HYDANTOIN DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY DISORDERS

BACKGROUND OF THE INVENTION

Field of the Invention

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

Description

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

Metalloproteases (MPs) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the

administration of MP inhibitors (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

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

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

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

TNF-α is a primary mediator in humans and animals of inflammation, fever and acute phase responses, similar to those observed during acute infection and shock. Excess TNF-α has been shown to be lethal. Blocking the effects of TNF-α with specific antibodies can be beneficial in a variety of conditions, including autoimmune diseases such as RA (Feldman et al,

Lancet, (1994) 344, 1105), non-insulin dependent diabetes mellitus (Lohmander L. S. et al., Arthritis Rheum. 36 (1993) 1214-22) and Crohn's disease (Macdonald T. et al., Clin. Exp. Immunol. 81 (1990) 301).

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

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

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

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

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

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

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

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

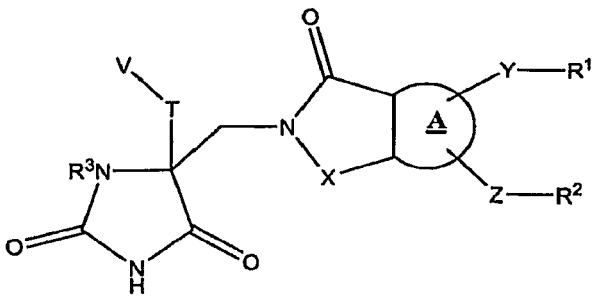
PCT Publication WO2006/019768 refers to hydantoin derivatives that are TACE inhibitors.

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 represented by Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, ester or isomer 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 alkynyl;

V is selected from the group consisting H, alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, and N-oxides of said heteroaryl and heterocyclyl, wherein when each of said cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, and N oxides of said heteroaryl and heterocyclyl contains two radicals on same or adjacent carbon atoms, said radicals may optionally be taken together with the carbon atom(s) to which they are attached to form a five- to eight-membered cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl ring, wherein each of the aforementioned cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl, optionally with said five- to eight-membered cycloalkyl, cycloalkenyl, 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, 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, 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;

R^{10} is selected from the group consisting of hydrogen, cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$ $-S(O)_2N(R^4)_2$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -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, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$ $-S(O)_2N(R^4)_2$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -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 $-N(alkyl)_2$;

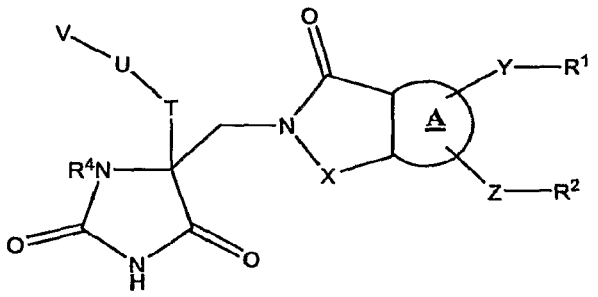
or when two R^{20} moieties when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;;

R^{30} is selected from the group consisting of cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$ $-S(O)_2N(R^4)_2$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -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.

In another embodiment, the present application discloses a 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.

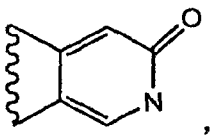
DETAILED DESCRIPTION OF THE INVENTION

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)-(IV) 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 one embodiment, the labeled 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 Formula (I).

In another embodiment, in Formula (I), ring A is phenyl which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

