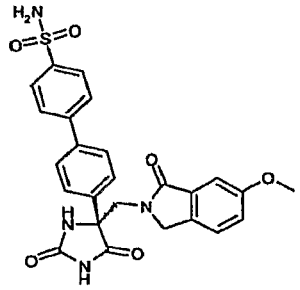
79		553.20	554.5[M+H]$^+$	TBD
80		456.15	457.5[M+H]$^+$	A
81		452.46	453.2[M+H]$^+$	A
82		556.2	557.3[M+H]$^+$	A
83		557.2	558.3[M+H]$^+$	A

84		500.2	501.3[M+H]$^+$	A
85		486.1	487.3[M+H]$^+$	A
86		501.2	502.3[M+H]$^+$	A
87		556.2	557.3[M+H]$^+$	A
88		514.2	515.3[M+H]$^+$	A

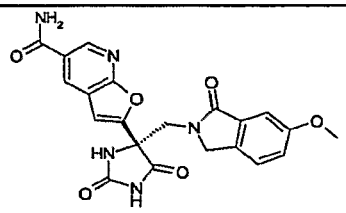
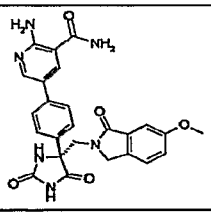
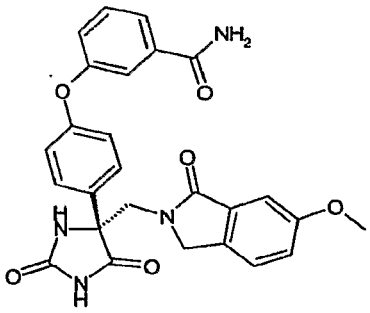
89		500.2	501.3[M+H]$^+$	A
90		557.2	558.3[M+H]$^+$	A
91		419.2	420.2[M+H]$^+$	A
92		435.1	436.2[M+H]$^+$	A
93		438.2	439.2[M+H]$^+$	A

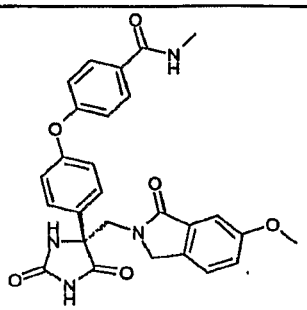
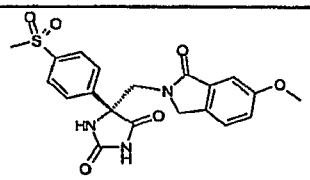
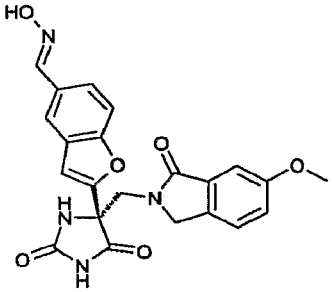
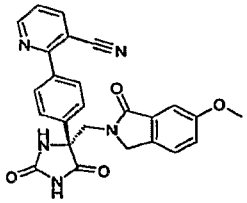
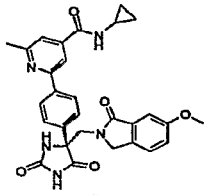
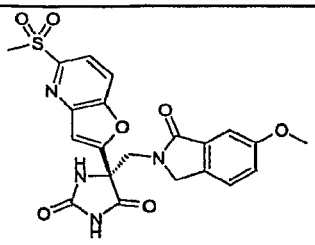
94		452.15	453.2[M+H]$^+$	A
95		452.15	453.2[M+H]$^+$	B
96		470.20	471.3 [M+H]$^+$	B
97		434.12	435.2[M+H]$^+$	A
98		435.12	436.1 [M+H]$^+$	A

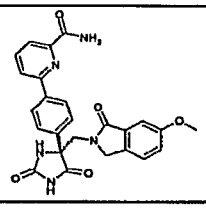
99		464.17	465.3[M+H]$^+$	A
100		395.11	396.2[M+H]$^+$	A
101		376.12	377.2[M+H]$^+$	A
102		416.11	417.2[M+H]$^+$	A
103		394.13	395.2[M+H]$^+$	A
104		453.14	454.2[M+H]$^+$	A

105		506.13	507.3 $[M+H]^+$	A

In another embodiment, the compound of Formula (I) is selected from the group consisting of:

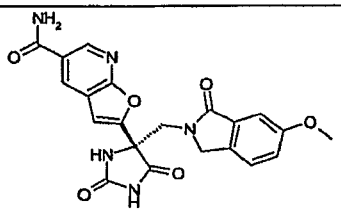
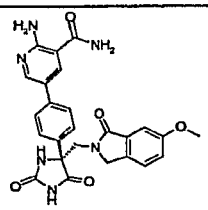
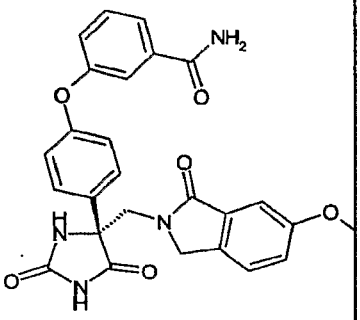
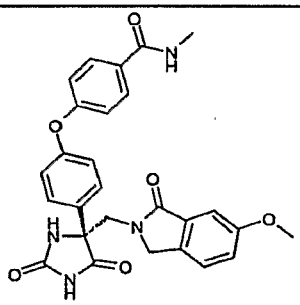
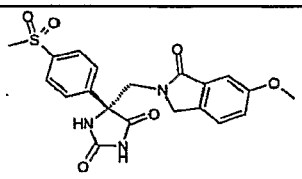
Compound ID	Structures
98	
68	
85	

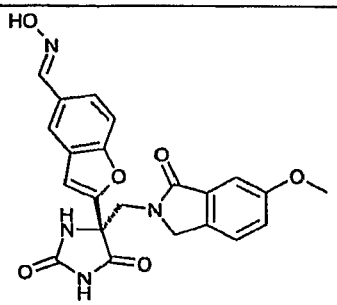
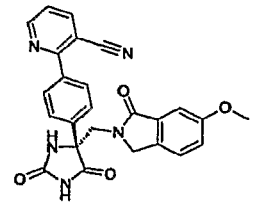
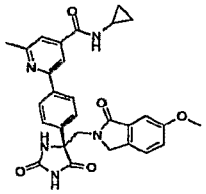
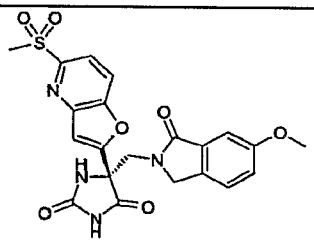
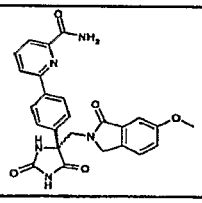
84	
43	
97	
66	
64	
50	

76	

or a pharmaceutically acceptable salt, solvate, or ester thereof.

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

Compound ID	Structures	Exact Mass	Mass Obsvd	Ki (nM)
98		435.12	436.1 $[M+H]^+$	0.71
68		486.48	487.3 $[M+H]^+$	0.23
85		486.1	487.3$[M+H]^+$	0.46
84		500.2	501.3$[M+H]^+$	4.0
43		429.10	430.1$[M+H]^+$	0.26

97		434.12	435.2[M+H]$^+$	0.39
66		453.45	454.2 [M+H]$^+$	0.09
64		525.56	526.3 [M+H]$^+$	0.15
50		470.09	471.5[M+H]$^+$	1.04
76		471.15	472.3 [M+H]$^+$	0.66

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. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. 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.

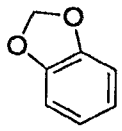
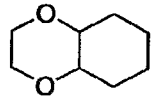
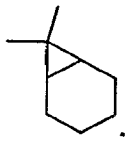
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" 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.

"Cycloalkenyl" 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 which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl 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 cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

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

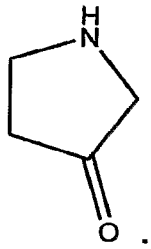
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, 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:

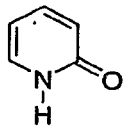
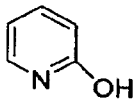


and

.

"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. "Heterocyclyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:



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

 and 

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. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems,"

Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-

carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

"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, aggrecanase, 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 (I).

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

In another aspect, the invention provides a method of treating disorders associated with TACE, aggrecanase, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising administering to a patient in need of such treatment an effective amount of at least one compound of formula (I).

In another aspect, the invention provides a use of a compound of formula (I) for the manufacture of a medicament to treat disorders associated with TACE, aggrecanase, 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, aggrecanase, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of formula (I) 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, solvates, or esters of said compound, said compound being selected from the compounds of structures listed in **Table 1** set forth above.

In another aspect, the invention provides a pharmaceutical composition for treating disorders associated with TACE, aggrecanase, 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 (I) or a pharmaceutically acceptable salt, solvate, ester, or isomer thereof.

In another aspect, the invention provides a compound of formula (I) 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 (I) or a pharmaceutically acceptable salt, solvate, ester 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 (I) or a pharmaceutically acceptable salt, solvate, ester 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 (I) or a pharmaceutically acceptable salt, solvate, ester, 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 (I) or a pharmaceutically acceptable salt, solvate, ester 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 Formula (I) or a pharmaceutically acceptable salt, solvate, ester 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 (I) or a pharmaceutically acceptable salt, solvate, ester, 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 (I) or a pharmaceutically acceptable salt, solvate, ester 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 (I) or a pharmaceutically acceptable salt, solvate, ester, 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 (I) or a pharmaceutically acceptable salt, solvate, ester 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 (I) or a pharmaceutically acceptable salt, solvate, ester 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 (I) or a pharmaceutically acceptable salt, solvate, ester, 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 (I), or a pharmaceutically acceptable salt, solvate, ester, 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 (I) or a pharmaceutically acceptable salt, solvate, ester 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 (I) 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 Formula (I) or a pharmaceutically acceptable salt, solvate, ester, 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 Formula (I), or a pharmaceutically acceptable salt, solvate, ester 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. □-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-TNF□ 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 □M $ZnCl_2$, 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.

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 may be used in the procedures and schemes below:

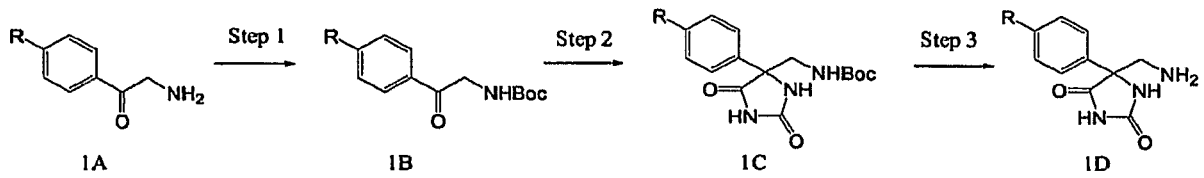
ACN	Acetonitrile
AcOH	Acetic acid
Aq	Aqueous
BOC	tert-Butoxycarbonyl
BOC_2O	BOC Anhydride
C	degrees Celsius
CBZCl	Benzyl chloroformate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane

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
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1h)-pyrimidinone
DMSO	Dimethyl sulfoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron impact
eq	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
g	grams
h	hours
hr	hours
^1H	proton
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HOBT	1-Hydroxybenzotriazole
HMPA	Hexamethyl phosphoramide
HPLC	High pressure liquid chromatography
HPLC/MS	High pressure liquid chromatography/Mass spectroscopy
LC/MS	Liquid chromatorgraphy/mass spectroscopy
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
M	Molar
mmol	millimoles
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
SEM	2-(Trimethylsilyl)-ethoxymethyl
sgc	Silica gel 60 chromatography
tBOC	tert-Butoxycarbonyl
TACE	Tumor Necrosis Factor-alpha converting enzyme
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
T_R	Retention time
X-PHOS	2-dicyclohexylphosphino-2', 4', 6'-tri-isopropyl-1', 1-biphenyl

SYNTHETIC ROUTES AND EXAMPLES

Example 1



1A 1B 1C 1D

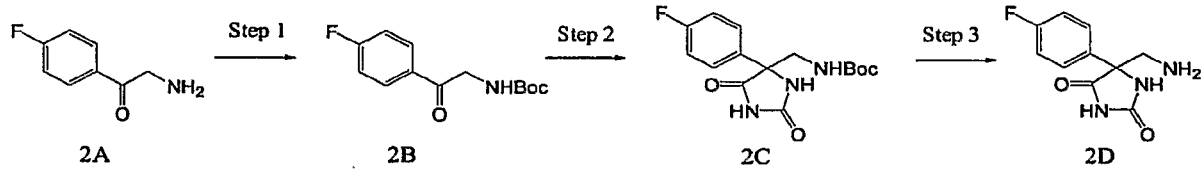
General procedures for Example 1:

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 an 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.

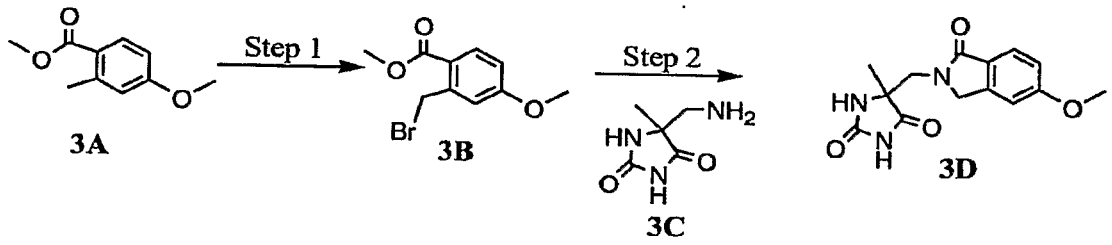
Step 2

Compound **2B** (9.06 g, 35.8 mmol), KCN (3.49 g, 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%).

Example 3



Step 1

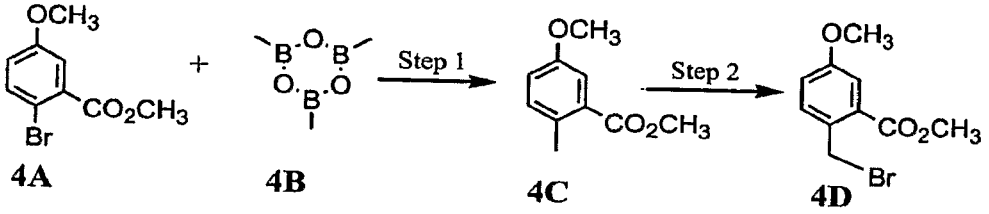
Compound **3A** (prepared according to the procedure described by Wyrick, S. D. et al. *Journal of Medicinal Chemistry*, **1987**, 30(*10*), 1798-806) (3.33 g, 18.5 mmol) was dissolved in dry benzene (40 mL). NBS (3.45 g, 19.4 mmol) and benzoyl peroxide (134 mg, 0.55 mmol) were added. The solution was 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 **3B** which was used without further purification. ^{1}H-NMR appeared to indicate that approximately 75% of this material was compound **3B**.

Step 2

Compound **3B** (4.62 mmol), Compound **3C** (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 purified via reverse phase MPLC (CH_3CN/water, 5% to 90%, containing 0.1%HCO_2H) to give compound **3D** (198 mg, 15%).

Example 4



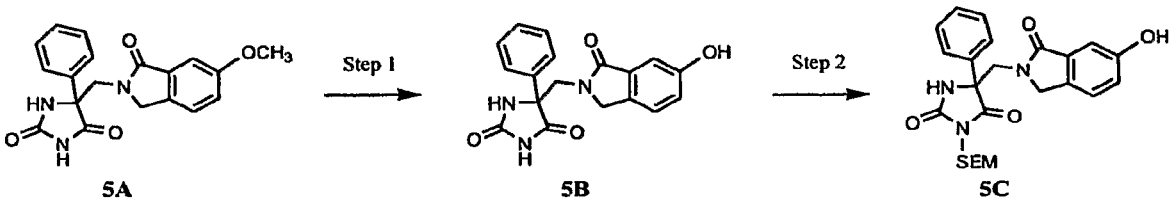
Step 1

Compound **4A** (20g, 81.61 mmol), **4B** (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 **4C** (12.1g, 80%).

Step 2

Compound **4C** was converted to Compound **4D** using a procedure similar to that described in Example 3.

Example 5



5A 5B 5C

Compound **5A** was prepared using chemistry similar to that described in Examples 1, 2, 3 and 4.

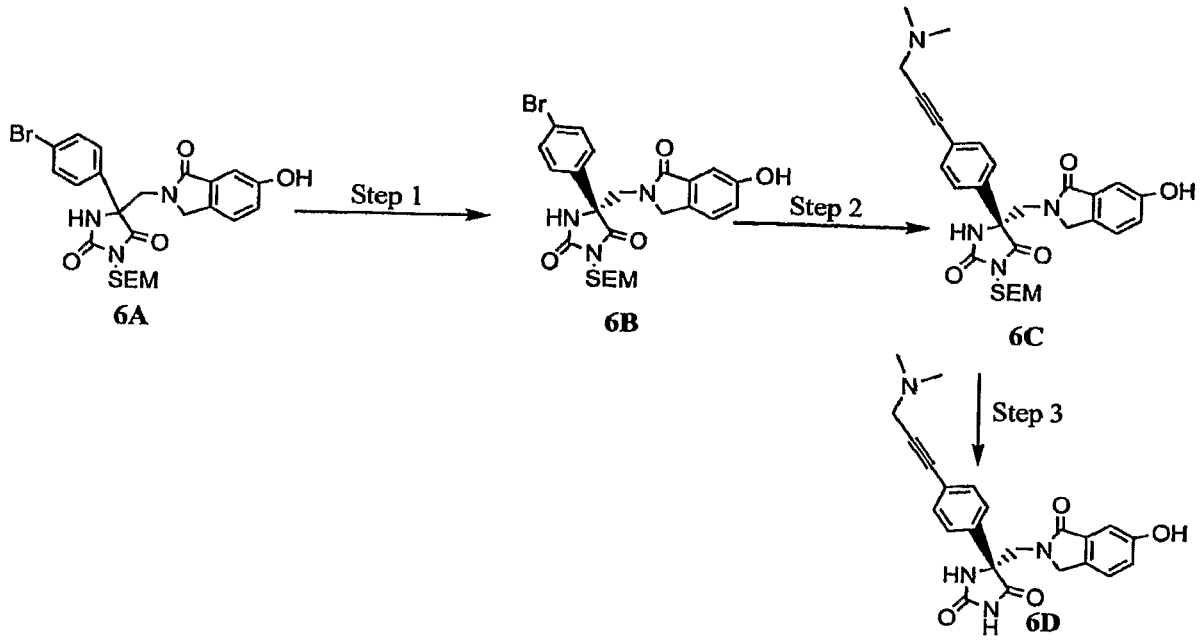
Step1

Compound **5A** (1.18 g, 3.36mmol) and pyridine hydrochloride (2.33 g, 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 reverse phase chromatography on a C-18 cartridge (CH_3CN/water 5% to 90%, with 0.1% HCO_2H) to give compound **5B** (0.87 g, 77%).

Step 2

Compound **5B** (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 **5C** (0.81 g, 78%).

Example 6



Compound **6A** was prepared using chemistry similar to that described in Examples 1, 2, 3 4, and 5.

Step 1

Compound **6A** was resolved by Chiralcel OD column (Mobile phase: Hexane:2-propanol 4:1). The first peak was collected and concentrated to give compound **6B**.

Step 2

Compound **6B** (0.2 g, 0.36 mmol), allyl palladium chloride dimer (3 mg, 0.008 mmol), and DMF (3 mL) were added to a round bottomed flask and cycled between vacuum and nitrogen three times. Tri-tert-butyl phosphine (30 microliters of 10% solution in hexanes-Strem), piperidine (61 mg, 0.7 mmol), and 3-dimethylamino-1-propyne were added via syringe. The reaction was left stirring overnight at rt. The following morning, the reaction was stirred for 1hr at 50 °C. The resulting material was diluted with EtOAc, washed with water, dried with $MgSO_4$, and concentrated to dryness. The crude product was purified via flash silica gel chromatography using a gradient elution of

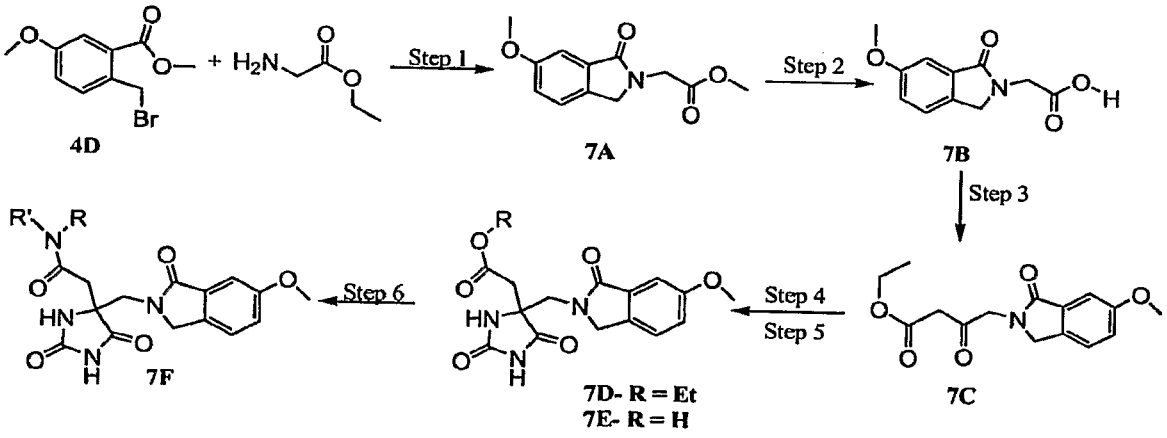
70% (5% Methanol in EtOAC) in hexanes to 100% (5% Methanol in EtOAc) giving 55 mg of compound **6C**.