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

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

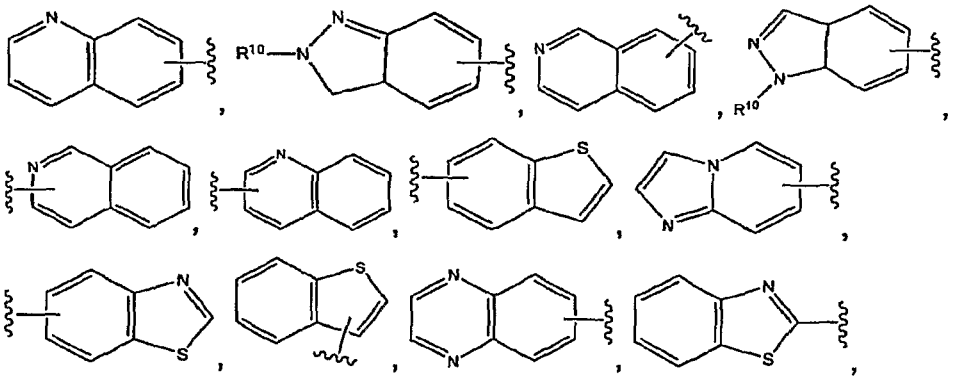
In another embodiment, in Formula (I), R^3 is H.

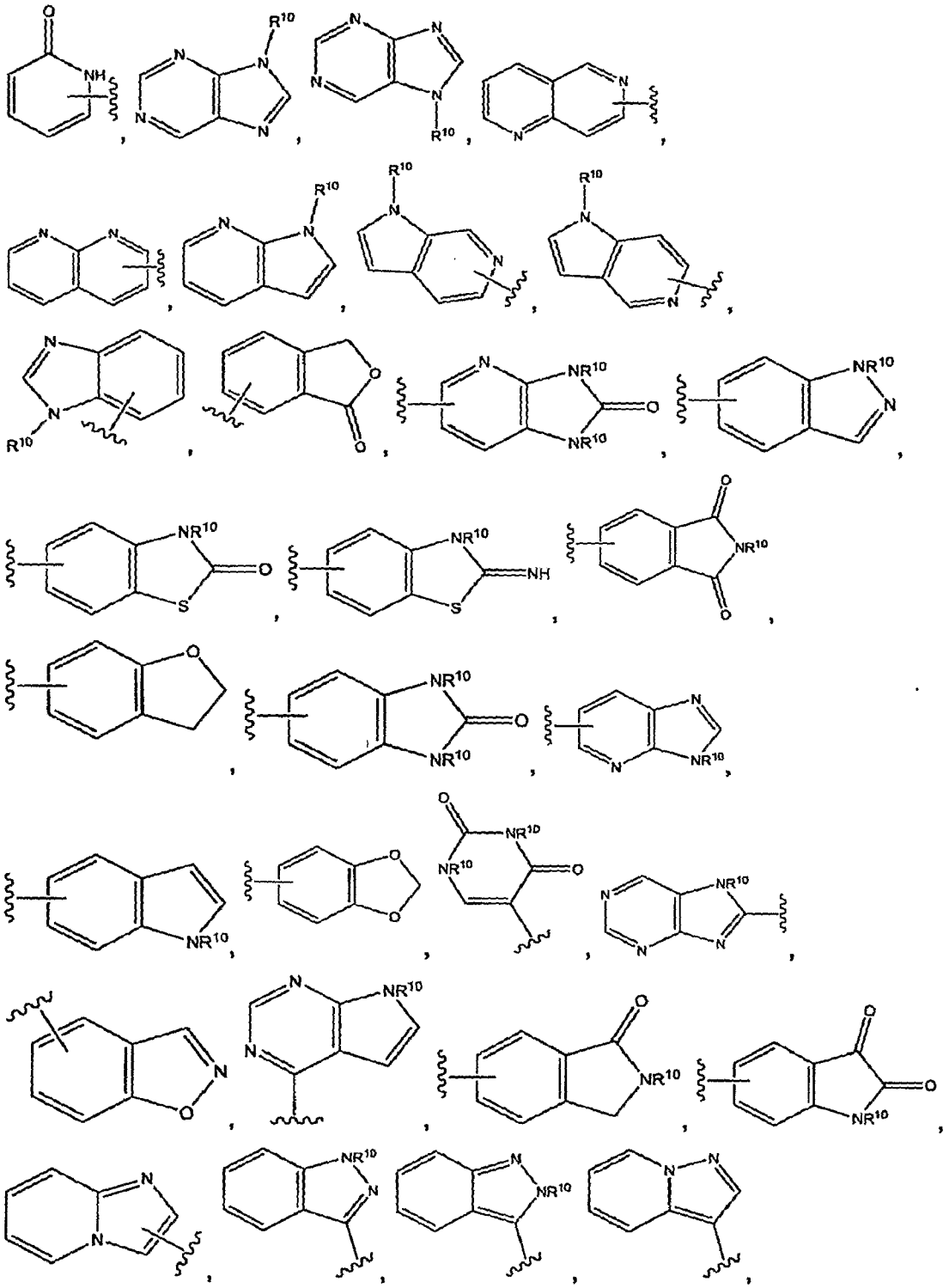
In another embodiment, in Formula (I), X is is $-(C(R^3)_2)_m$, wherein m 1, and wherein R^3 is H.

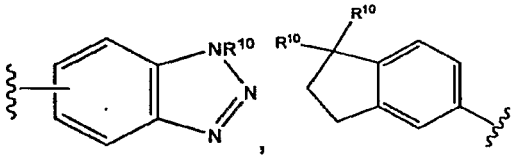
In another embodiment, in Formula (I), T is -C≡C-.

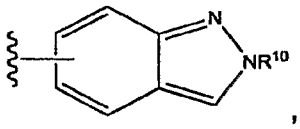
In another embodiment, in Formula (I), wherein V is selected from the group consisting of H, aryl, heteroaryl, and N-oxide of said heteroaryl; wherein when each of the aforementioned aryl, and heteroaryl contains two radicals on same or adjacent carbon atoms, said radicals may optionally be taken together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

In another embodiment, in Formula (I), V is selected from the group consisting of phenyl, naphthyl, pyrrolyl, furanyl, thiophenyl, pyrrazolyl, benzopyrazolyl, imidazoly, benzimidazolyl, furazanyl, pyridyl, pyridyl-N-oxide, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indazolyl, indolizinyl, quinolinyl, isopquinolinyl, quinazolinyl, pteridinyl, tetrazolyl, oxazolyl, isothiazolyl, thiazolyl,









, each of which is optionally substituted with one or more R^{10} moieties such that the number of R^{10} moieties per V group does not exceed four.

In another embodiment, in Formula (I), R^{10} is selected from the group consisting of hydrogen, cyano, nitro, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)_2R^4$-, $-S(O)_2N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-C(R^4)$=N-OR, halogen, alkyl, haloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, aryl, heteroaryl, and heterocyclyl 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 carbon atom are taken together with the carbon atom to which they are attached to form a heterocyclyl ring;

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; and

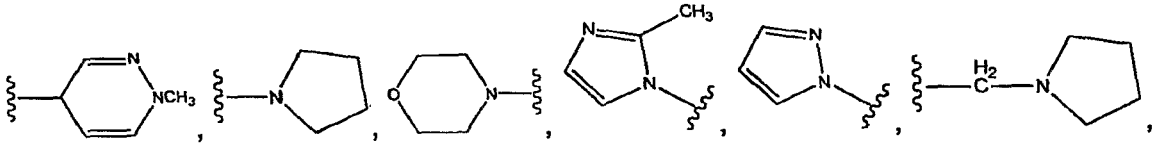
R^{30} is selected from the group consisting of halogen, alkyl, haloalkyl, hydroxy, alkoxy, heterocyclyl, $-C(R^4)$=N-OR, -O-alkyl-cycloalkyl, $-N(R^4)_2$, and $-C(O)N(R^4)_2$, wherein said R^{30} alkyl is substituted with a $-NH_2$.