Step 3

Compound **6C** (55 mg) was dissolved in 10 mL of 4 M HCl in dioxane (Aldrich) and 10 ml of methanol and the solution was added to a pressure tube. The tube was capped and heated to 90 °C. The reaction mixture was stirred at 90 °C for 4 hr, then allowed to cool to room temperature. The reaction mixture was concentrated to dryness. Methanol was added and the reaction mixture was reconcentrated to dryness. Methanol (5 ml) and triethylamine (1mL) were added and the reaction mixture was stirred at rt for 2 hr. The resulting solution was concentrated to dryness. The crude product was purified on a C-18 Isco cartridge using an (acetonitrile:water (+0.1% formic acid)) gradient as the mobile phase to give **6D**.

Chemistry similar to the procedures described in Examples 6, 8, 1, 2, 3, 4, and 5 was used to prepare compounds 18, 19, 20, 21, and 22 in Table 1.

Example 7



Step 1

Compound **4D** (16.26 g, 62.77 mmol) was dissolved in 100 mL of DMF and glycine ethyl ester hydrochloride (9.68 g, 69.35 mmol) was added. Diisopropylethylamine (21 mL, 15.6 mmol) was added and the reaction

mixture was placed in a 70 °C oil bath. The reaction mixture was stirred overnight at 70°C. After 17 hr, the reaction mixture was allowed to cool to rt. EtOAc, water, and 5 mL of 1M aq $NaHSO_4$ were added and the layers were separated. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered and concentrated to an orange oil (14.8 g). The crude product was purified via flash silica gel chromatoghraphy using a 20% to 60% EtOAc:Hexanes gradient as the mobile phase to give 6.8 g of **7A** as product.

Step 2

Compound **7A** (6.31 g, 25.3 mmol) was dissolved in dioxane (88 mL). A 1.0 M aq soln of LiOH (28 mL, 28 mmol) was added followed by 10 mL of absolute ethanol. The reaction mixture was stirred at rt for 3 hr, then partially concentrated on the rotary evaporator. Dichloromethane and 1M aq $NaHSO_4$ were added and the layers were separated. The aq layer was extracted with CH_2Cl_2. The combined organic layer was filtered, dried with $MgSO_4$, filtered again, and concentrated to dryness giving 4.04 g of **7B**.

Step 3

Compound **7B** (2.02 g, 9.13 mmol) was suspended in 15 mL of THF. Carbonyl diimidazole was added in one portion. After 10 min, acetonitrile (10 mL) was also added. The reaction mixture was stirred at rt for 1hr. Magnesium chloride and ethyl potassium malonate were added. The reaction mixture was left stirring overnight at room temperature under a drying tube. The reaction mixture was concentrated to near dryness. EtOAc and 1.0 M pH 5.5 sodium phosphate buffer were added. The layers were separated. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated to dryness. An off white solid was obtained. The crude product was purified via silica gel chromatoghraphy using a 50% to 100% EtOAc: Hexanes gradient as the mobile phase to give 1.87 g of **7C**.

Step 4

Compound **7C** was dissolved in 18 mL of absolute ethanol and 8 mL of water. The solution was added to a thick walled glass pressure bottle and ammonium carbonate (2.21 g, 23.0 mmol) was added. The bottle was capped and the reaction mixture was stirred at rt for 15 min. Potassium cyanide was added, the bottle was recapped, and the reaction mixture was stirred at 70°C for 16 hr. The resulting mixture was poured into 250 mL of water and suction filtered to give **7D** (1.86 g) as a white solid.

Step 5

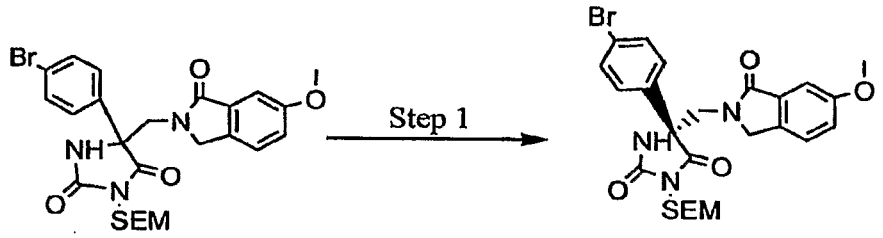
Compound **7D** (0.83 g, 2.29 mmol) was suspended in 9 mL of dioxane. Aq 1.0 M LiOH (4.6 mL, 4.6 mmol) was added, causing the material to dissolve. The reaction mixture was stirred at rt for 5.5 hr. Additional LiOH was added (1.0 mL. 1.0 mmol) and the reaction mixture was stirred for 1hr. The reaction mixture was concentrated to near dryness. The resulting mixture was acidified with aq 1M $NaHSO_4$ causing a precipitate to form. The flask was placed in an ice water bath and stirred for 30 min. The resulting mixture was suction filtered to give **7E** (0.70 g) as a white solid.

Step 6

Compound **7E** (31 mg, 0.093 mmol) was dissolved in DMF (400 μL). Carbonyl diimidazole (18 mg, 0.11 mmole) was added and the reaction mixture was stirred at rt for 30 min. Pyrrolidine (20 μL) was added and the reaction mixture was stirred at rt for 5 hr. Aq 1M $NaHSO_4$ was added (7 mL) followed by EtOAc. The layers were separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated to dryness. the crude product was purified via reverse phase (C-18 Isco cartridge) chromatography using a 10% to 60% acetonitrile:water + (0.1% formic acid) gradient as the mobile phase. A white solid was obtained as product giving compound 5 in Table 1, which is one embodiment of the class of compounds **7F**.

The procedures described in Example 7 were used to prepare compounds 1 through 17 in Table 1.

Example 8



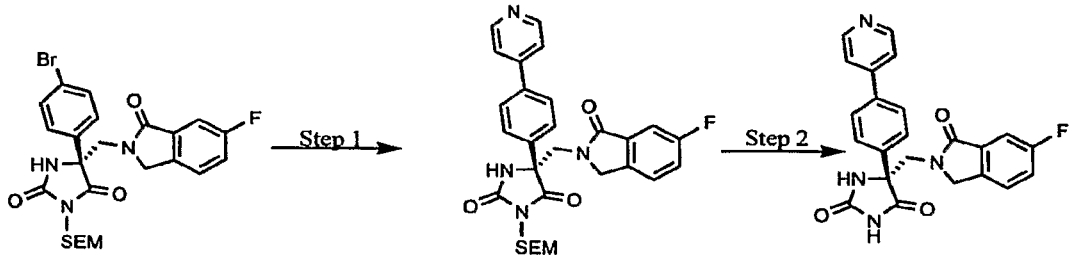
8A **8B**

Compound **8A** was prepared using chemistry similar to that described in Examples 1, 2, 3, 4 and 5.

Step 1

Compound **8A** was resolved by Chiralcel OD column (Mobile phase: Hexane:2-propanol 4:1). The first peak was collected and concentrated to give compound **8B**.

Example 9:



9A **9B** **9C**

Racemic compound **9A** was prepared using chemistry similar to that described in Examples 1, 2, 3, 4 and 5. The enantiomers were resolved by Chiralcel OD column (Mobile phase: Hexane/2-propanol 3:1). The first peak was collected and concentrated to give compound **9A** in its enantiomerically pure form.

Step 1

To a dry flask was added compound **9A** (1.5 g, 2.73 mmol) and 4-pyridyl boronic acid (670 mg, 5.50 mmol). The flask was subjected to vacuum and

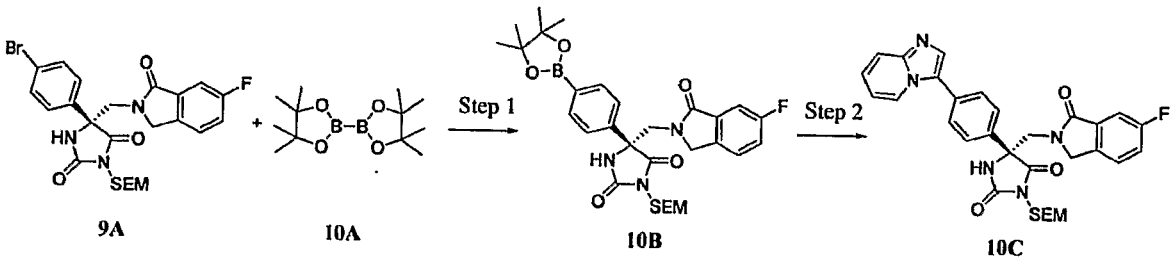
refilled with nitrogen three times. $Pd(dppf)Cl_2$ (220 mg, 0.30 mmol) was added and followed by addition of CH_3CN (20 mL) and aq. K_2CO_3 (1 M, 15 mL). The solution was stirred at 80 °C (oil bath) for 16 hours. After cooling down, CH_3CN (100 mL) was added and the solid was removed by filtration. The 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 **9B**.

Step 2

Compound **9B** 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 **9C** (815 mg).

Chemistry similar to that described in Examples 8 and 9 was used to prepare compound 24 in Table 1.

Example 10



Step 1

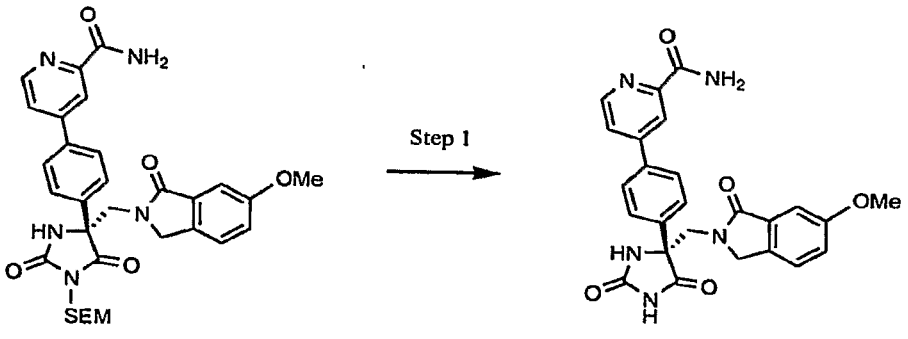
A mixture of compound **9A** (0.3 g, 0.55 mmol), bis(pinacolato)diboron (**10A**; 170 mg, 0.65 mmol), potassium acetate (170 mg, 1.70 mmol), and $[PdCl_2(dppf)]CH_2Cl_2$ (50 mg, 0.05 mmol) in 1,4-dioxane (10 mL) was cycled

between vacuum and 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 **10B** (300 mg, 91% yield).

Step 2

A solution of compound **10B** (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 subjected to vacuum 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 **10C** (42 mg, 71% yield).

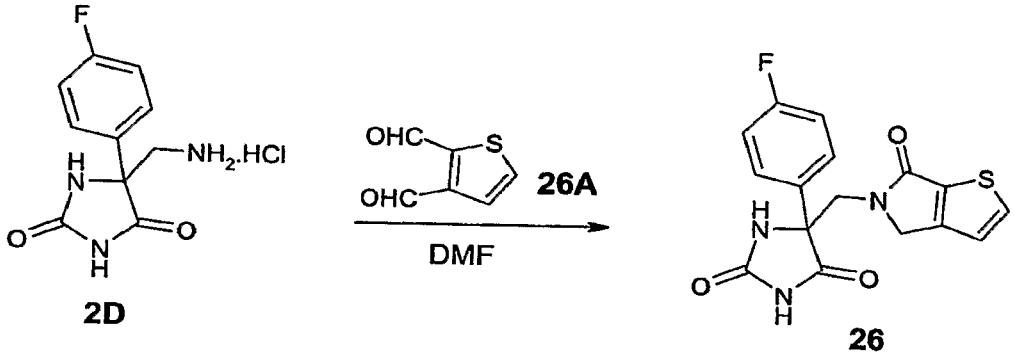
Example 11



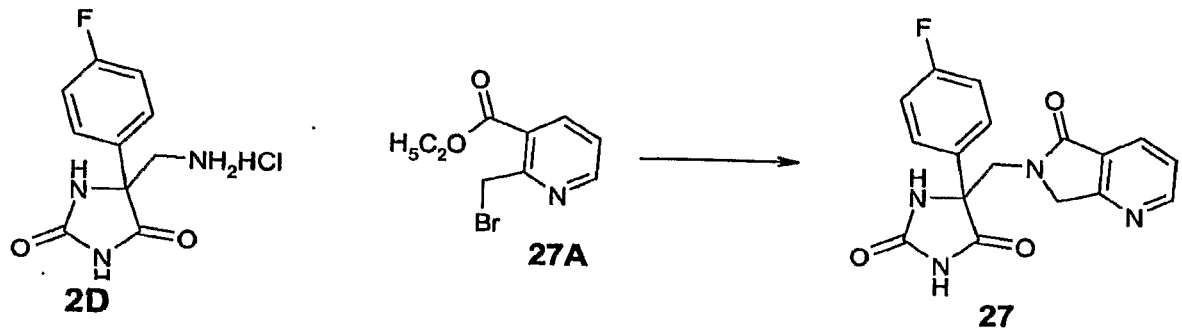
Compound **11A** was prepared via procedure similar to those described in Examples 8 and 10.

Step 1

Compounds **11A** (53 mg) was dissolved in 2 mL methanol in a 15 mL pressure tube. HCl (4M in dioxane, 1 mL) was added. The tube was sealed and put into an 80 °C oil bath for 16 h. After cooling down, the solution was transferred into a 100 mL flask and the solvent was removed. NH_3 (7N in methanol, 3 mL) was added and the solution was transferred into a 15 mL pressure tube. The tube was sealed and put into a 70 °C oil bath for three hours. After cooling down, the solution was transferred into 100 mL flask and the solvent was removed. The product was purified by C18 reverse phase chromatography (CH_3CN/water, 5% to 90%, with 0.1% HCO_2H) to give compound **23**. Compound **23** was dissolved in methanol, and HCl (4M in dioxane, 0.5 mL) was added. The solution was stirred at 25 °C for 30 minutes. The solvent was removed and the product was suspended in water. The water was removed by lyophilizer to give compound **23** (22 mg) in Table 1.



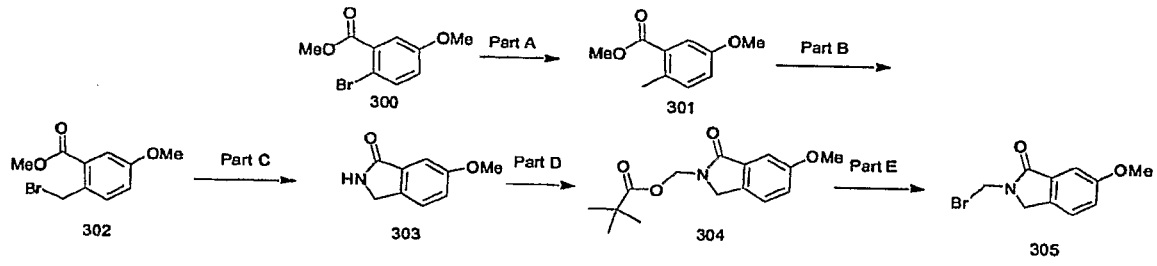
Amine hydrochloride **2D** (1.13g, 3.75 mmol) in DMF (30 mL) was treated with thiophenedialdehyde (0.3g, 1.9 mmol) and the mixture was stirred at ambient temperature for 1 h. The reaction was diluted with ethyl acetate (100 mL) and the organics were washed with water (3 X 50 mL) and brine (1 X 50 mL), dried over $MgSO_4$ and concentrated to provide a crude oil. The crude product was subjected to silica-gel chromatography using CH_2Cl_2-5% CH_3OH/CH_2Cl_2 as the gradient eluting solvent to yield **26** (0.08 g).



Amine hydrochloride **2D** (2.7 g, 8 mmol) in DMF (30 mL) was treated with bromoethylester **27A** (3.6 g, 15 mmol) and diisopropylethylamine (2.6 mL). The mixture was heated to 55 ^{0}C and stirred for 24 h. The reaction was diluted with ethyl acetate (200 mL) and the organics were washed with water (3 X 50 mL) and brine (1 X 50 mL), dried over $MgSO_4$ and concentrated to provide crude solid. The product **27** (1.8 g) was isolated by recrystallization (ethyl acetate : ether; 2:1). The product **27A** was prepared from commercially available (Aldrich) ethyl nicitinate using the process described in step 1 example **3**.

Compound #25 (Table 1) was prepared analogously using appropriate starting materials.

Example 300A



Part A:

Compound **300** (20.0 g, 81.61 mmol), trimethylboroxine (13.36 mL, 97.93 mmol), $Pd(dppf)Cl_2$ (1.0 g, 1.36 mmol), dioxane (350 mL), water (50 mL), and cesium carbonate (22.5 g, 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 (10:1 EtOAc/hexanes) to give **301** (12.1 g, 80%).

Part B:

Compound **301** (4.4 g, 24.2 mmol) was dissolved in carbon tetrachloride (80 mL) and N-bromosuccinimide (4.48 g, 24.2 mmol) and benzoyl peroxide (276 mg, 1.13 mmol) were added. The reaction mixture was stirred at reflux for 3 hours and then solids were filtered and washed with ether. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated to provide the desired product **302** (6.1 g, 98%).

Part C:

Compound **302** (32.0 g, 124.0 mmol) was dissolved in 7 M ammonia in MeOH (150 mL) and stirred in a sealed pressure flask at 60 °C overnight. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was suspended in ethyl acetate and stirred for 30 minutes. The solids were filtered and dissolved in methylene chloride. The methylene chloride was washed with water, dried over sodium sulfate, and concentrated to provide the desired product **303** (13.5 g, 67%).

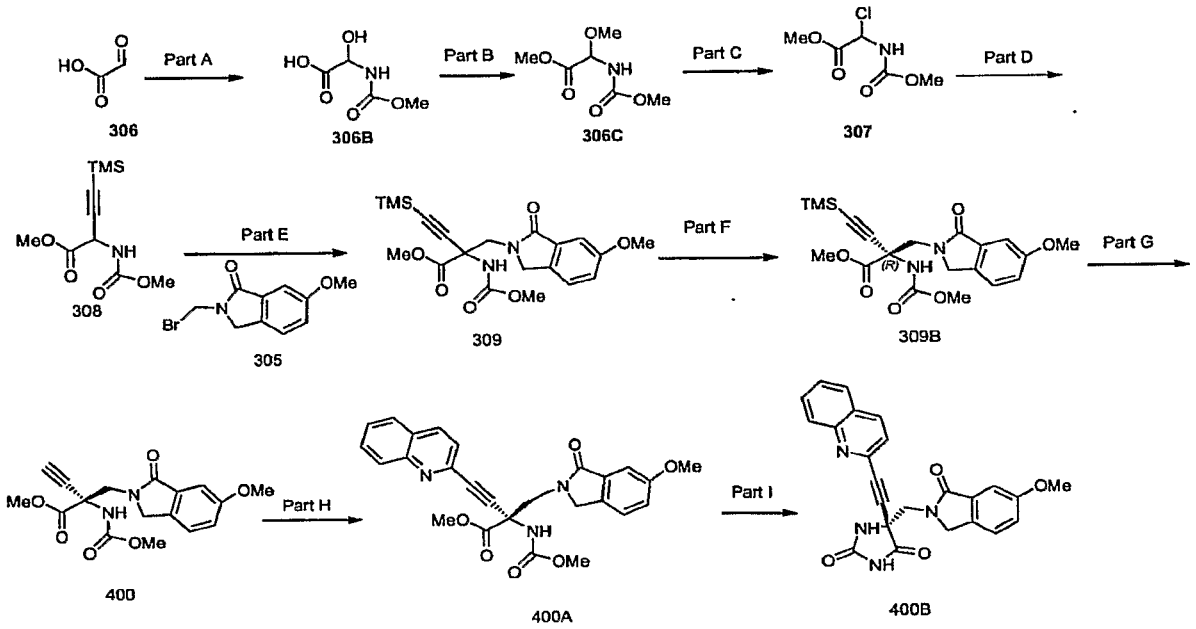
Part D:

Compound **303** (2.2 g, 13.4 mmol) was dissolved in THF (250 mL) and DMPU (40 mL). Sodium t-butoxide (1.55 g, 16.13 mmol) was added and stirred for 5 hours. Chloromethylpivalate (3.0 mL, 20.1 mmol) was added dropwise and stirred overnight. The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined ethyl acetate layers were washed with water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded the desired product **304** (2.5 g, 67%).

Part E:

Compound **304** (288 mg, 1.04 mmol) was dissolved in methylene chloride (5 mL) and cooled in an ice bath. Bromotrimethylsilane (0.3 mL, 2.08 mmol) was added dropwise and stirred in the ice bath for 30 minutes followed by 2 hours at room temperature. The reaction mixture was concentrated and re-dissolved in methylene chloride (2 mL). Hexanes (8 mL) was added and the solids were filtered to provide the desired product **305** (218 mg, 83%).