In another embodiment, in Formula (I), R^{10} is selected from the group consisting of nitro, alkyl, halogen, haloalkyl, haloalkoxy, alkoxy, cyano, $-S(O)_2$-alkyl, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, cycloalkyl, aryl, heteroaryl, heterocyclyl, -alkyl-heterocyclyl, -cycloalkyl-NH_2, $-S(O)_2-NH_2$, $-S(O)_2$alkyl, $-C(O)NH_2$, hydroxy, -C(O)N(H)(cycloalkyl), -C(O)N(H)(alkyl), -N(H)(cycloalkyl), -C(O)O-alkyl, -C(O)OH, $-S(O)_2N(H)$(alkyl), $-S(O)_2OH$, -S-haloalkyl, $-S(O)_2$-haloalkyl, hydroxyalkyl, alkoxyalkyl, -O-alkyl-cycloalkyl, -alkyl-O-alkyl-cycloalkyl, -C(O)alkyl, aminoalkyl, -alkyl-NH(alkyl), -alkyl-$N(alkyl)_2$, -CH=N-O-alkyl, $-C(O)NH$-alkyl-$N(alkyl)_2$, -C(O)-heterocyclyl, and -NH-C(O)-alkyl, wherein each

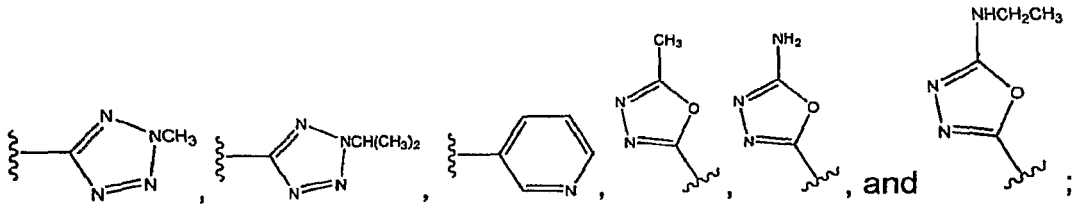
of said R^{10} aryl and heteroaryl is optionally substituted with 1-2 moieties selected from the group consisting of alkyl, $-NH_2$, -NH(alkyl), and $-N(alkyl)_2$;

or wherein two R^{10} moieties attached to the same carbon atom are taken together with the carbon atom to which they are attached to form a heterocyclyl ring.

In another embodiment, in Formula (I), R^{10} is selected from the group consisting of hydrogen, nitro, methyl, fluoro, bromo, trifluoromethyl, chloro, difluoromethoxy, trifluoromethoxy, methoxy, hydroxyl, cyano, $-S(O)_2CH_3$, $-NH_2$, isopropyl, cyclopropyl, -cyclopropyl-NH_2,

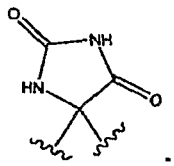


-NH(cyclopropyl), $-NH(CH_3)$, $-S(O)_2-NH_2$, $-C(O)NH_2$, $-C(O)OCH_3$, -C(O)OH, $-S(O)_2N(H)CH_3$, $-C(O)NH(CH_3)$, -C(O)NH(cyclopropyl), $-S(O)_2OH$, $-S-CF_3$, $-S(O)_2-CF_3$, ethoxy, hydroxymethyl, methoxymethyl, isopropoxy, $-OCH_2$-cyclopropyl, $-CH_2O-CH_2$-cyclopropyl, $-C(O)CH_3$, $-C(O)CH_3$, $-CH(CH_3)OH$, $-CH_2NH_2$, $-CH(CH_3)NH_2$, $-CH_2NH-CH_3$, $-CH(CH_3)OH$, $-CH_2NHCH_3$, -CH=N-OCH_3, $-C(CH_3)=N-OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)NHCH_2CH_2N(CH_3)_2$, -NH-$C(O)CH_3$,



; and

or wherein two R^{10} moieties, when attached to the same carbon atom are taken together with the carbon atom to which they are attached to form



.

In another embodiment, in Formula (I), Y is selected from the group consisting of a covalent bond and –O-.

In another embodiment, in Formula (I), Y is a covalent bond.

In another embodiment, in Formula (I), Y is –O-.

In another embodiment, in Formula (I), Z is selected from the group consisting of a covalent bond and –O-.