Example 400:



Part A:

Glyoxylic acid monohydrate (20.0 g, 218 mmol) and methyl carbamate (16.3 g, 218 mmol) were dissolved in diethyl ether (200 mL) and stirred overnight. The solids were filtered to provide the desired product **306B** (32.0 g, 98%).

Part B:

Compound **306B** (32.0 g, 214 mmol) was dissolved in MeOH (200 mL) and cooled in an ice bath. Concentrated sulfuric acid (8 mL) was added dropwise and the reaction was stirred overnight. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried over

sodium sulfate, and concentrated to provide compound **306C** that was used without purification (27.0 g, 71%).

Part C:

Compound **306C** (27.0 g, 152 mmol) was dissolved in carbon tetrachloride (700 mL). Phosphorus pentachloride (50 g, 240 mmol) was added and the suspension was stirred for 18 hours (solution became clear over time). The solvent was removed under reduced pressure and the residue was stirred in petroleum ether (500 mL) overnight. The solids were filtered to provide compound **307** with no need for purification (26.5 g, 96%). Trituration step was repeated if mass yield was too high.

Part D:

Compound **307** (15.0 g, 82.7 mmol) was dissolved in methylene chloride (140 mL) and cooled in an ice bath. Bis(trimethylsilyl)acetylene (15.0 g, 88.2 mmol) was added in methylene chloride (20 mL). Freshly crushed aluminum chloride (11.0 g, 82.7 mmol) was added in portions over 20 minutes. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction was cooled in an ice bath and slowly quenched with water. The organic layer was washed several times with water, dried over sodium sulfate, and concentrated. The residue was triturated/recrystallized from hexanes to provide the desired product **308** (14.8 g, 69%). HPLC-MS t_R = 1.84 min (ELSD); mass calculated for formula $C_{10}H_{17}NO_4Si$ 243.09, observed LCMS m/z 244.1 (M+H).

Part E:

Compound **308** (24.0 g, 98.7 mmol) and compound **305** (25.1 g, 99.0 mmol) were dissolved in THF (300 mL) and cooled to -78°C. A 1M solution of LiHMDS (198 mL, 198 mmol) was added dropwise over 30 minutes and the reaction mixture was stirred for 2 hours. Saturated ammonium chloride solution was added slowly and the reaction was allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate. The

combined organic layers were washed with water, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) afforded the desired product **309** (26.0 g, 63%). HPLC-MS t_R = 1.90 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{26}N_2O_6Si$ 418.15, observed LCMS m/z 419.2 (M+H).

Part F:

The two isomers were separated using a chiral OD column. One gram of material was injected into the column and the two peaks were separated by using a solvent mixture of 85% hexanes/ethanol. The second isomer was the desired compound **309B** (400 mg, 80%).

Part G:

Compound **309B** (8.0 g, 19.1 mmol) was dissolved in THF (250 mL) and cooled to 0°C. Tetrabutylammonium fluoride (1 M in THF, 22.9 mL, 22.9 mmol) was added dropwise and the reaction was stirred for 1 hour at room temperature. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated to provide compound **400** (5.8 g, 88%). The product was used without purification.

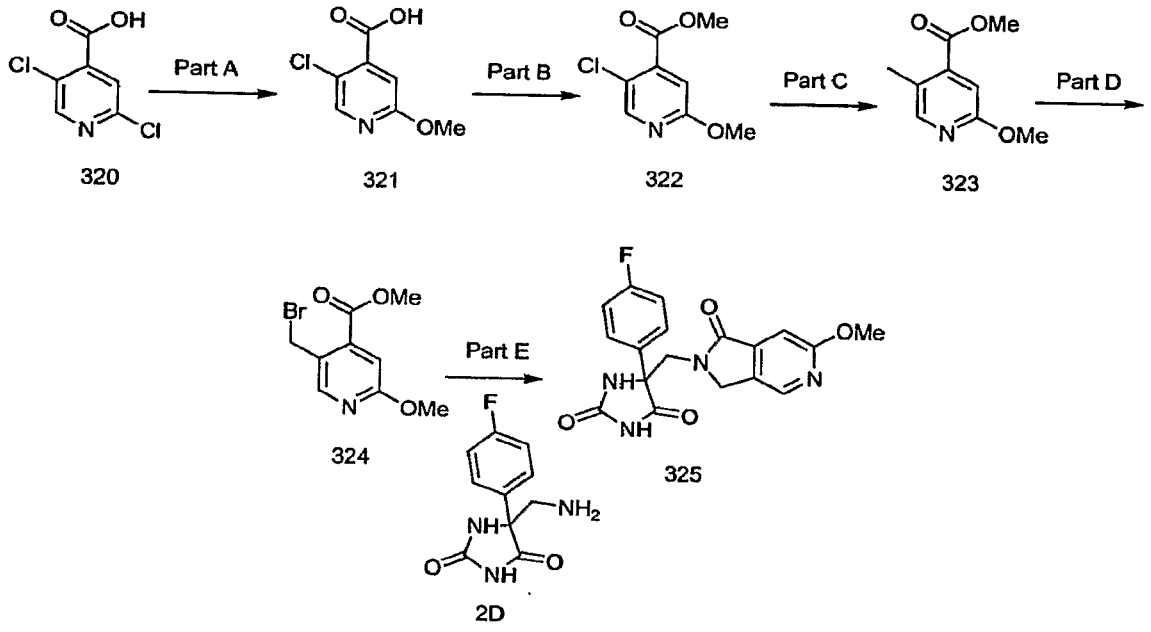
Part H:

Compound **400** (75 mg, 0.22 mmol) was combined with 3-bromoquinoline (0.032 mL, 0.24 mmol), $Pd(PPh_3)_2Cl_2$ (3 mg, 0.0044 mmol), CuI (2 mg, 0.009 mmol), diisopropylamine (0.062 mL, 0.44 mmol) in DMF (1 mL) and stirred overnight at 80 °C. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexane to 80% ethyl acetate/hexane) afforded the desired product **400A** (93 mg, 89%). HPLC-MS t_R = 1.66 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{23}N_3O_6$ 473.16, observed LCMS m/z 474.1 (M+H).

Part I:

Compound **400A** (77 mg, 0.16 mmol) was dissolved in 7 M ammonia solution (3 mL) and stirred in a sealed pressure tube at 90 °C overnight. The reaction mixture was cooled to room temperature and concentrated to afford compound **400B**. HPLC-MS t_R = 1.41 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{18}N_4O_4$ 426.13, observed LCMS m/z 427.0 (M+H).

Example 300E



Part A:

Sodium pellets (3.6 g, 156 mmol) were dissolved in MeOH (100 mL) at 0 °C. Compound **320** (3.0 g, 15.6 mmol) was added and stirred at 100°C in a sealed pressure flask overnight. The reaction was cooled to room temperature and diluted with ethyl acetate and 1N HCl. The organic layer was dried over sodium sulfate and concentrated to provide the desired product **321** with no need for purification (2.1 g, 72%).

Part B:

Compound **321** (2.1 g, 11.1 mmol) was dissolved in toluene (30 mL) and methanol (30 ml) and cooled in an ice bath. TMS diazomethane (2M in hexanes, 11 mL) was added dropwise until yellow color persisted. The solvent was evaporated under reduced pressure to provide the desired product **322** with no need for purification (2.2 g, quant.).

Part C:

Compound **322** (1.0 g, 5.0 mmol) was combined with $Pd(P\text{-}tBu_3)_2$ (128 mg, 0.25 mmol), $Pd(dba)_3$ (250 mg, 0.25 mmol), trimethylboroxine (1.0 mL, 6.5 mmol), potassium phosphate monohydrate (3.69 g, 15 mmol) in dioxane (25 mL) and stirred at 90 °C overnight. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded the desired product **323** (0.500 g, 55%).

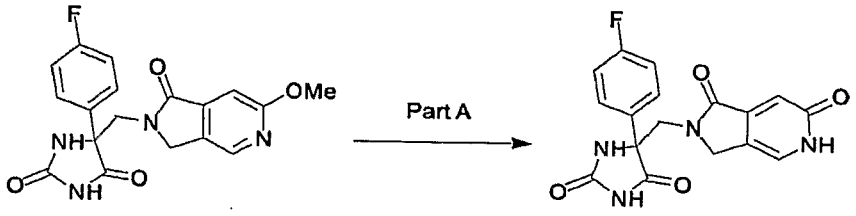
Part D:

Compound **323** (210 mg, 1.16 mmol) was dissolved in carbon tetrachloride (6 mL) and N-bromosuccinimide (228 mg, 1.28 mmol) and benzoyl peroxide (10 mg) were added. The reaction mixture was stirred at reflux overnight, cooled to room temperature, and filtered (solids were washed with ether). The combined organic layers was washed with water, dried over sodium sulfate, and concentrated to provide the desired product **324** (0.20 g, 67%).

Part E:

Compound **324** (75 mg, 0.29 mmol) and compound **2D** (75 mg, 0.29 mmol) were dissolved in DMF (5 mL) and DIEA (0.15 mL, 0.87 mmol) and stirred at 70 °C overnight. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, brine, dried over sodium sulfate, and concentrated. The residue was purified by reverse phase chromatography to provide the desired product **325** (24.1 mg, 22%). HPLC-MS t_R = 1.269 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{15}N_4O_4F$ 370.10, observed LCMS m/z 371.1 (M+H).

Example 300F

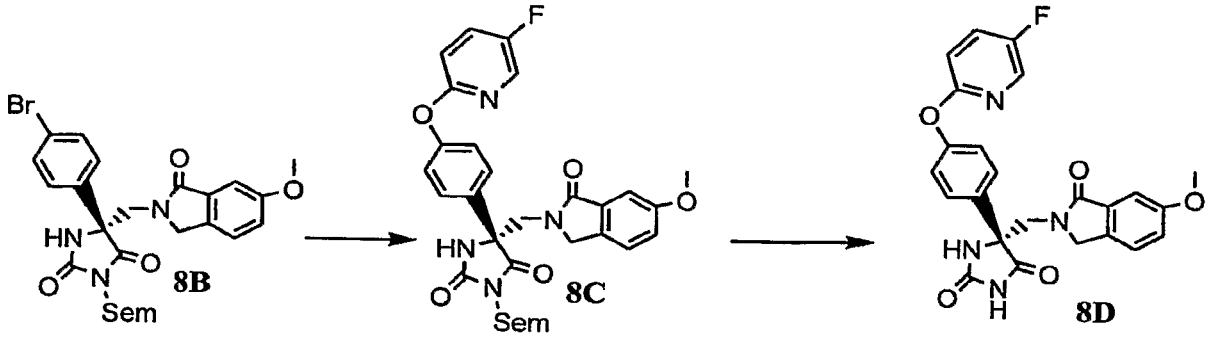


325 326

Part A:

Compound **325** (140 mg, 0.378 mmol), chlorotrimethylsilane (226 mg, 1.89 mmol), and sodium iodide (283 mg, 1.89 mmol) were dissolved in acetonitrile (5 mL) and stirred at reflux for 10 minutes. Water (0.3 mL) was added and the reaction was refluxed for 3 hours. The reaction mixture was cooled and diluted with ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated. Purification by reverse phase chromatography provided the desired product **326** (7.1 mg, 5%). HPLC-MS t_R = 0.855 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{13}N_4O_4F$ 356.09, observed LCMS m/z 357.1 (M+H).

Example 82



The aryl ether compounds **82** to **90** were prepared from compound **8B** using a procedure based on that described by E. Buck and Z. J. Song in *Organic*

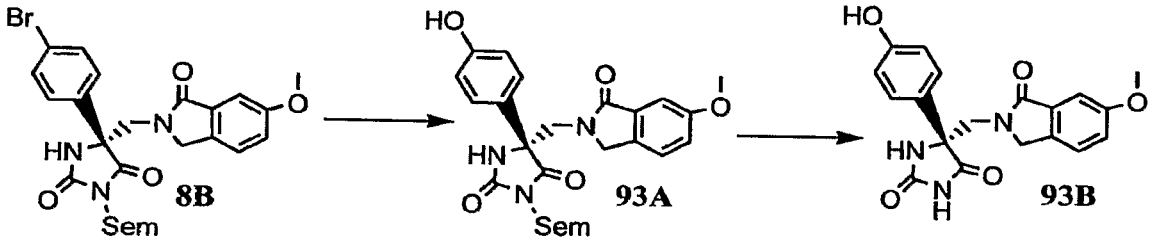
Synthesis Vol *82*, p. 69, followed by a standard SEM deprotection sequence. An example is provided below.

Compound **8B** (0.248 g, 0.442 mmol), 5-Fluoro-2-hydroxypyridine (128 mg, 1.13 mmol), cesium carbonate (374 mg, 1.14 mmol), and copper (I) chloride (48 mg, 0.48 mmol) were added to a 10 mL Schlenck tube equipped with a stir bar. The tube was capped with a septum and cycled between vacuum and N_2 three times. N-methyl-2-pyrrolidinone (2mL) was added via syringe and the Schlenck tube was cycled between vacuum and N_2 three times. 2,2,6,6,6-Tetramethyl heptane-3,5-dione (33 μL) was added via syringe. The Schlenck tube was placed in a 100°C oil bath and heated to 150°C. The reaction mixture was stirred for 23 h at 150°C. The reaction mixture was allowed to cool to rt, then diluted with EtOAc and water. Aqueous 1% EDTA was added and the layers were separated. The organic layer was washed with 1% aq EDTA, water, and brine. The resulting organic solution was dried with $MgSO_4$, filtered, and concentrated to dryness. A brown solid was obtained. The crude product was purified via sgc using a Biotage SiO_2 cartridge and a 1%-2.5% MeOH/CH_2Cl_2 gradient as the mobile phase. The major spot was collected as product, giving 0.04 g of compound **8C**.

Compound **8C** (0.04g) was dissolved in (10 mL) anhydrous acetonitrile and concentrated to dryness on the rotovap. This step was repeated. The compound was redissolved in anhydrous acetonitrile (3 mL) and placed under N_2. The flask was cooled in an ice water bath. BF_3 etherate (90μL) was added, the ice bath was removed, and the reaction mixture was stirred at rt for 7 h. The reaction mixture was capped and stored in a 4°C freezer overnight. The reaction mixture was cooled in an ice-water bath. Diisopropylethylamine (1.5 mL) was added, followed by aq 3.0 M sodium hydroxide. The reaction was stirred for 15 min. The ice bath was removed, and the reaction mixture was stirred for 3 h at rt. Acetic acid was added until the reaction mixture was weakly acidic. The reaction mixture was partially concentrated on the rotovap. EtOAc and water were added. The layers were separated. The

organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified via reverse phase chromatography using an Isco C-18 cartridge (43g). The mobile phase was a 15% to 80% CH_3CN/H_2O gradient with 0.1% (volume) formic acid added to both components of the mobile phase. The main peak was isolated as product giving compound **8D**.

Example 93A

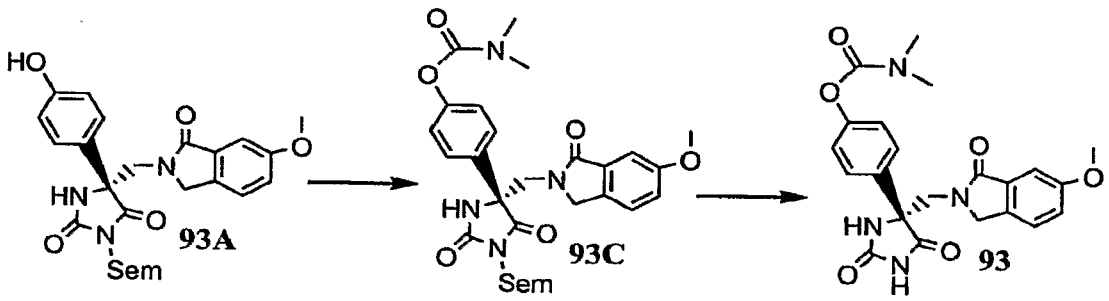


Compound **8B** (1.50 g, 2.68 mmol), pinocolatodiboron (816 mg, 3.21 mmol), potassium acetate (785 mg, 8.0 mmol), and palladium (II) dichloride(dppf) CH_2Cl_2 complex (250 mg, 0.306 mmol) were added to a 100 mL Schlenck flask equipped with a stir bar. The flask was caped with a septum, then cycled between vacuum and nitrogen four times. Dioxane (20 mL, Aldrich anhydrous) was added via syringe. The flask was cycled between vacuum and nitrogen three times, then placed in an 85°C oil bath. The bath was heated to 100°C, then stirred for 1.5 h. the reaction mixture was allowed to cool to RT and diluted with EtOAc (80 mL). The resulting mixture was filtered through Celite. The Celite was rinsed with additional EtOAc. The combined filtrate was concentrated to near dryness then redissolved in EtOAc. The organic solution was washed with 1.0 M aq pH 7 sodium phosphate buffer, water, and brine. After drying with $MgSO_4$, the organic layer was concentrated to dryness. The crude product was purified via sgc using a 2%-4% MeOH/ CH_2Cl_2 gradient as the mobile phase. A brown solid was obtained (1.9 g). The solid was dissolved in dioxane (16 mL) and water (11 mL) was added. Sodium perborate (3.0 g, 19.5 mmol) was added and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with

EtOAc and aq 1M NH_4Cl. The layers were separated. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered and concentrated to dryness, giving an off white solid (1.37 g). SGC using a gradient of 25% to 100% (5%Methanol in EtOAc)/Hexanes as the mobile phase gave 0.25 g of pure **93A** and 0.62 g of impure **93A**.

Compound **93A** (0.70 g, 1.40 mmol) was dissolved in 50 mL of Aldrich 4N HCl in dioxane and 50 mL of methanol. The solution was added to a pressure tube equipped with a stir bar. The tube was capped, placed in an oil bath, and heated to 95 C. The reaction was stirred at 95°C for 4 h, then allowed to cool to rt. The reaction mixture was concentrated to dryness. Methanol was added and the reaction mixture was reconcentrated. Methanol (50 mL) was added, followed by triethylamine (5 mL). The reaction mixture was stirred at rt for 1 h, then concentrated to dryness. EtOAc and 1.0 M aq pH 5.5 sodium phosphate buffer were added. The layers were separated. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified via SiO_2 chromatography. The mobile phase was a gradient of 10% to 100% of (100:10:1-CH_2Cl_2:MeOH:concentrated NH_4OH) in CH_2Cl_2.. The main UV active peak was isolated as product giving 0.42 g of compound **93B** as white solid.

Example 93

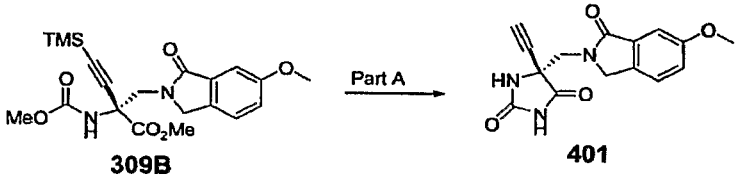


Compound **93A** (0.05 g, 0.10 mmol) was dissolved in CH_2Cl_2 (5mL). N, N-Dimethylcarbamyl chloride (18 μL) and DMAP (8mg) were added and the

reaction mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1.0 M aqueous pH 7.0 sodium phosphate buffer, water, and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified via sgc using a 0.5% to 5% MeOH/CH_2Cl_2 gradient on a 40 g Isco SiO_2 Cartridge. The major UV active peak was isolated as compound **93C**.

Compound **93C** was converted to compound **93** using SEM deprotection procedures similar to those described previously.

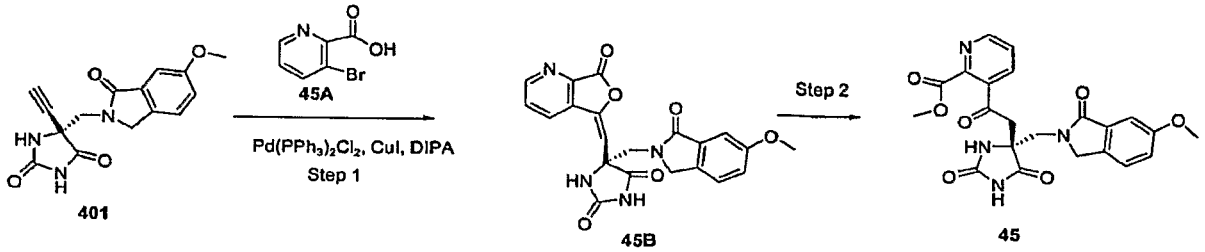
Example 401:



Part A:

Compound **309B** (1.26 g, 3.0 mmol) in 7 M ammonia in methanol (20 mL) was heated to 85 °C in a pressure bottle overnight. The reaction mixture was concentrated to afford **401** (900 mg, 100%) which was used without further purification. HPLC-MS t_R = 1.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{13}N_3O_4$ 299.09, observed LCMS m/z 300.1 (M+H).