In another embodiment, in Formula (I), Z is –O-.

In another embodiment, in Formula (I), R^1 is selected from the group consisting of hydrogen, cyano, halogen, alkyl, aryl, heteroaryl, haloalkyl, and alkynyl; wherein said R^1 alkyl is unsubstituted or substituted with an aryl, heteroaryl, or heterocyclyl, wherein when said aryl, heteroaryl, or heterocyclyl 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 said aryl, heteroaryl or heterocyclyl substitutent of said R^1 alkyl optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties.

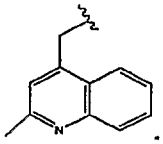
In another embodiment, in Formula (I), R^2 is selected from the group consisting of hydrogen, cyano, halogen, alkyl, aryl, heteroaryl, haloalkyl, and alkynyl; wherein said R^1 alkyl is unsubstituted or substituted with an aryl, heteroaryl, or heterocyclyl, wherein when said aryl, heteroaryl, or heterocyclyl 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 said aryl, heteroaryl or heterocyclyl substitutent of said R^1 alkyl optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties.

In another embodiment, in Formula (I), R^1 is halogen or cyano.

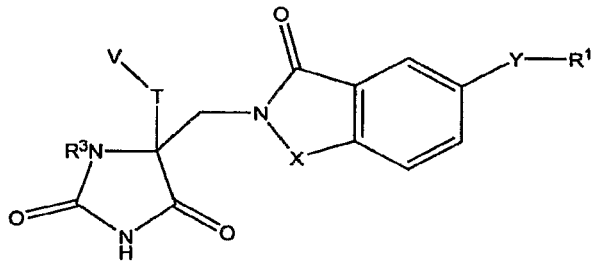
In another embodiment, in Formula (I), R^1 is fluoro, chloro, or cyano.

In another embodiment, in Formula (I), Y is –O-, and R^1 is selected from the group consisting of alkyl, haloalkyl, and alkynyl; wherein said R^1 alkyl is unsubstituted or substituted with a 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- or six-membered aryl; wherein said heteroaryl substituent of said R^1 alkyl, optionally with said five- or six-membered aryl is substituted with alkyl. In another embodiment, in Formula (I), Y is –O-, and R^1 is selected from the group consisting of CH_3, $-CH_2-C\equiv C-CH_3$, difluoromethyl, and



In another embodiment, the compound of Formula (I) is represented by the compound of formula (III):

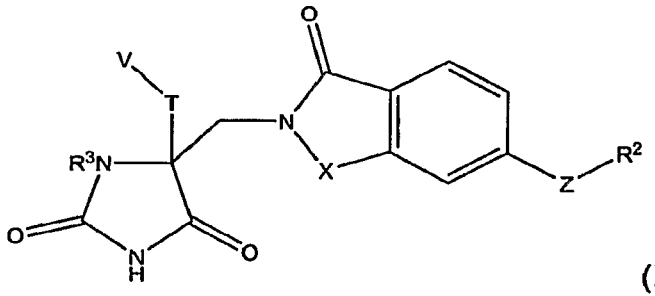


(III),

wherein in formula (III), X is $-(CH_2)_{1-2}-$, and T, V, Y, R^1, and R^3 are as set forth in Formula (I).

In another embodiment, in Formula (III), X is $-CH_2-$.

In another embodiment, the compound of Formula (I) is represented by the compound of formula (IV):



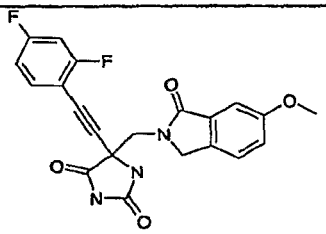
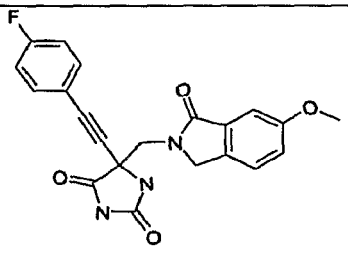
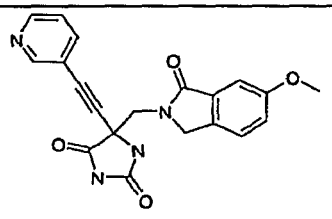
(IV),