Example 45

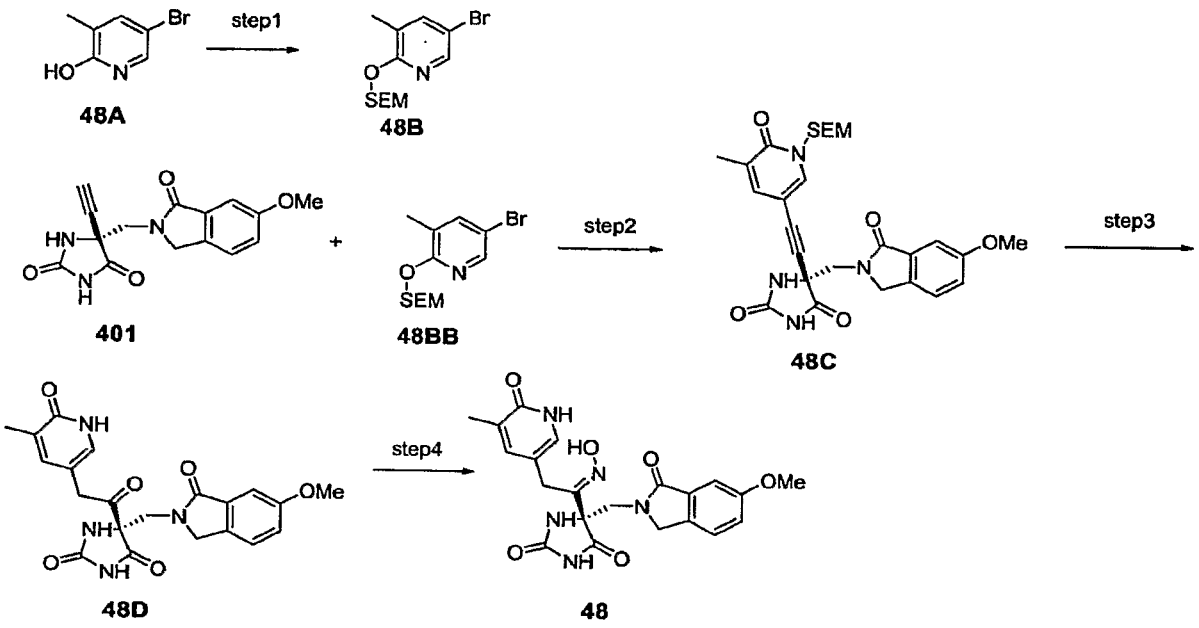


Step1. Compound **401** (100 mg, 0.33 mmol) was combined with compound **45A** (80 mg, 0.4 mmol), $Pd(PPh_3)_2Cl_2$ (8 mg, 0.012 mmol), CuI (17 mg, 0.1 mmol), diisopropylamine (0.08 mL, 0.58 mmol) in DMF (1 mL) and stirred at

85°C for 2 h. The reaction mixture was purified on a Gilson reverse phase HPLC (0-40% acetonitrile in H_2O with formic acid 0.1%) afforded the desired product **45B**(18 mg, 13%).

Step 2. Compound **45B** (20 mg, 0.23 mmol) was stirred in MeOH (5 mL) and HCl (1N, aq., cat.). The reaction was stirred at rt for 2 h. Solvent was removed and the crude material was purified on a Gilson reverse phase HPLC (0-50% acetonitrile in H_2O with 0.1% formic acid) afforded the desired product **45** (20 mg, 99%).

Example 48



Step 1

A mixture of **48A** (161 mg, 0.86 mmol), SEMCl (0.17 mL, 0.94 mmol), and diisopropylethylamine (0.22 mL, 1.28 mmol) in CH_2Cl_2 (3 mL) was stirred at 25 °C for 2 h. The mixture was added to an aqueous $NaHCO_3$ solution and the organic layers were extracted with CH_2Cl_2. The combined organic solution was washed with brine solution, dried (Na_2SO_4), and concentrated in

vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/hexane = 2:1). to afford **48B** (200 mg, 74% yield).

Step 2

A mixture of **401** (100 mg, 0.33 mmol), **48B** (165 mg, 0.52 mmol), $Pd(PPh_3)_2Cl_2$ (4.9 mg, 7 □mol), CuI (1.9 mg, 10 □mol), and diisopropylethylamine (0.17 mL, 0.99 mmol) in DMF (1.5 ml) was purged with N_2 and heated to 70 °C. After heating for 17 h, the mixture was cooled to 25 °C and purified by column chromatography on a reverse phase C-18 column (0.01%HCO_2H in water/0.01% HCO_2H in CH_3CN) to afford **48C** (78 mg, 44% yield).

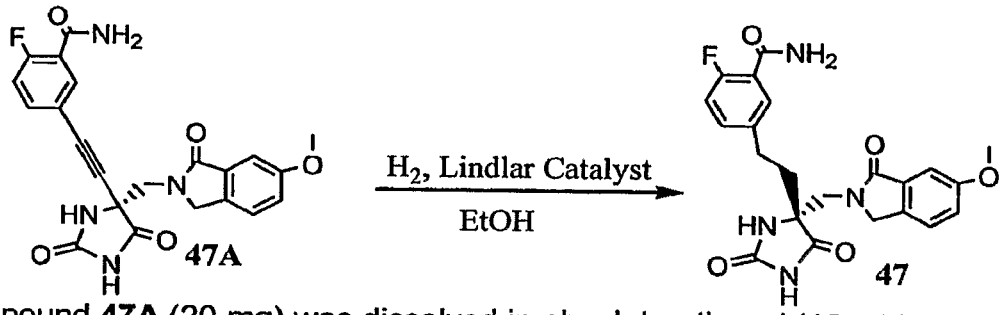
Step 3

48C (78 mg, 0.14 mmol) was dissolved in MeOH (15 mL) and treated with 4 N HCl in dioxane (3 mL). The mixture was heated to 60 °C in a pressure vessel for 16 h and cooled to 25 °C. The mixture was neutralized with NH_3-MeOH (7 N solution) and the resulting precipitate was filtered off. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC (10% MeOH in CH_2Cl_2) to afford **48D** (25 mg, 40% yield).

Step 4

To a solution of **48D** (12 mg, 0.028 mmol) in EtOH (4 mL) were added NH_2OH HCl salt (10 mg, 0.14 mmol) and pyridine (34 mL, 0.42 mmol) at 25 °C. The mixture was heated to reflux for 16 h and concentrated in vacuo. The residue was purified by preparative TLC (10% MeOH in CH_2Cl_2) to afford **48** (5 mg, 42% yield).

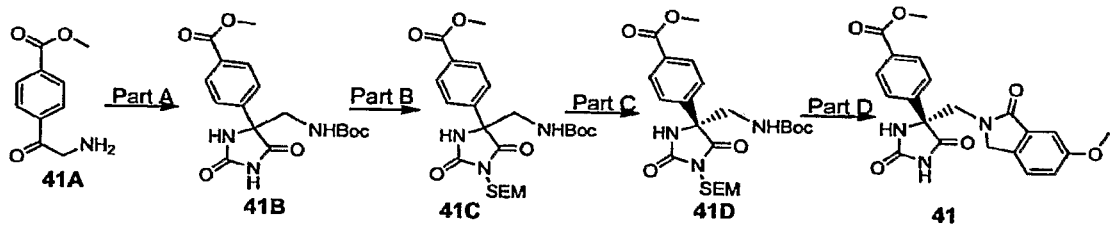
Example 47



Compound **47A** (20 mg) was dissolved in absolute ethanol (10 mL). Lindlar catalyst was added (18 mg) and the reaction mixture was placed under balloon pressure of hydrogen gas. The reaction mixture was left stirring overnight at rt. The reaction mixture was concentrated to dryness. CH_2Cl_2 was added and the resulting material was loaded onto a 1g SiO_2 Sep-Pak. The product was eluted with 95:5 CH_2Cl_2: MeOH. The filtrate was concentrated to give **457** as a clear oil.

Compound **47A** was prepared using Example **400**.

Example 41:



Part A:

Compound **41B** was prepared from compound **41A** according to the procedures described in Example 300D part A and B.

Part B:

To a mixture of **41b** (7.87 g, 21.7 mmol) and diisopropylethylamine (7.5 mL, 43.4 mmol) in DMF (80 mL) was added 2-trimethylsilylethoxy methyl chloride (4.7 mL, 23.8 mmol). The mixture was stirred at room temperature overnight, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate and

concentrated. The residue was purified by column chromatography (SiO_2, 15% EtOAc/hexane to 30 % EtOAc/hexane) to afford **41C** as a white solid (10.2 g, 95%). HPLC-MS t_R = 2.17 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{35}N_3O_7Si$ 493.2, observed LCMS m/z 516.1 (M+Na).

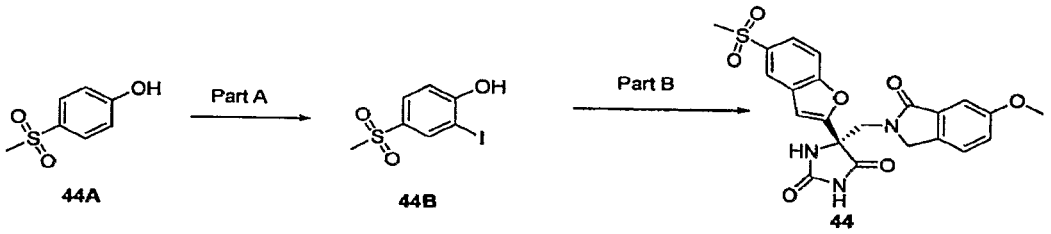
Part C:

The two isomers of **41C** were separated using a chiral AD column. One gram of material was injected into the column and the two peaks were separated by using a solvent mixture of 80% hexanes/2-propanol. The second isomer was the desired compound **41D** (400 mg, 80%).

Part D:

Compound **41** was prepared from **41D** following the procedures described in Example 2 step 3, Example 300E part C and Example 8. HPLC-MS t_R = 1.32 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{19}N_3O_6$ 409.13, observed LCMS m/z 410.2 (M+H).

Example 44



44A 44B 44

Part A:

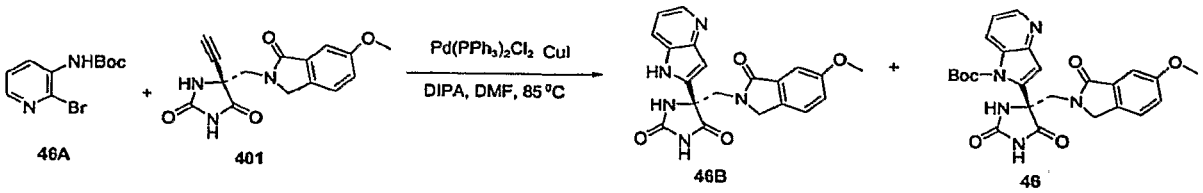
Compound **44A** (670 mg, 3.91 mmol) and iodine (2.10 g, 8.0 mmol) were dissolved in THF (20 mL) and 1M sodium carbonate (20 mL) and stirred for 4 hours. The reaction was diluted with ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated (1.05 g mixture of unseparable mono and di-iodinated products). The residue was combined with methyl iodide (1.5 mL) and cesium carbonate (5 g) in DMF (20 mL) and stirred at 60 °C for 3 hours. The reaction was diluted with water and ethyl

acetate. The organic layer was dried over sodium sulfate and concentrated. Column chromatography (2:1 hexanes/ethyl acetate) provided the mono-iodinated methyl ether (460 mg). The methyl ether was dissolved in methylene chloride (7 mL) and 1M boron tribromide (7 mL) and stirred at room temperature for 5 hours. The reaction was quenched slowly with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to provide the desired product (390 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, 1H), 7.85-7.8 (m, 1H), 7.1 (d, 1H), 3.0 (s, 3H).

Part B:

Compound **401** (130 mg, 0.43 mmol), compound **44B** (130 mg, 0.43 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg), CuI (8 mg), and triethylamine (0.4 mL) were dissolved in DMF (3 mL) and stirred at 80 °C under an inert atmosphere. The solvent was evaporated and the residue was purified by reverse phase chromatography to provide the desired product (112.3 mg, 55%). HPLC-MS t_R = 1.2 min ($UV_{254\ nm}$); mass calculated for formula C22H19N3O7S 469.47, observed LCMS m/z 470.0 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.2 (s, 1H), 9.0 (s, 1H), 8.3 (m, 2H), 7.9 (s, 1H), 7.5 (d, 1H), 7.35 (s, 1H), 7.2-7.1 (m, 2H), 4.5-4.3 (m, 4 H). 3.8 (s, 3H), 3.2 (s, 3H).

Example 46

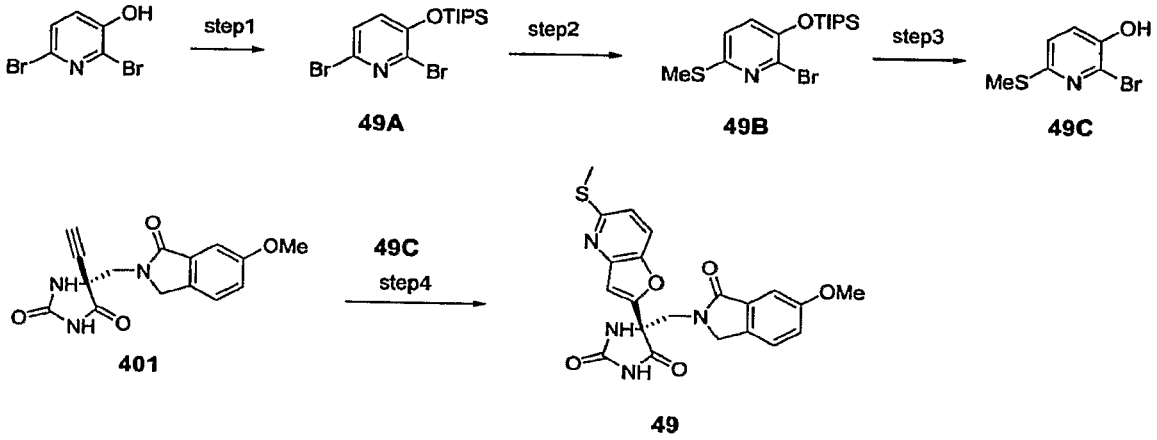


Step 1

Compound **46A** (80 mg, 0.29 mmol) was combined with compound **401** (100 mg, 0.33 mmol), $Pd(PPh_3)_2Cl_2$ (5 mg, 0.007 mmol), CuI (12 mg, 0.06 mmol), diisopropylamine (0.16 mL, 1.13 mmol) in DMF (1 mL) and stirred at 85 °C. The reaction mixture was neutralized with acetic acid and purified with Gilson reverse phase (0-40% acetonitrile in H_2O with 0.1% formic acid) afforded the

desired product **46B** (3 mg, 3%) mass calculated for formula $C_{20}H_{17}N_5O_4$ 391.13, observed LCMS m/z 392.2. (M+H) and compound **46** (22 mg, 15%), mass calculated for formula $C_{25}H_{25}N_5O_6$ 491.18, observed LCMS m/z 492.2. (M+H)

Example 49



Step 1

The commercially available 2,6-dibromo-3-hydroxypyridine (588 mg, 2.32 mmol) was dissolved in THF (6 mL) and the solution was treated with triethylamine (0.49 mL, 3.48 mmol) and triisopropylsilyl triflate (0.75 mL, 2.78 mmol) at 0 °C. The mixture was stirred at the temperature for 10 mim then added to an aqueous $NaHCO_3$ solution. The organic layers were extracted by CH_2Cl_2 and the combined organic solution was washed with brine solution, dried (Na_2SO_4), and concentrated in vacuo to afford a crude **49A** (1.11 g, quantitative) which was used without further purification.

Step 2

A solution of **49A** (100 mg, 0.24 mmol) in toluene (1 mL) was treated with t-BuLi (1.7 M in pentane, 0.32 mL, 0.54 mmol) at -78 °C. After stirring for 0.5 h at the temperature, methyl disulfide (65 μL, 0.72 mmol) was added to the mixture slowly and the resulting mixture was stirred for 4.5 h at -78 °C to 25

°C. The mixture was quenched by MeOH (0.3 mL) and diluted in CH_2Cl_2 followed by filtration through SiO_2 pad. The clear filtrate was concentrated in vacuo to afford a mixture of **49B** and its bromide regioisomer (~1:1, 62 mg) which was used without further purification.

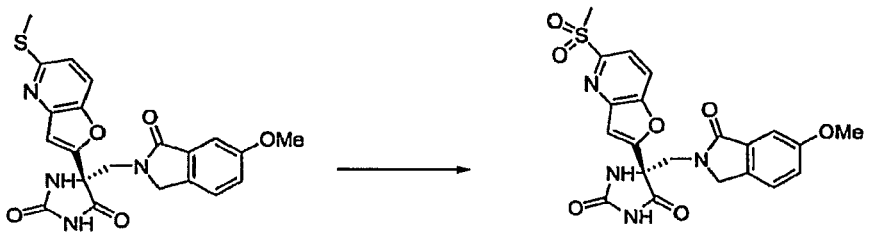
Step 3

A mixture of **49B** and its regioisomer (62 mg, ~0.16 mmol) was dissolved in THF and solution was treated with TBAF (1M in THF, 0.24 mL, 0.24 mmol) at 0 °C. The mixture was stirred at the temperature for 1 h and poured to a cold mixture of EtOAc and water. The organic layers were extracted by EtOAc and the combined organic solution was washed with brine solution, dried (Na_2SO_4), and concentrated in vacuo to afford a crude mixture of **49C** and its bromide regioisomer (~1:1, 41 mg) which was used without further purification.

Step 4

A mixture of **401** (150 mg, 0.50 mmol), **49C** (~50% purity, 460 mg, ~1 mmol), $Pd(PPh_3)_2Cl_2$ (7 mg, 10 μmol), CuI (1.9 mg, 10 μmol), and diisopropylethylamine (0.43 mL, 2.5 mmol) in DMF (3 ml) was purged with N_2 and heated to 60 °C. After heating for 18 h, the mixture was cooled to 25 °C and purified by column chromatography on a reverse phase C-18 column (0.01%HCO_2H in water/0.01% HCO_2H in CH_3CN) to afford a crude **49** which was further purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford pure **49** (27 mg, 12% yield).

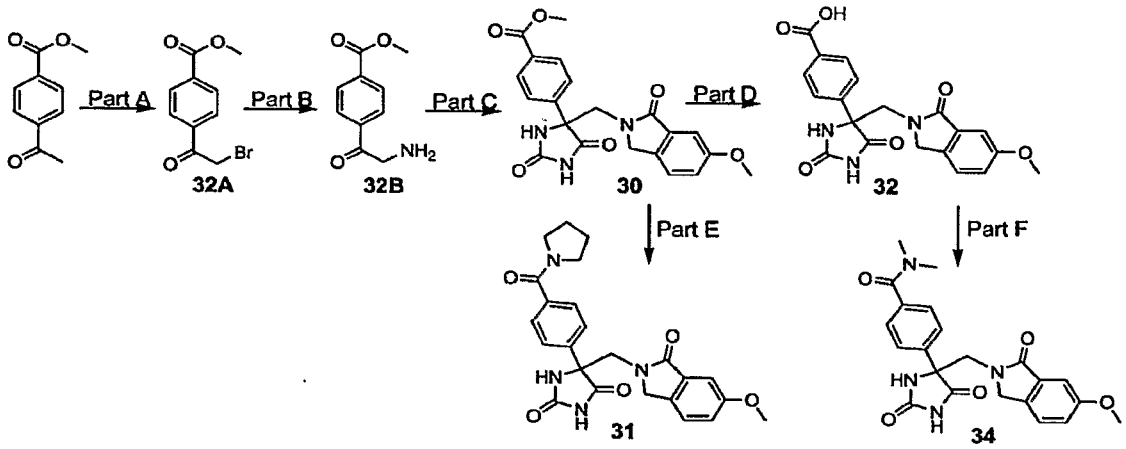
Example 50



49 50

A solution of **49** (27 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) was treated with 3-chloroperbenzoic acid (ca 70% purity, 30 mg, 0.12 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 h. The suspension was dissolved in 10% MeOH-CH_2Cl_2 and treated with ion exchange resin (Amberlyst, A-21, weakly basic) followed by filtration. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC (10% MeOH in CH_2Cl_2) to afford **50** as a white solid (18 mg, 61% yield).

Example 32:



Part A

To a solution of methyl 4-acetylbenzoate (1.9 g, 10.6 mmol) in acetic acid (10 mL) was added dropwise bromine (1.7 g, 21.3 mmol). The mixture was heated at 60 °C for 30 min, then stirred at room temperature for 1 hour, and poured into cold water (30 mL). The light yellow precipitate was collected, washed with water and dried (2.6 g, 96%).

Part B

Compound **32A** was treated with one equivalent of hexamethylene tetraamine in chloroform for about 1 hour. The product was collected by filtration and then treated with HCl in methanol for 2 hours. The solid was then collected by filtration to give compound **32B**.

Part C

Compound **30** was prepared following the procedures described in Example 2 Steps 1, 2, 3 and in Example 300E Part E: HPLC-MS t_R = 1.36 min ($UV_{254\ nm}$); mass calculated for formula C21H19N3O6 409.1, observed LCMS m/z 410.1 (M+H).

Part D

Compound **30** (60 mg, 0.147 mmol) was heated in 5% KOH in MeOH (2 mL) at 60 °C overnight, cooled to room temperature and concentrated. The residue was dissolved in water (5 mL), acidified with conc. HCl and filtered. The solid was collected and dried to give compound **32** (23 mg, 40%): HPLC-MS t_R = 1.04 min ($UV_{254\ nm}$); mass calculated for formula C20H17N3O6 395.1, observed LCMS m/z 396.1 (M+H).

Part E

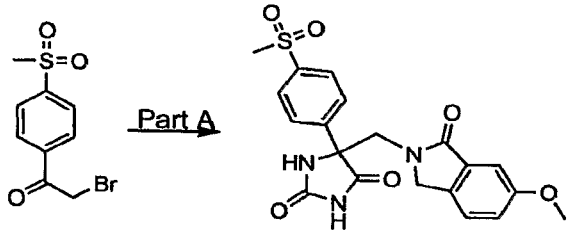
Compound **30** (39 mg, 0.095 mmol) was heated in pyrrolidine (2 mL) at 60 °C overnight, cooled to room temperature and concentrated. The residue was purified by reverse phase chromatography to give **31**: HPLC-MS t_R = 1.19 min ($UV_{254\ nm}$); mass calculated for formula C24H24N4O5 448.2, observed LCMS m/z 449.2 (M+H).

Part F

A mixture of compound **32** (49 mg, 0.12 mmol), dimethylamine hydrochloride (20 mg, 0.25 mmol), HATU (61 mg, 0.16 mmol), DMAP (2 mg, 0.012 mmol) and diisopropylethylamine (0.065 mL, 0.37 mmol) was stirred in

DMF (2 mL) at room temperature overnight. The mixture was diluted with ethyl acetate, washed with 0.1 N HCl, water and brine, dried over sodium sulfate and evaporated. The residue was purified by reverse phase chromatography to give **34**: HPLC-MS t_R = 1.09 min ($UV_{254\ nm}$); mass calculated for formula C22H22N4O5 422.2, observed LCMS m/z 423.1 (M+H).

Example 33:

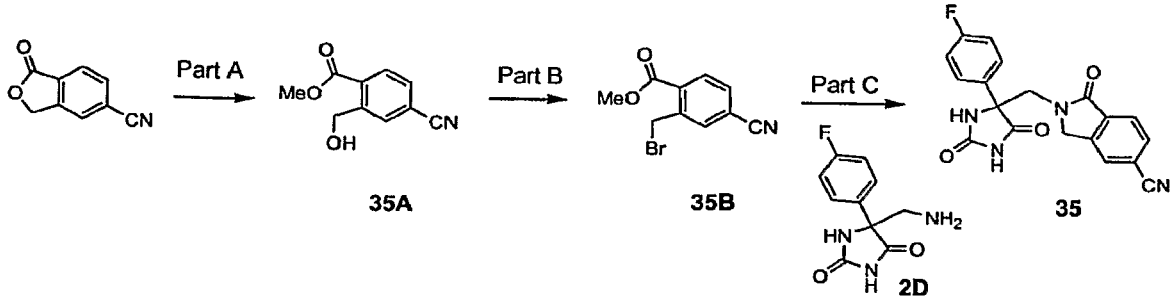


33A 33

Part A

Compound **33** was prepared from **33A** following procedures described in **Example 32** Part B and Part C: HPLC-MS t_R = 1.08 min ($UV_{254\ nm}$); mass calculated for formula C20H19N3O6S 429.1, observed LCMS m/z 430.0 (M+H).

Example 35:



35A 35B 35 2D

Part A:

A mixture of 5-cyanophthalide (5.0 g, 31.4 mmol) and 1N of NaOH (31.4 mL) was stirred at 100 °C for 1 h. The solution was concentrated to dryness with azotropic distillation with toluene. The resulting white solid was dissolved in dry DMF (30 mL). Methyl iodide (5.88 mL, 94.2 mmol) was added slowly, and the reaction mixture was allowed to stir at room temperature for 2 h. It was then diluted with H_2O and back extracted with EtOAc (30 mL x 4). EtOAc extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography on silica (EtOAc / hexane 40:60) gave compound **35A** as a white solid (5.5 g, 91%)

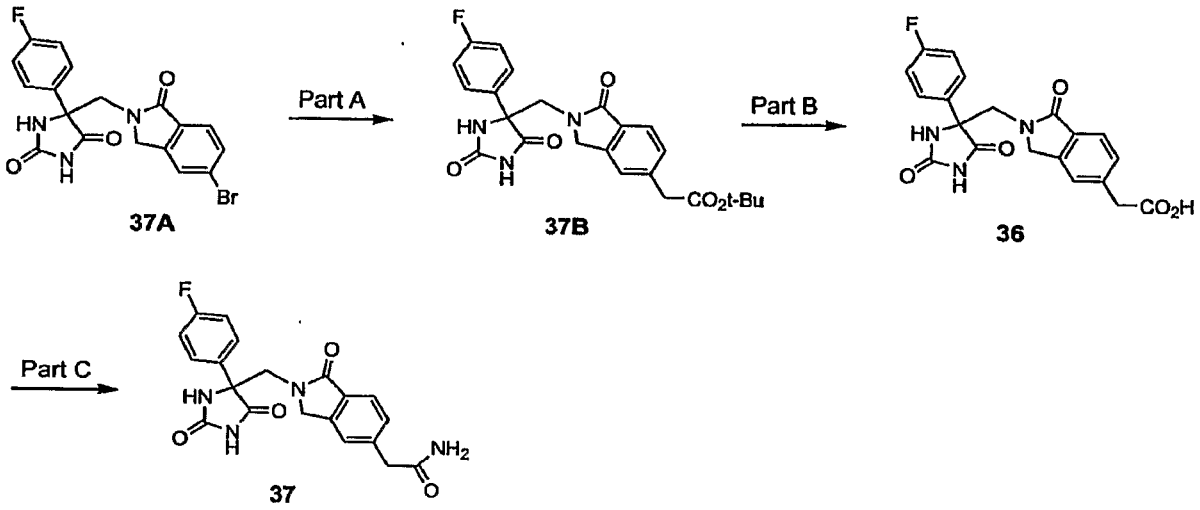
Part B:

To compound **35A** (5.5 g, 28.77 mmol) in THF (60 mL) was added carbon tetrabromide (11.45 g, 34.52 mmol). The solution was cooled to 0 °C in an ice/water bath, and triphenylphosphine (9.05 g, 34.52 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 3 h under argon. After removing the precipitate by filtration, the solution was concentrated. The residue was dissolved in EtOAc (100 mL), washed with 1N HCl, H_2O, brine, dried over Na_2SO_4, and concentrated. Flash column chromatography on silica (EtOAc / hexane 20:80) gave compound **35B** as a pale yellow solid (6.8 g, 93%).

Part C:

Compound **35** was prepared using previously described methods from **2D** and **35B**. HPLC-MS t_R = 2.943 min ($UV_{254\,nm}$), Mass calculated for formula $C_{19}H_{13}FN_4O_3$ 364.1, observed LCMS m/z 365.0 (M+H).

Example 37:



37A 37B 36 37

Compound **37A** was prepared using procedures described in Example 375.

Part A:

Compound **37A** (550 mg, 1.32 mmol) and Pd(*t*-$Bu_3P)_2$ (34 mg, 0.066 mmol, 5 mol%) in NMP (5 mL) were added with a 0.5 M solution of 2-*tert*-butoxy-2-oxoethylzinc chloride in THF (10.5 mL, 5.2 mmol) under argon. The reaction mixture was allowed to stir at 90 °C overnight. After cooling to room temperature, it was diluted with EtOAc, washed with water, brine, dried over Na_2SO_4, and concentrated. Column chromatography on silica gel (MeOH / DCM, 10:90) afforded **37B** as a pale yellow solid (260 mg, 43%). HPLC-MS (5 min) t_R = 1.69 min ($UV_{254\ nm}$), Mass calculated for formula $C_{19}H_{13}FN_4O_3$ 453.2, observed LCMS m/z 454.1 (M+H).

Part B:

Compound **37B** (40 mg, 0.088 mmol) was treated with TFA in DCM at room temperature to afford **36** as a white solid (20 mg, 27%). HPLC-MS t_R = 2.64min ($UV_{254\ nm}$), Mass calculated for formula $C_{20}H_{16}FN_3O_5$ 397.1, observed LCMS m/z 398.0 (M+H).

Part C:

Compound **36** (20 mg, 0.05 mmol) in DMF (1 mL) was added with HOBt (14 mg, 0.1 mmol) and EDC (19 mg, 0.1 mmol). After stirring at room temperature for 10 min, NH_4Cl (20 mg, 0.15 mol) was added, followed by the addition of DIEA (0.026 mL). The reaction mixture was then stirred at room temperature overnight. It was diluted with EtOAc, washed with 1N HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. Recrystallization in EtOAc gave **37** (7.4 mg, 37%) as a white solid. HPLC-MS t_R = 2.64min ($UV_{254\ nm}$), Mass calculated for formula $C_{20}H_{17}FN_4O_4$ 396.1, observed LCMS m/z 397.1 (M+H).

NMR spectral data for the some of the above compounds are provided below:

Compound 50. ^{1}H NMR (500 Hz, CD_3OD) δ 8.27 (d, 1H, J = 8.6 Hz), 8.14 (d, 1H, J = 8.6 Hz), 7.45 (d, 1H, J = 8.3 Hz), 7.37 (s, 1H), 7.29 (d, 1H, J = 2.5 Hz), 7.20 (dd, 1H, J = 8.3 Hz, 2.5 Hz), 4.56 (d, 1H, J = 8.7 Hz), 4.53 (d, 1H, J = 8.7 Hz), 4.50 (d, 1H, J = 12.5 Hz), 4.46 (d, 1H, J = 12.6 Hz), 3.87 (s, 3H), 3.30 (s, 3H).

Compound 98. ^{1}H NMR (400 Hz DMSO-d_6) δ (ppm): 11.24 (s, 1H), 8.97 (s, 1H), 8.80 (d, *J* = 2.01 Hz, 1H), 8.57 (d, *J* = 2.46 Hz, 1H), 8.17 (s, 1H), 7.60 (s, 1H), 7.49 (d, *J* = 8.19 Hz, 1H), 7.24 (s, 1H), 7.17-7.14 (m, 2H), 4.46 – 4.25 (m, 4H), 3.79 (s, 3H).

Compound 68. ^{1}H NMR (500 Hz, CD_3OD) δ 8.42 (s, 1H), 8.32 (d, 1H, J = 2.1 Hz), 7.79 (d, 2H, J = 8.5 Hz), 7.74 (d, 2H, J = 8.5 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.28–7.32 (m, 1H), 7.19 (dd, 1H, J = 8.4, 2.5 Hz), 4.32–4.46 (m, 3H), 4.24 (d, 1H, J = 14.2 Hz), 3.87 (s, 3H).

Compound 66. ^{1}H NMR (500 Hz, CD_3OD) δ 8.88 (d, 1H, J = 5.0 Hz), 8.30 (s, 1H), 8.19 (d, 2H, J = 8.5 Hz), 7.88 (d, 2H, J = 8.2 Hz), 7.67 (dd, 1H, J = 5.1, 1.3 Hz), 7.41 (d, 1H, J = 8.6 Hz), 7.31 (d, 1H, J = 2.5 Hz), 7.19 (dd, 1H, J = 8.2, 2.5 Hz), 4.34–4.47 (m, 3H), 4.26 (d, 1H, J = 14.7 Hz), 3.87 (s, 3H).

Compound 64. ^{1}H NMR (500 Hz, CD_3OD) δ 8.10 (d, 2H, J = 8.5 Hz), 7.99 (s, 1H), 7.84 (d, 2H, J = 8.5 Hz), 7.56 (s, 1H), 7.37 (d, 1H, J = 8.2 Hz), 7.27 (d,

1H, J = 2.7 Hz), 7.15 (dd, 1H, J = 8.4, 2.5 Hz), 4.28–4.43 (m, 3H), 4.24 (d, 1H, J = 14.5 Hz), 3.84 (s, 3H), 2.65 (s, 3H), 0.84–0.89 (m, 1H), 0.69–0.74 (m, 2H), 0.49–0.52 (m, 2H).

Compound 97. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.19 (s, 1H) , 7.83 (s,1H), 7.66-7.70 (m,1H), 7.55-7.58 (m,1H), 7.41-7.44 (m,1H), 7.29-7.32 (m,1H), 7.17-7.21 (m,1H) , 7.07 (s,1H), 4.35-4.55 (m,4H), 3.87 (s,3H).

Compound 85. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.70-7.75 (m, 2H) 7.65-7.70 (m,1H), 7.41-7.56 (m, 3H), 7.28-7.31 (m, 1H), 7.17-7.23 (m, 2H), 7.08-7.13 (m, 2H) , 4.29-4.47 (m, 3H), 4.15-4.24 (m, 1H), 3.87 (s, 3H).

Compound 84. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.80-7.88 (m, 2H), 7.70-7.78 (m, 2H) 7.38-7.46 (m, 1H), 7.26-7.33 (m, 1H), 7.16-7.24 (m, 1H), 7.08-7.15 (m, 2H) , 6.98-7.06 (m, 2H), 4.29-4.46 (m, 3H), 4.15-4.26 (m, 1H), 3.87 (s, 3H), 2.93 (s, 3H).

Compound 43 (400 Hz DMSO-d6)
δ 8.99 (s, 1H), 7.98 (dd, J = 14.8 Hz, 2 Hz, 2H), 7.90 (dd, J = 14.8 Hz, 2 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.14 (m, 2H), 4.26 (m, 3H), 4.08 (m, 1H), 3.79 (s, 3H), 3.22 (s, 3H).

Compound 76. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.00 (d, J = 2.0 Hz, 1H), 8.39 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 7.5 Hz, 1H), 8.08 (t, J = 7.5 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.75 (br. s, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.5, 2.5 Hz, 1H), 4.34 (d, J = 17.5 Hz, 1H), 4.26 (d, J = 17.5 Hz, 1H), 4.24 (d, J = 14.5 Hz, 1H), 4.17 (d, J = 14.5 Hz, 1H), 3.81 (s, 3H).

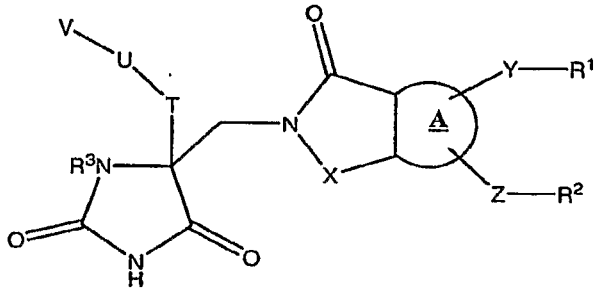
It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not

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.

Each document referred to herein is incorporated by reference in its entirety for all purposes.

THEREFORE, WE CLAIM:

1. A compound represented by Formula (I):



(I)

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

ring **A** is selected from the group consisting of aryl and heteroaryl, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown;

X is selected from the group consisting of –S-,-O-, $-S(O)_2$, -S(O)-, $-(C(R^3)_2)_m-$ and $-N(R^3)-$;

T is absent or present, and if present, T is selected from the group consisting of alkyl, aryl, and heteroaryl, wherein when each of said T aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl or heteroaryl ring, wherein each of the aforementioned T aryl, and heteroaryl, optionally with said five- to eight-membered aryl or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different;

U is absent or present or absent, and if present, U is selected from the group consisting of –O-, -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-;

V is absent or present, and if present V is selected from the group consisting of alkyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and N-oxides of said heterocyclyl and heteroaryl, wherein when each of said V cycloalkyl, heterocyclyl, aryl, heteroaryl, and N-oxides of said heterocycyl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl

ring; wherein each of said V alkyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl heterocyclyl, optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl, or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different;

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 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 $-S(O)_2-$;

m is 1 to 3;

n is 1 to 3;

R^1 is selected from the group consisting of H, cyano, -C(O)OH, -C(O)O-alkyl, $-C(O)NH_2$, -C(O)NH(alkyl), $-C(O)N(alkyl)_2$, alkynyl, halogen, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, and heterocyclyl, wherein when each of said cycloalkyl, heterocyclyl, aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of the R^1 alkyl, alkynyl, aryl, heteroaryl, and heterocyclyl, optionally with the five or six-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different; with the proviso that when Y is $-N(R^4)-$, -S -or –O-, then R^1 is not halogen or cyano;

R^2 is selected from the group consisting of H, cyano, -C(O)OH, -C(O)O-alkyl, $-C(O)NH_2$, -C(O)NH(alkyl), $-C(O)N(alkyl)_2$, alkynyl, halogen, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, and heterocyclyl; wherein when each of said cycloalkyl, heterocyclyl, aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of the

R^2 alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, optionally with the five or six-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different; with the proviso that when Y is –$N(R^4)$-, -S -or –O-, then R^2 is not halogen or cyano;

each R^3 is the same of different and is independently selected from the group consisting of H, alkyl, and aryl;

each R^4 is the same or different and is independently selected from the group consisting of H, alkyl, cycloalkyl, haloalkyl, hydroxy, -alkylcycloalkyl, -alkyl-$N(alkyl)_2$, heterocyclyl, aryl, and heteroaryl, wherein when each of said cycloalkyl, heterocyclyl, ayl, and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring;

R^{10} is selected from the group consisting of hydrogen, cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-N(R^4)-C(O)-N(R^4)_2$, $-N(R^4)-C(O)-OR^4$, $-OC(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-S(O)_2N(R^4)_2$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl, wherein each of the R^{10} alkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{30} moieties which can be the same or different;

or wherein two R^{10} moieties, when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;

R^{20} is selected from the group consisting of cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-N(R^4)-C(O)-N(R^4)_2$, $-N(R^4)-C(O)-OR^4$, $-OC(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, -

$S(O)_2N(R^4)_2$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl; wherein when each of said R^{20} aryl, heteroaryl, heterocyclyl and cycloalkyl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of said R^{20} alkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl, optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or substituted with one to four moieties selected independently from the group consisting of alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkyl, cyano, nitro, $-NH_2$, -NH(alkyl), and $-N(alkyl)_2$;

or when two R^{20} moieties when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;

R^{30} is selected from the group consisting of cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-N(R^4)-C(O)-N(R^4)_2$, $-N(R^4)-C(O)-OR^4$, $-OC(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-S(O)_2N(R^4)_2$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, halogen, alkyl, haloalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl; wherein when each of said R^{30} aryl, heteroaryl, heterocyclyl and cycloalkyl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein each of said R^{30} alkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl, optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or substituted with one to four moieties selected independently from the group consisting of alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro, $-NH_2$, -NH(alkyl), and $-N(alkyl)_2$;

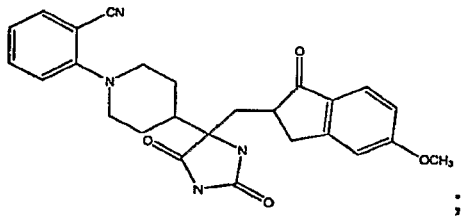
or when two R^{30} moieties when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;

with the proviso that at least one of T, U, and V must be present; and further that at least one of conditions (1) – (5) below are satisfied:

(1) at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-N(R^4)-C(O)-R^4$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$,

$-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, and $-C(R^4)=N-OR^4$, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is

$-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



;

(2) U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-;

(3) at least one T and V is present, and each of $-Y-R^1$ and $-Z-R^2$ is independently selected from the group consisting of cyano, $-(C(R^4)_2)_n-$

C(O)OH, $-(C(R^4)_2)_n$-C(O)O-alkyl, $-(C(R^4)_2)_n$-$C(O)NH_2$, $-(C(R^4)_2)_n$-C(O)NH(alkyl), and $-(C(R^4)_2)_n$-C(O)N(alkyl)$_2$, wherein each R^4 independently is H or alkyl; and n is 1-3;

(4) T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties; and

(5) at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl.

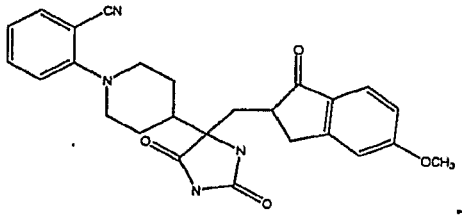
2. The compound of claim 1, wherein X is selected from the group consisting of $-(C(R^3)_2)_m$- and $-N(R^3)$-.

3. The compound of claim 2, wherein X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

4. The compound of claim 3, wherein m is 1.

5. The compound of any of claims 1-4, wherein R^3 is H.

6. The compound of claim 1, wherein at least one of T and V is present, and V is other than alkynyl; wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, -C(O)OR^4, -C(O)R^4, -C(O)N(R^4)$_2$, -C(O)N(R^4)C(O)R^4, -C(O)N(R^4)C(O)NR^4, -SR^4, -S(O)$_2$R^4, -N(R^4)-C(O)OR^4, -OC(O)N(R^4)$_2$, -N(R^4)C(O)N(R^4)$_2$, -N(R^4)-C(O)-R^4, -S(O)$_2$N(R^4)$_2$, -S(O)$_2$N(R$_4$)-C(O)-R^4, -N(R^4)-C(=NR^4)-N(R^4)$_2$, -N(R^4)-C(=N-CN)-N(R^4)$_2$, and -C(R^4)=N-OR^4, wherein each R^4 independently is selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein when each of said R^4 cycloalkyl, heterocyclyl, aryl, and heteroaryl contains contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; with the proviso that when R^{10} is $-S(O)_2R^4$, V is other than piperidinyl, and when R^{10} is cyano, the compound of Formula (I) is other than



7. The compound of claim 6, wherein said T or V is substituted with at least one R^{10} moiety selected from the group consisting of cyano, -$C(O)OR^4$, -$C(O)R^4$, -$C(O)N(R^4)_2$, and -$C(R^4)$=N-OR^4.

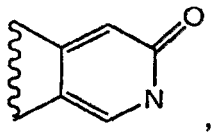
8. The compound of claim 6, wherein said T or V is substituted with at least one R^{10} moiety that is cyano.

9. The compound of claim 6, wherein said T or V is substituted with at least one R^{10} moiety that is $-SR^4$.

10. The compound of claim 6, wherein said T or V is substituted with at least one R^{10} moiety that is -$S(O)_2R^4$.

11. The compound of claim 6, wherein said T or V is substituted with at least one R^{10} moiety that is -$S(O)_2N(R^4)_2$.

12. The compound of claim 6, wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and



, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

13. The compound of claim 12, wherein said ring **A** is phenyl.

14. The compound of claim 6, wherein X is selected from the group consisting of $-(C(R^3)_2)_m$- and $-N(R^3)$-.

15. The compound of claim 14, wherein X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

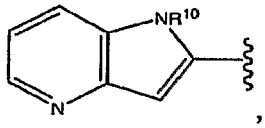
16. The compound of claim 15, wherein m is 1.

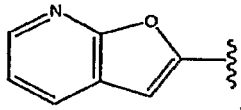
17. The compound of claim 14, wherein R^3 is H.

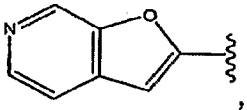
18. The compound of claim 6, wherein T is selected from the group consisting of alkyl, aryl, heteroaryl, wherein when each of said T aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached

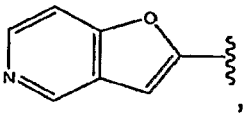
to form a five- to eight-membered aryl or heteroaryl ring; wherein each of the aforementioned T aryl, and heteroaryl, optionally with said five- to eight-membered aryl or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different.

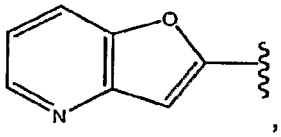
19. The compound of claim 18, wherein T is selected from the group consisting of $-CH_2-$, phenyl,

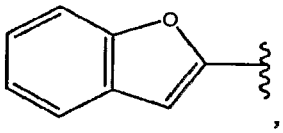


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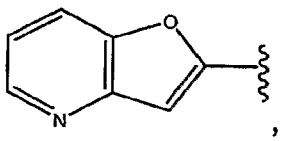
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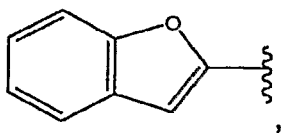
, each of which except $-CH_2-$ is optionally substituted with one to four R^{10} moieties such that the number of R^{10} moieties per each T does not exceed four.

20. The compound of claim 6, wherein U is absent or present, and if present is selected from the group consisting of –C(O)-, and -C(O)O-.

21. The compound of claim 6, wherein V is absent or present, and if present is selected from the group consisting of aryl, and heteroaryl, wherein when each of said V aryl and heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl or heteroaryl ring; wherein each of the aforementioned V aryl, and heteroaryl, optionally with said five- to eight-membered aryl or heteroaryl is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different.

22. The compound of claim 21, wherein V is selected from the group consisting of phenyl, pyridyl, pyrazinyl, indazolyl,



, and


,

each of which is optionally substituted with one to four R^{10} moieties which can be the same or different.

23. The compound of claim 6, wherein each of Y and Z is independently selected from the group consisting of a covalent bond and –O-.

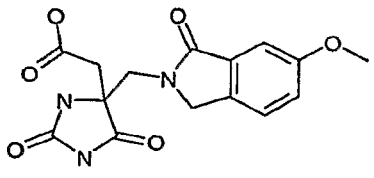
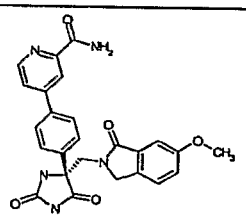
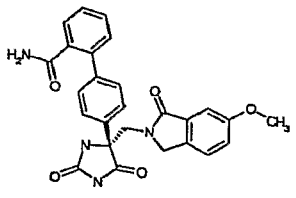
24. The compound of claim 23, wherein Y is –O- and Z is a covalent bond.

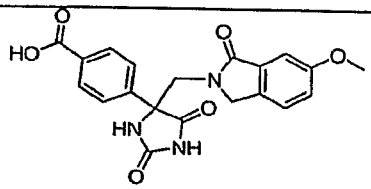
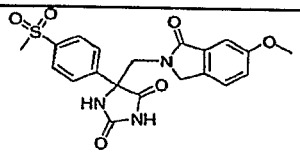
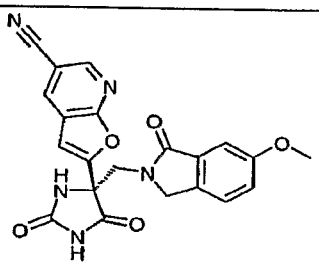
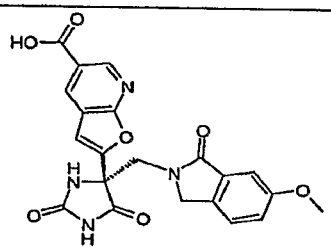
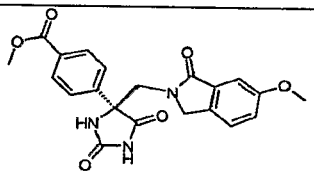
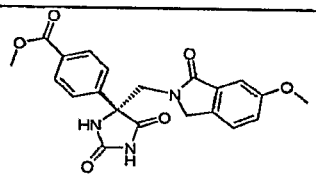
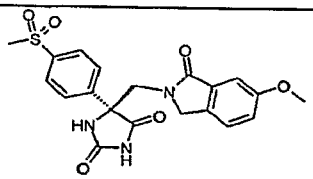
25. The compound of claim 6, wherein each of R^1 and R^2 is independently selected form the group consisting of H and alkyl.

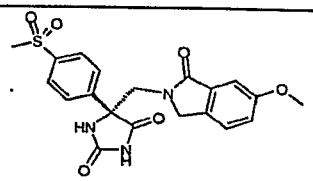
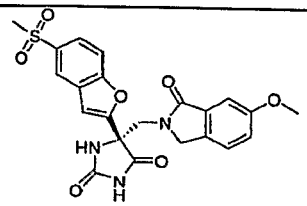
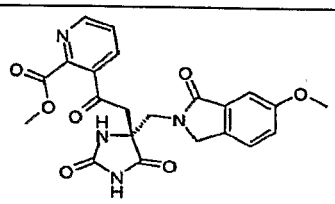
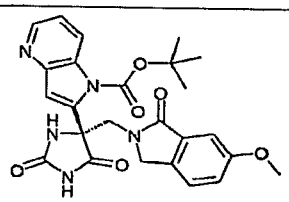
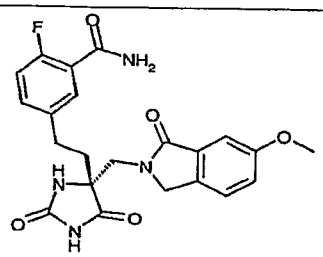
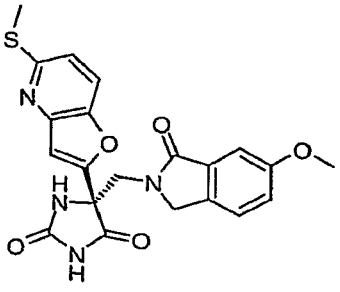
26. The compound of claim 25, wherein R^1 is alkyl and R^2 is H.

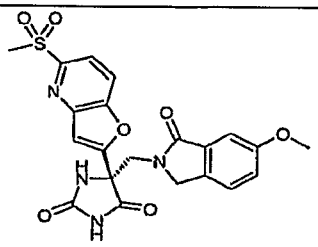
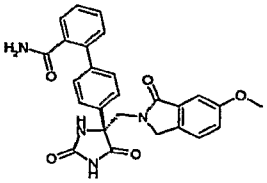
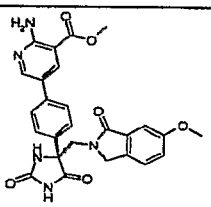
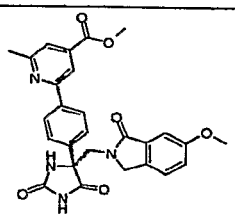
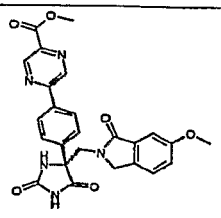
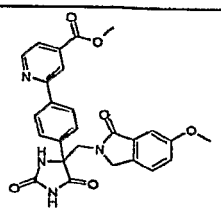
27. The compound of claim 26, wherein R^1 is methyl.

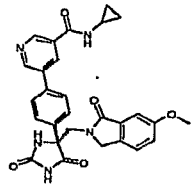
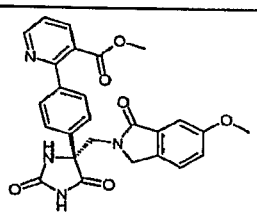
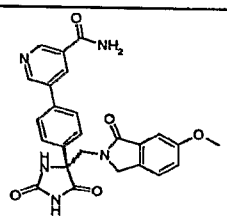
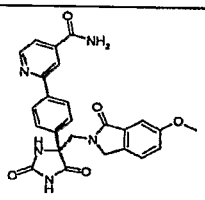
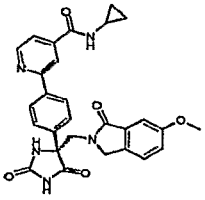
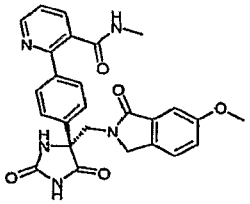
28. The compound of claim 6, selected from the group consisting of:

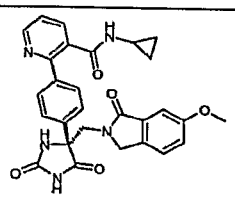
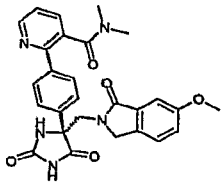
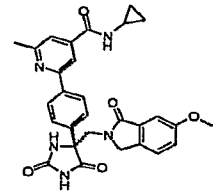
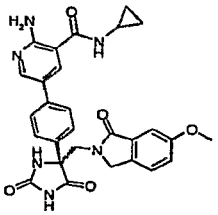
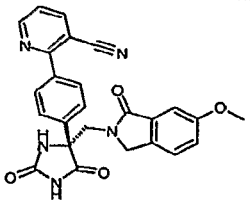
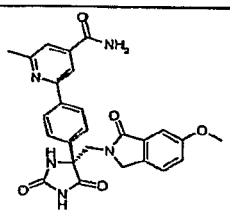
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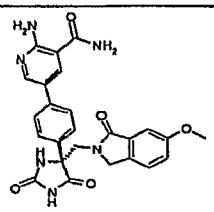
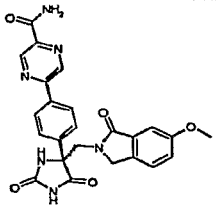
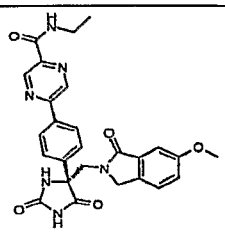
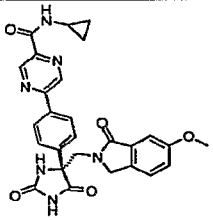
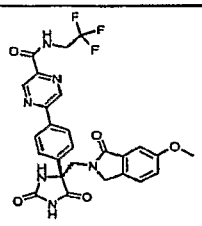
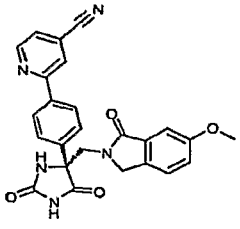
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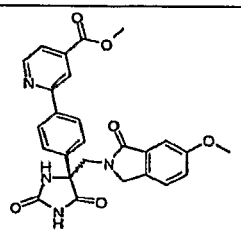
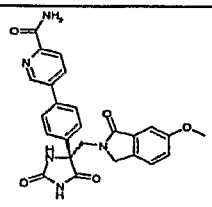
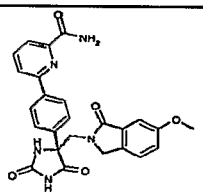
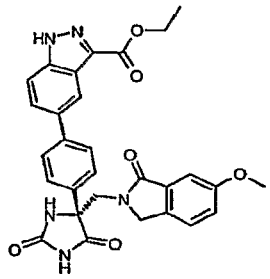
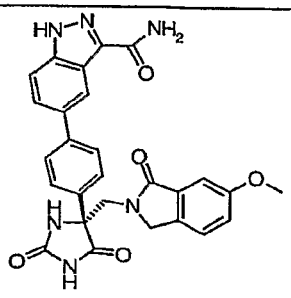
Compound ID	Structures
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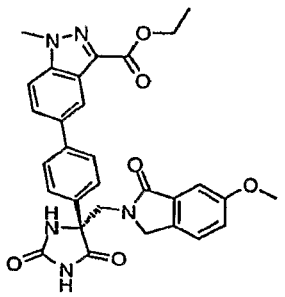
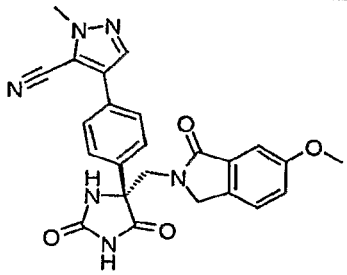
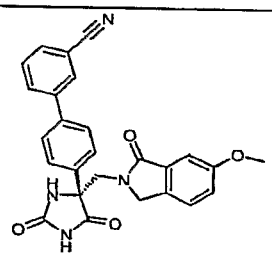
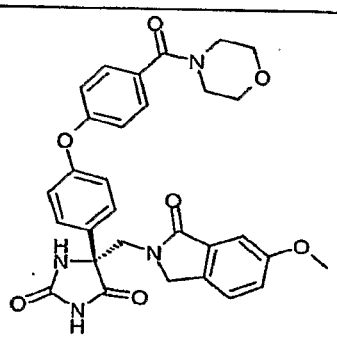
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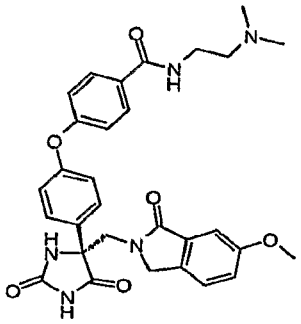
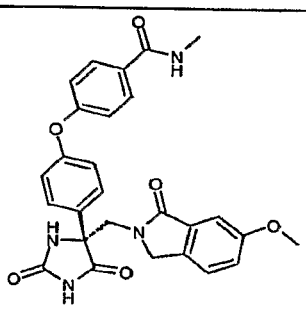
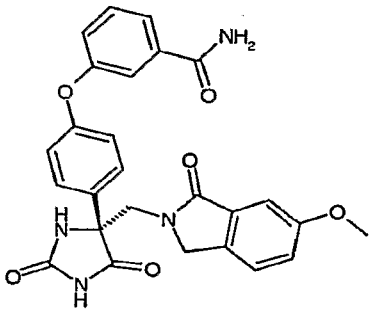
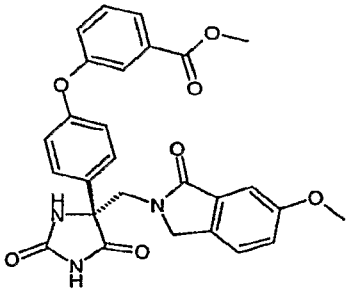
Compound ID	Structures
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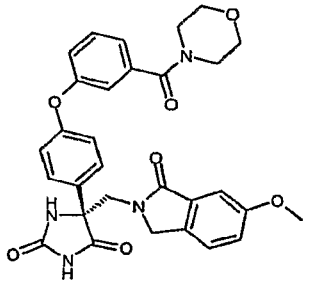
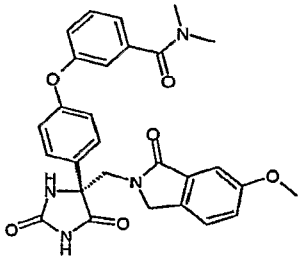
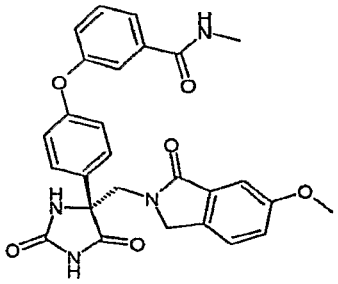
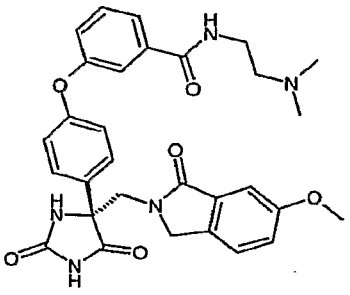
Compound ID	Structures
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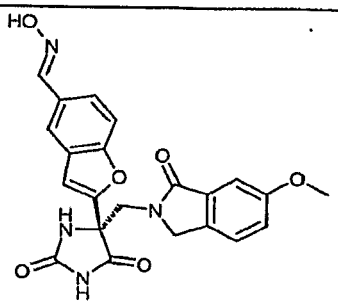
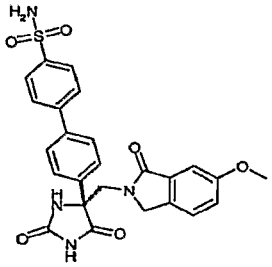
Compound ID	Structures
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Compound ID	Structures
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Compound ID	Structures
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Compound ID	Structures
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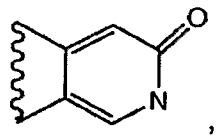
Compound ID	Structures
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Compound ID	Structures
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or a pharmaceutically acceptable salt, solvate or ester thereof.

29. The compound of claim 1, wherein U and V are present; and U is selected from the group consisting of -O-C(O)NH-, -OC(O)N(alkyl)-, –C(O)-, -C(O)O-, –C(O)NH-, -C(O)N(alkyl)-, –C(=N-OH)-alkyl-, and –C(=N-O-alkyl)-alkyl-.

30. The compound of claim 29, wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and

 , each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

31. The compound of claim 30, wherein ring **A** is phenyl.

32. The compound of claim 29, wherein X is selected from the group consisting of $-(C(R^3)_2)_m-$ and $-N(R^3)-$.

33. The compound of claim 32, wherein X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

34. The compound of claim 33, wherein m is 1.

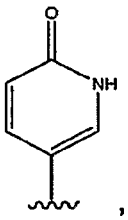
35. The compound of claim 32, wherein R^3 is H.

36. The compound of claim 29, wherein T is absent or present, and when present, is selected from the group consisting of alkyl, and aryl, each of which is unsubstitued or substituted with one to four R^{10} moieties which can be the same or different.

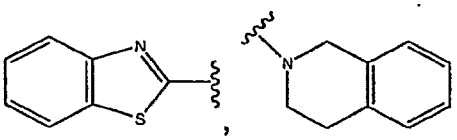
37. The compound of claim 36, wherein T is absent or present, and when present is selected from the group consisting of $-CH_2-$, and phenyl.

38. The compound of claim 29, wherein V is selected from the group consisting of alkyl, heterocyclyl, and cycloalkyl, wherein when each of said V heterocyclyl or cycloalkyl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; wherein each of aforementioned V alkyl, heterocyclyl, and cycloalkyl, optionally with said five- to eight-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring is is independently unsubstituted or substituted with one to four R^{10} moieties which can be the same or different.

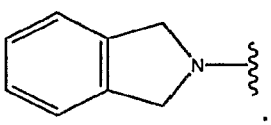
39. The compound of claim 38, wherein V is selected from the group consisting of methyl, ethyl, isopropyl, morpholinyl, cyclohexyl, piperidinyl optionally substituted with cyano or phenyl, $-CH_2-$ substituted with tetrahydrofuranyl and



, $-CH(CH_3)-$ substituted with phenyl, piperazinyl substituted wth methyl, pyrrolidinyl substituted wth $-CH_2$-phenyl,



substituted with cyclopropyl, and



40. The compound of claim 29, wherein each of Y and Z is independently selected from the group consisting of a covalent bond and –O-.

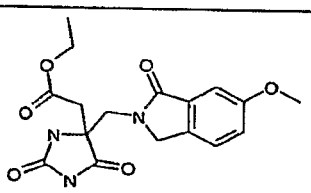
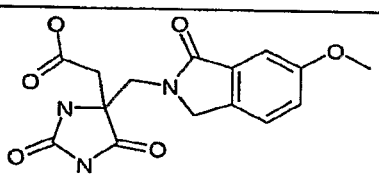
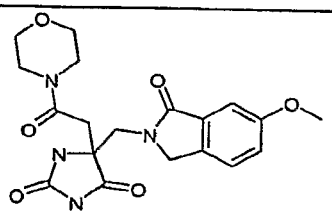
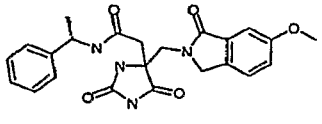
41. The compound of claim 40, wherein Y is –O- and Z is a covalent bond.

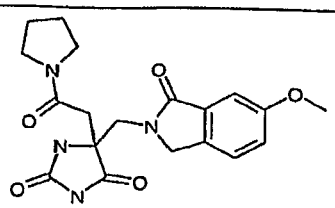
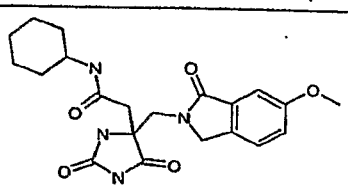
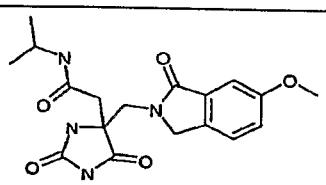
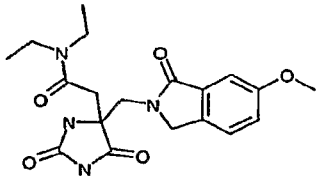
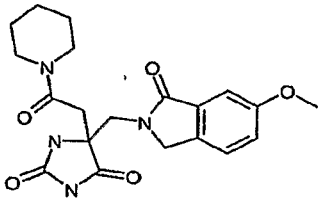
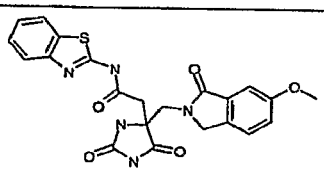
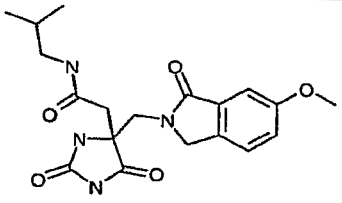
42. The compound of claim 29, wherein each of R^1 and R^2 is independently selected form the group consisting of H and alkyl.

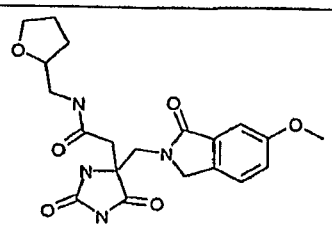
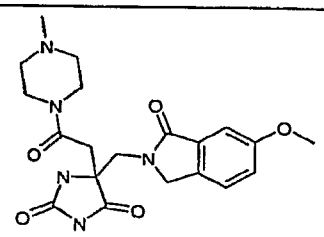
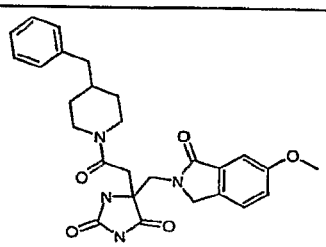
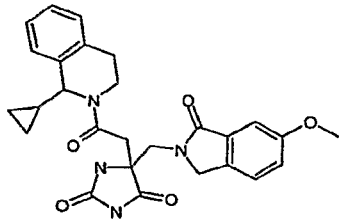
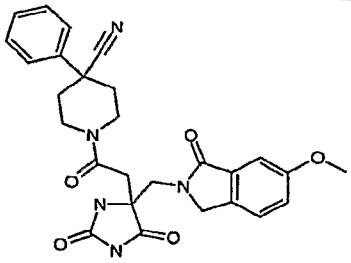
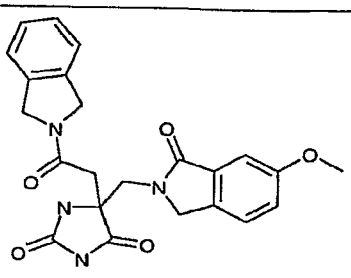
43. The compound of claim 42, wherein R^1 is alkyl and R^2 is H.

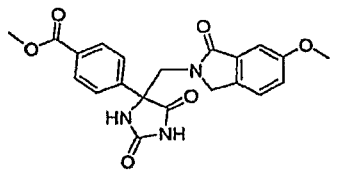
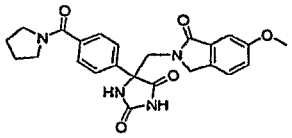
44. The compound of claim 43, wherein R^1 is methyl.

45. The compound of claim 29, selected from the group consisting of:

Compound ID	Structures
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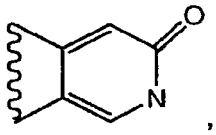
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or a pharmaceutically acceptable salt, solvate or ester thereof.

46. The compound of claim 1, wherein at least one T and V is present, and each of $-Y-R^1$ and $-Z-R^2$ is independently selected from the group consisting of cyano, $-(C(R^4)_2)_n-C(O)OH$, $-(C(R^4)_2)_n-C(O)O$-alkyl, $-(C(R^4)_2)_n-C(O)NH_2$, $-(C(R^4)_2)_n-C(O)NH$(alkyl), and $-(C(R^4)_2)_n-C(O)N(alkyl)_2$. wherein each R^4 independently is H or alkyl; and n is 1-3.

47. The compound of claim 46, wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and



, each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

48. The compound of claim 47, wherein said ring **A** is phenyl.

49. The compound of claim 46, wherein X is selected from the group consisting of $-(C(R^3)_2)_m-$ and $-N(R^3)-$.

50. The compound of claim 49, wherein X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

51. The compound of claim 50, wherein m is 1.

52. The compound of claim 49, wherein R^3 is H.

53. The compound of claim 46, wherein T or V is aryl which is unsubstituted or substituted with one to four R^{10} moieties.

54. The compound of claim 53, wherein said T or V is phenyl which is unsubstituted or substituted with one to four R^{10} moieties.

55. The compound of claim 54, wherein R^{10} is fluoro.

56. The compound of claim 55, wherein only one of T and V is present.

57. The compound of claim 46, wherein U is absent.

58. The compound of claim 46, wherein n is 1.

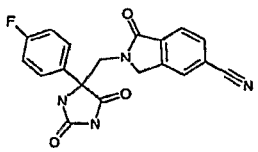
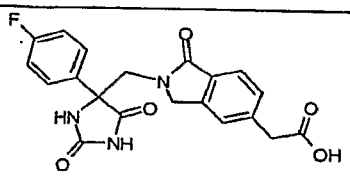
59. The compound of claim 46, wherein each of Y and Z is independently selected from the group consisting of a covalent bond and -CH_2-, and each of R^1 and R^2 is independently selected from the group consisting of cyano, -C(O)OH or -$C(O)NH_2$.

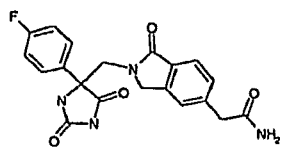
60. The compound of claim 55, wherein Y is a covalent bond, and R^1 is H.

61. The compound of claim 55, wherein Z is a covalent bond, and R^2 is cyano.

62. The compound of claim 55, wherein Z is –CH_2-, and R^2 is -C(O)OH or -$C(O)NH_2$.

63. The compound of claim 46, selected from the group consisting of:

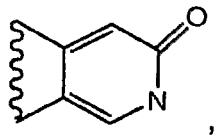
Compound ID	Structures
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or a pharmaceutically acceptable salt or solvate thereof.

64. The compound of claim 1, wherein T is aryl or heteroaryl, each of which is optionally substituted with one to four independently selected R^{10} moieties, and V is alkynyl which is optionally substituted with one or two independently selected R^{10} moieties.

65. The compound of claim 64, wherein ring **A** is selected from the group consisting of phenyl, thiophenyl, pyridyl, pyrimidyl, and

 , each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

66. The compound of claim 65, wherein said ring **A** is phenyl.

67. The compound of claim 64, wherein X is selected from the group consisting of $-(C(R^3)_2)_m-$ and $-N(R^3)-$.

68. The compound of claim 67, wherein X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

69. The compound of claim 68, wherein m is 1.

70. The compound of claim 66, wherein R^3 is H.

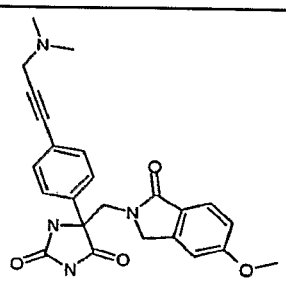
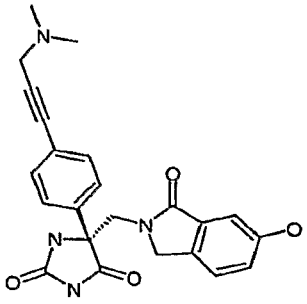
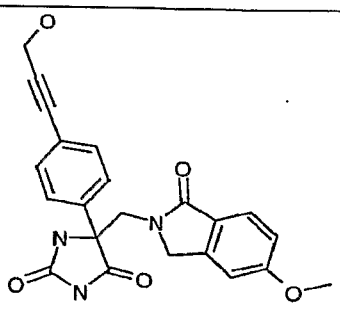
71. The compound of claim 64, wherein T is aryl, U is –O- or absent, and V is alkynyl which is unsubstituted or substituted with one or two R^{10} moieties selected from the group consisting of $-OR^4$, $-N(R^4)_2$, and heteroaryl; wherein when said heteroaryl contains two radicals on adjacent carbon atoms, said radicals may optionally be taken together with the carbon atoms to which they are attached to form a five- to eight-membered aryl, heteocyclyl, heteroaryl or cycloalkyl ring; wherein each R^4 independently is H or alkyl, and said R^{10} heteroaryl is optionally independently substituted with one to four R^{30} moieties which can be the same or different.

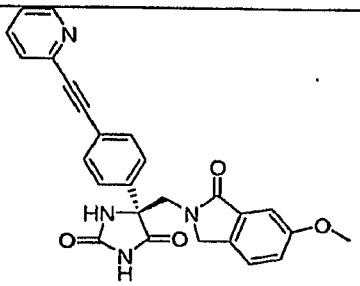
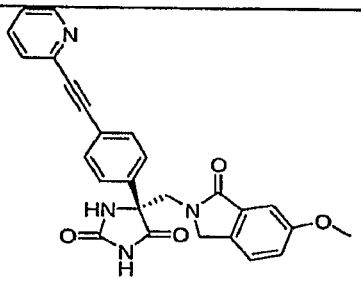
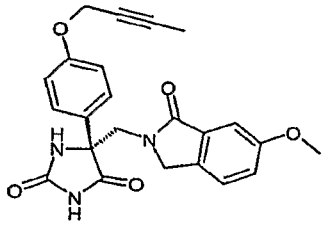
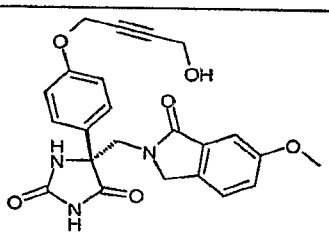
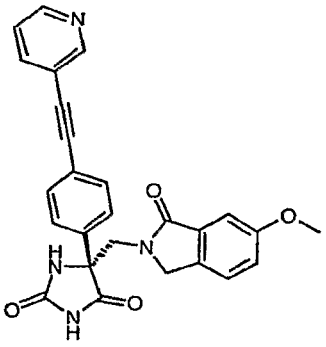
72. The compound of claim 71, wherein T is phenyl.

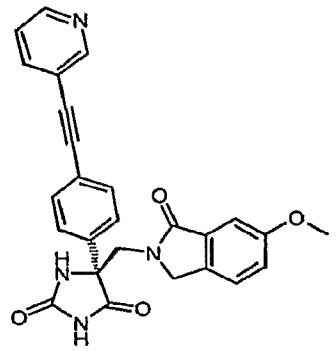
73. The compound of claim 71, wherein said V alkynyl is selected from the group consisting of $-CH_2-C\equiv C-CH_3$, R^{10} substituted $-C\equiv C-$ and R^{10} substituted $-CH_2-C\equiv C-CH_2-$.

74. The compound of claim 71, wherein said R^{10} substituents are selected from the group consisting of $-N(alkyl)_2$, -OH, $-OCH_3$, and pyridyl.

75. The compound of claim 64, selected from the group consisting of:

Compound ID	Structures
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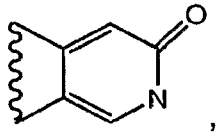
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or a pharmaceutically acceptable salt, solvate, or ester thereof.

76. The compound of claim 1, wherein at least one of T and V is present, ring A is heteroaryl, and V is other than alkynyl.

77. The compound of claim 76, wherein ring A is selected from the group consisting of thiophenyl, pyridyl, pyrimidyl, and

 , each of which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

78. The compound of claim 77, wherein X is selected from the group consisting of $-(C(R^3)_2)_m-$ and $-N(R^3)-$.

79. The compound of claim 78, wherein X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

80. The compound of claim 79, wherein m is 1.

81. The compound of claim 78, wherein R^3 is H.

82. The compound of claim 76, wherein T is selected from the group consisting of alkyl, and halo-substituted aryl.

83. The compound of claim 76, wherein U and V are absent.

84. The compound of claim 76, wherein Y is selected from the group consisting of a covalent bond and –O-, and Z is a covalent bond.

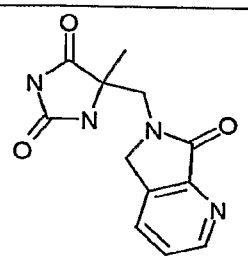
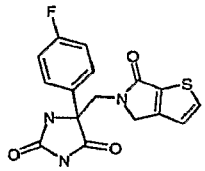
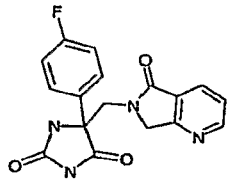
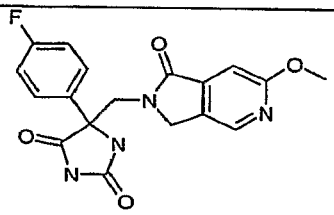
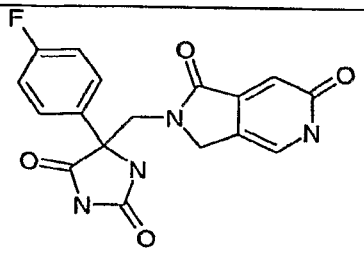
85. The compound of claim 76, wherein R^1 is selected from the group consisting of H and $-CH_3$; and R^2 is H.

86. The compound of claim 76, wherein Y is a covalent bond R^1 is H.

87. The compound of claim 76, wherein Y is is –O-and R^1 is $-CH_3$.

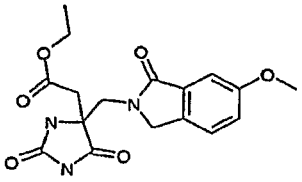
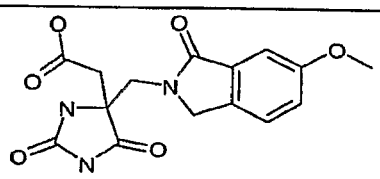
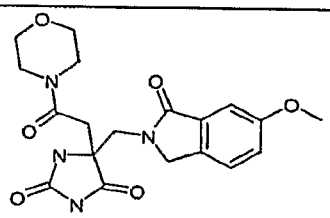
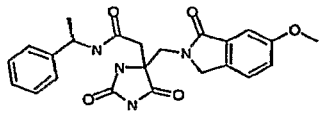
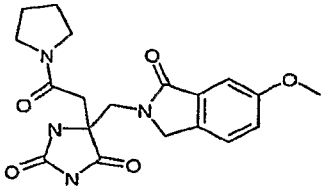
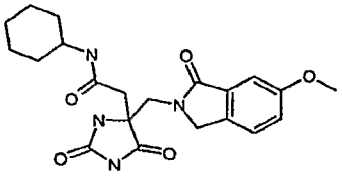
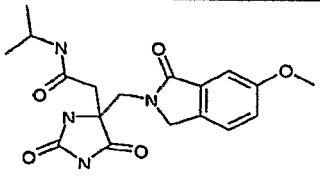
88. The compound of claim 76, wherein Z is a covalent bond and R^2 is H.

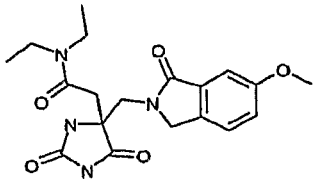
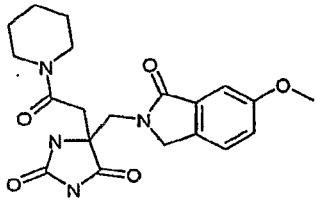
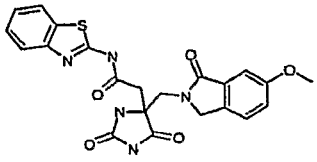
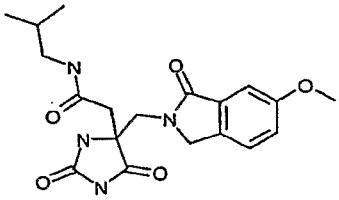
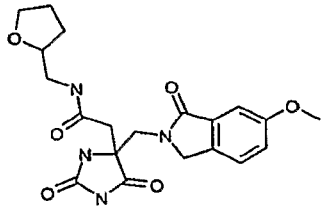
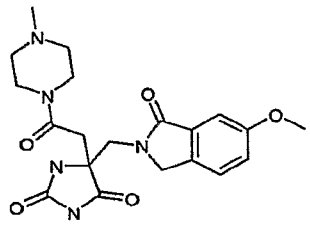
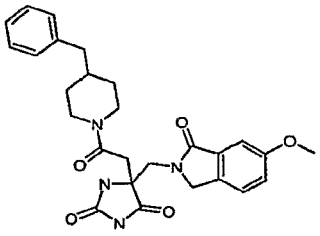
89. The compound of claim 76, selected from the group consisting of:

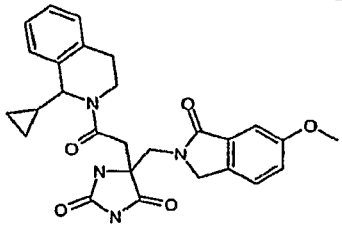
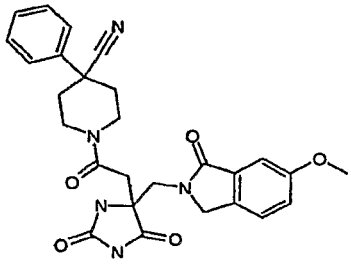
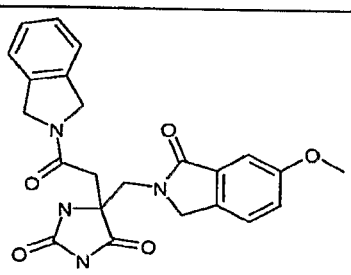
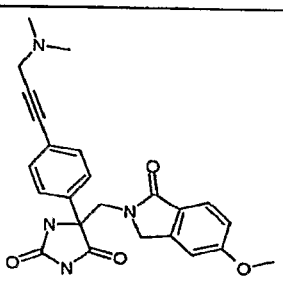
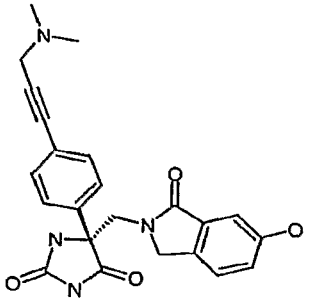
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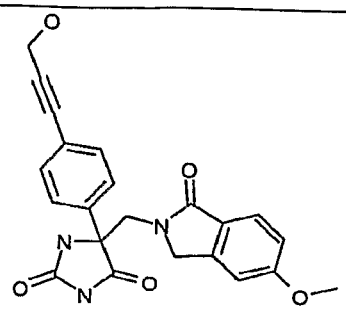
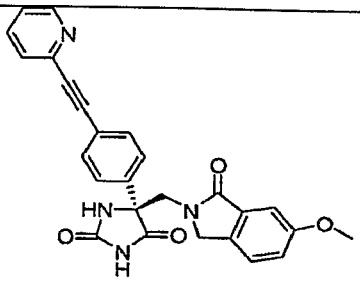
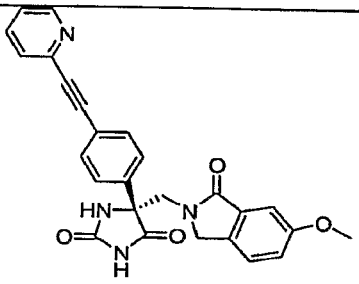
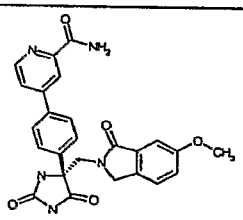
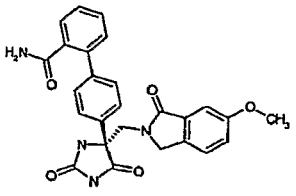
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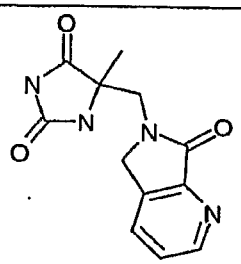
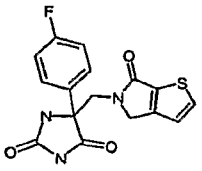
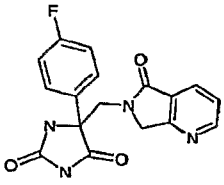
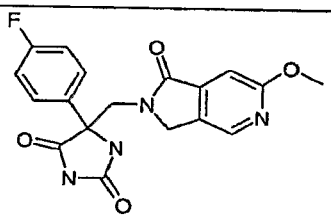
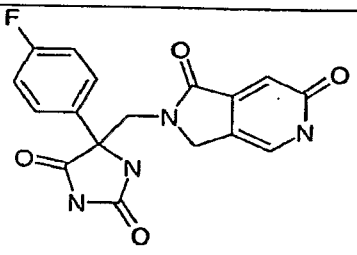
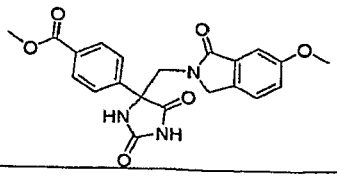
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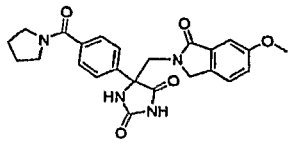
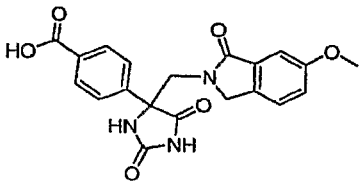
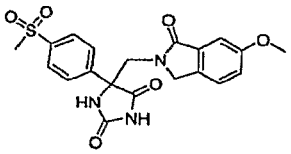
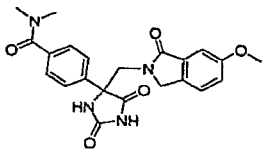
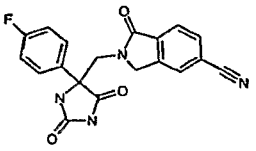
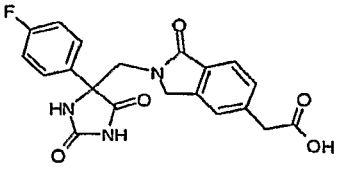
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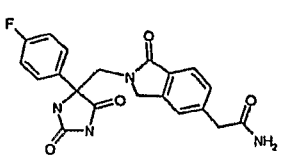
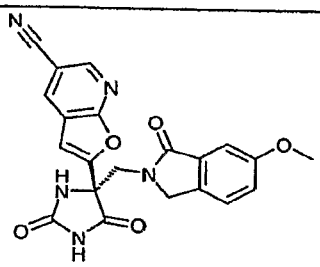
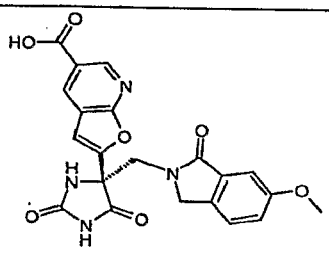
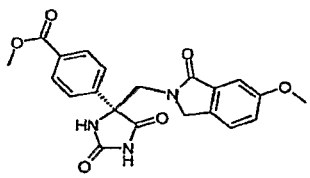
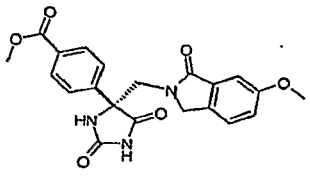
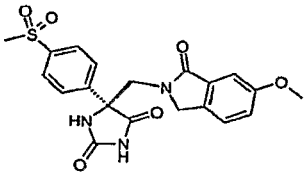
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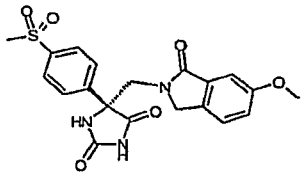
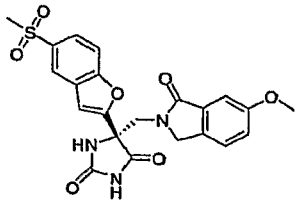
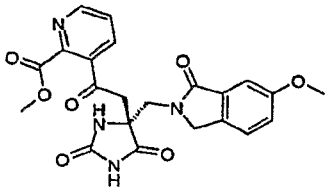
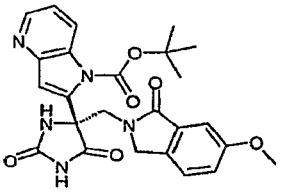
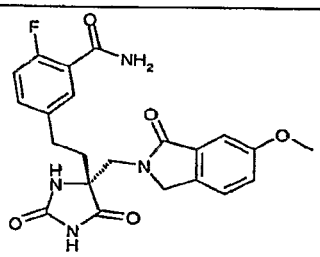
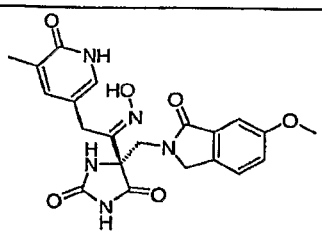
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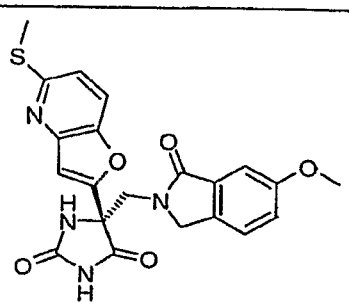
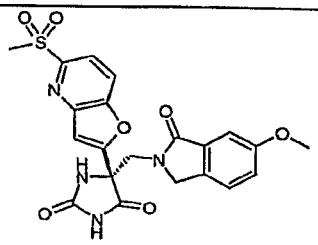
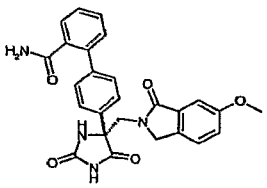
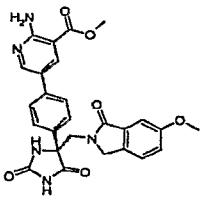
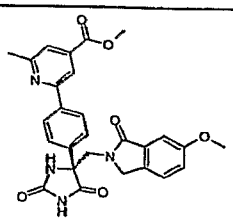
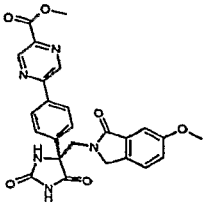
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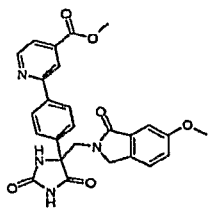
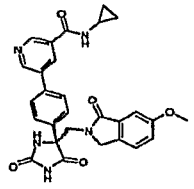
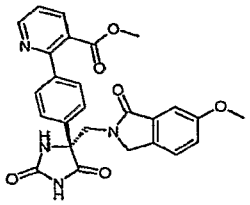
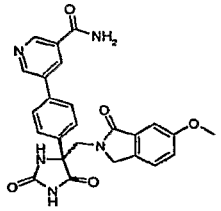
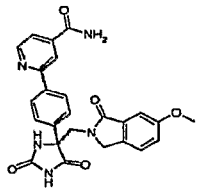
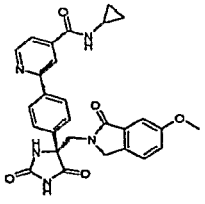
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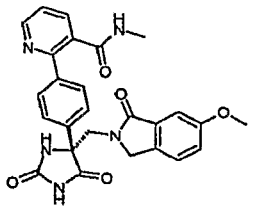
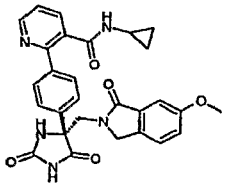
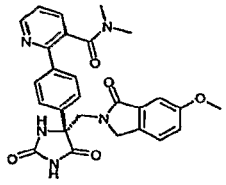
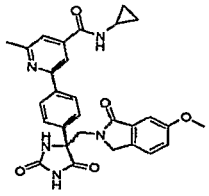
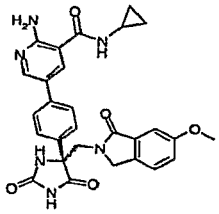
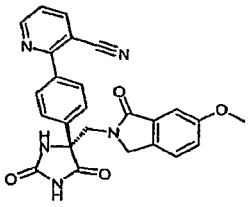
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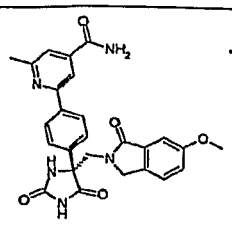
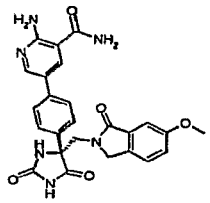
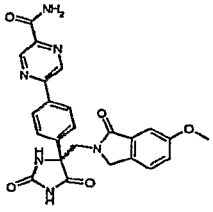
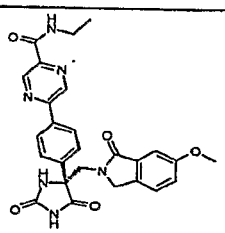
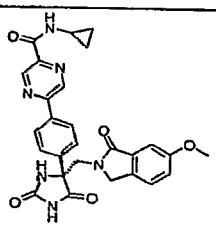
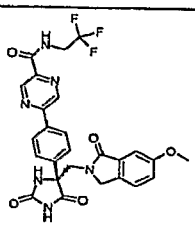
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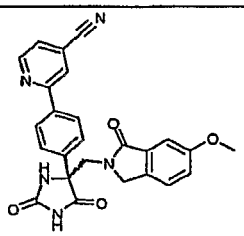
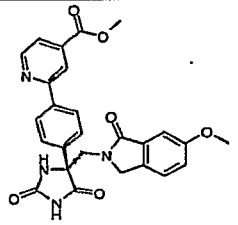
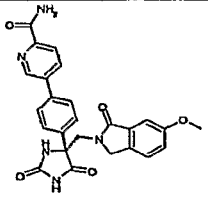
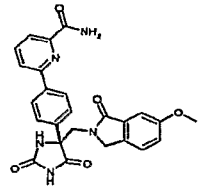
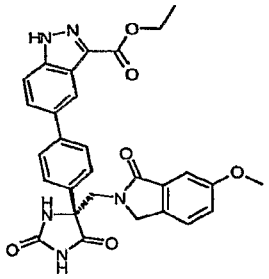
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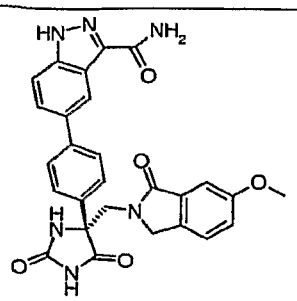
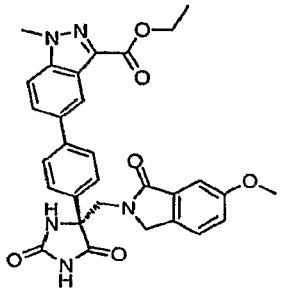
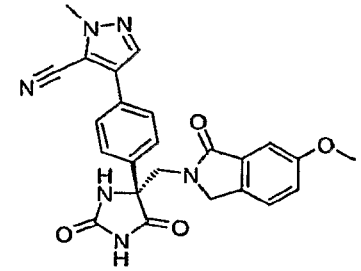
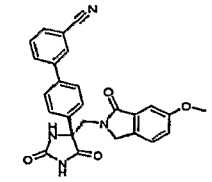
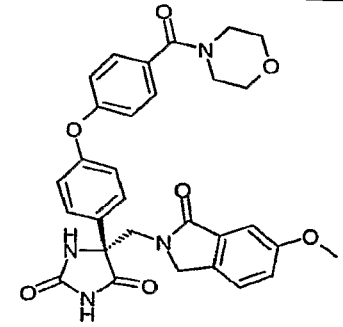
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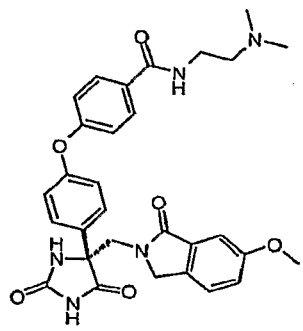
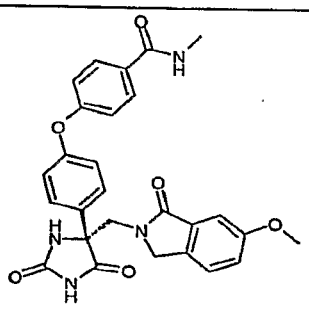
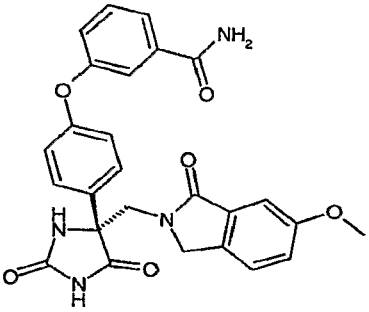
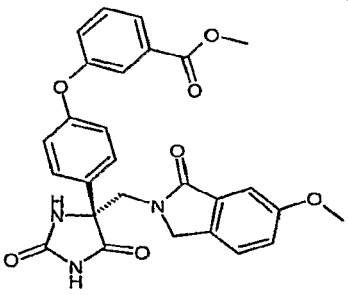
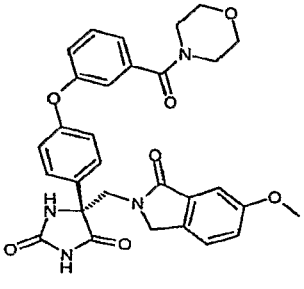
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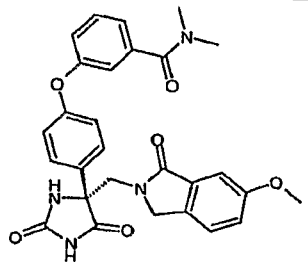
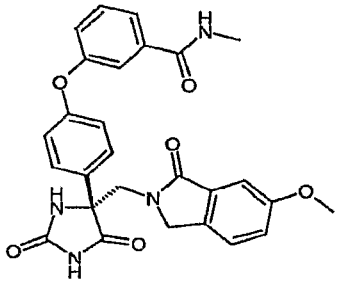
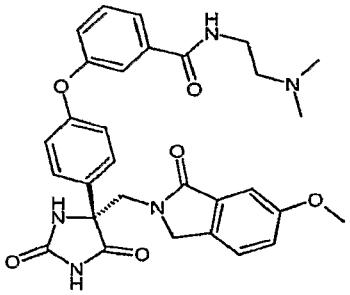
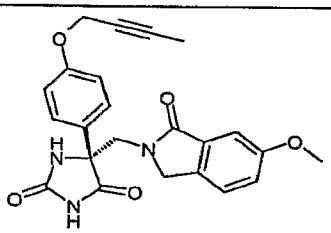
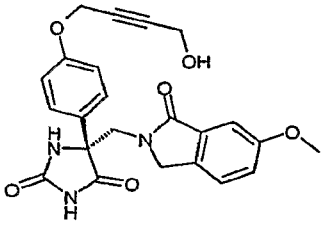
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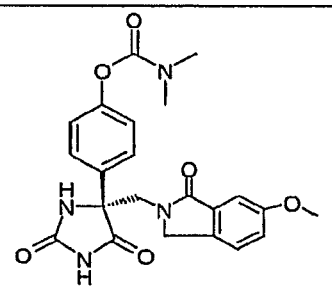
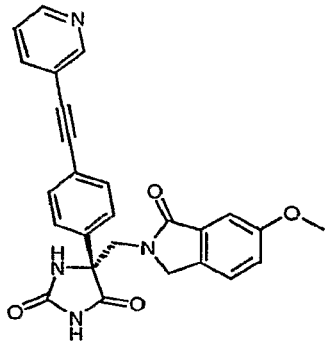
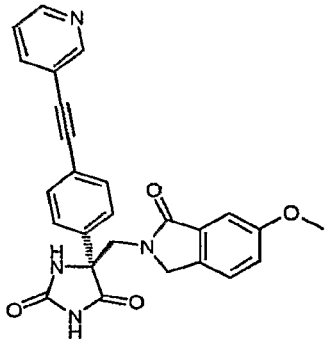
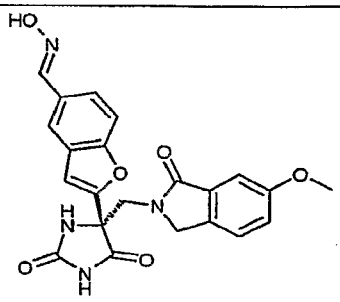
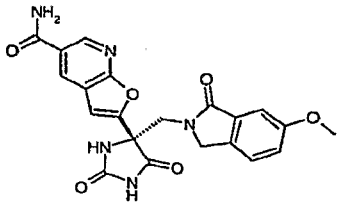
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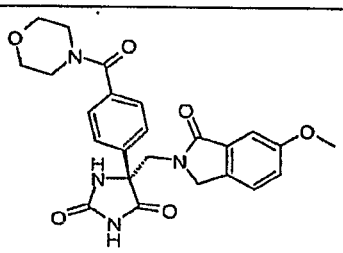
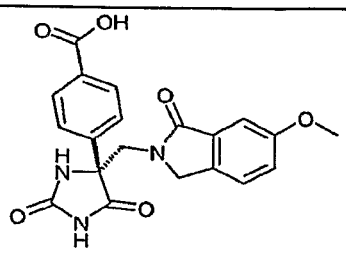
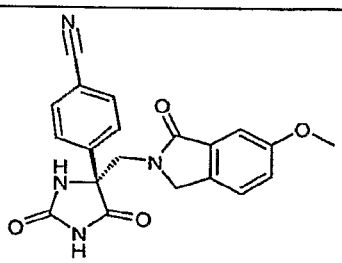
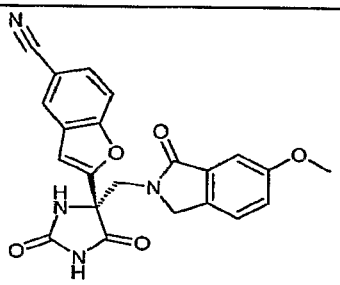
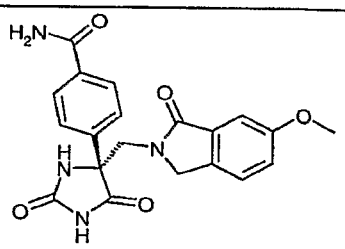
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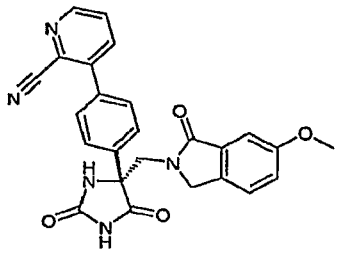
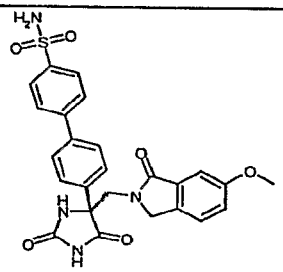
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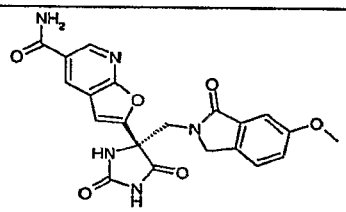
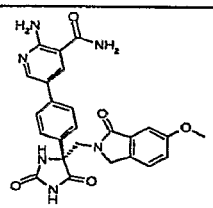
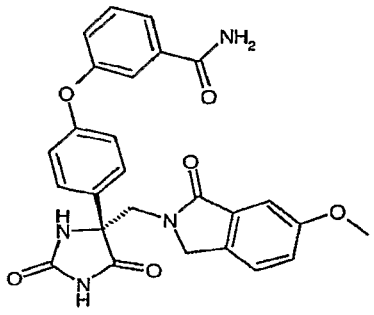
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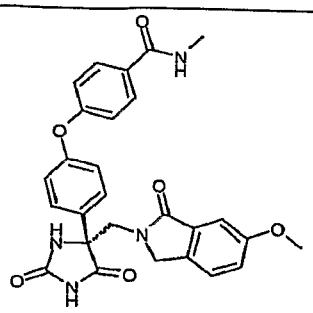
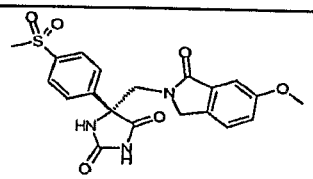
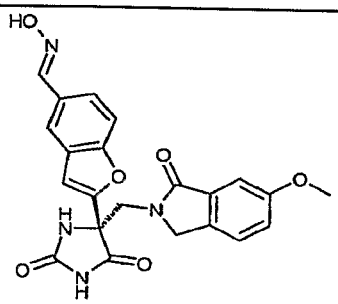
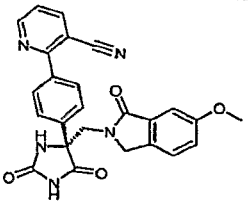
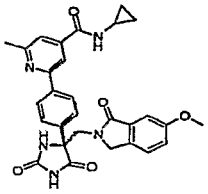
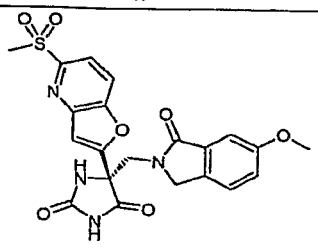
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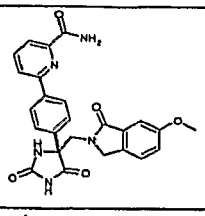
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or a pharmaceutically acceptable salt, solvate, or ester thereof.

91. The compound of claim 90, selected from the group consisting of:

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or a pharmaceutically acceptable salt, solvate, or ester thereof

92. A compound of claim 1 in purified form.

93. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof, and at least one pharmaceutically acceptable carrier.

94. A method of treating disorders associated with TACE, TNF-α, MMPs, aggrecanase, ADAMs or any combination thereof, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate or ester thereof.

95. A method of treating disorders associated with TACE, TNF-α, aggrecanase, MMPs, ADAMs or any combination thereof, said method comprising administering to a patient in need of such treatment the pharmaceutical composition of claim 92.

96. 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 ester thereof.

97. 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 ester thereof.

98. 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 ester thereof.

99. 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 ester thereof.

100. 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 ester thereof.

101. 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 ester thereof.

102. 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 ester thereof.

103. 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 claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

104. 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 ester thereof.

105. 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 ester thereof.

106. 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 ester thereof.

107. 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.

108. The method of claim 96, 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.

109. A method of claim 97, 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.

110. A method of claim 98, 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.