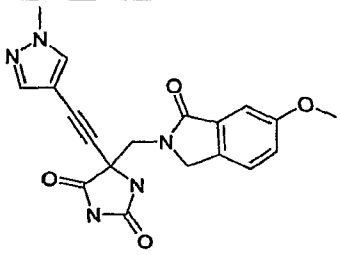
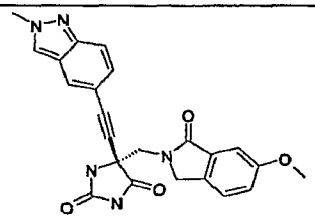
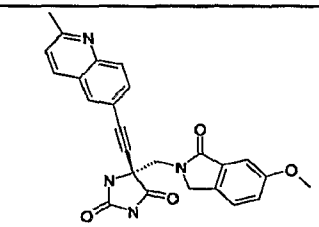
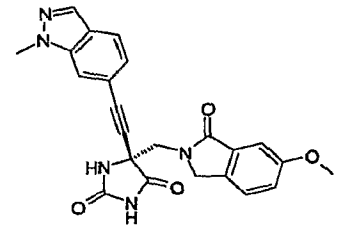
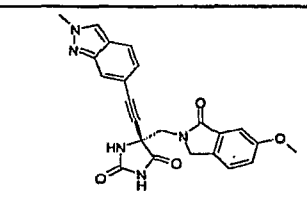
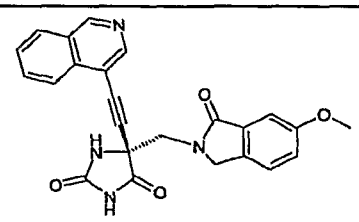
wherein in formula (IV), X is $-(CH_2)_{1-2}-$, T, V, Y, R^1, and R^3 are as set forth in Formula (I).

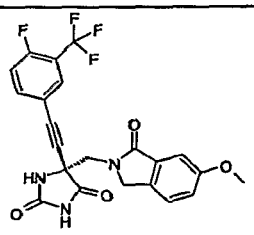
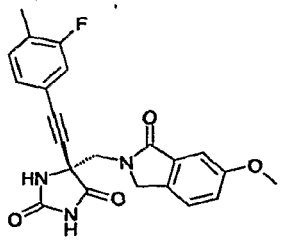
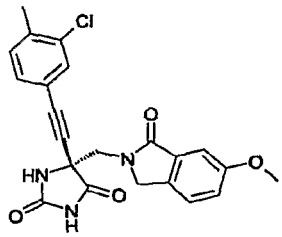
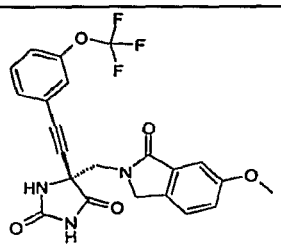
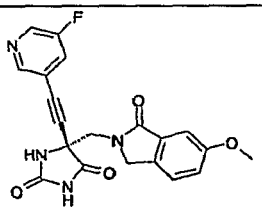
In another embodiment, in Formula (IV), X is $-CH_2-$.

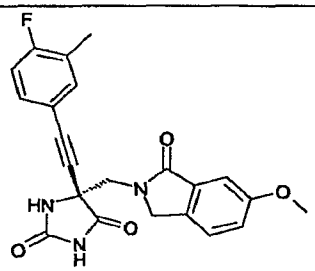
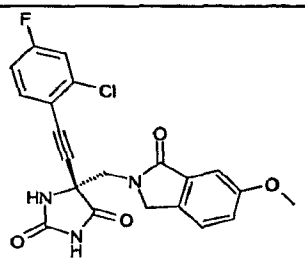
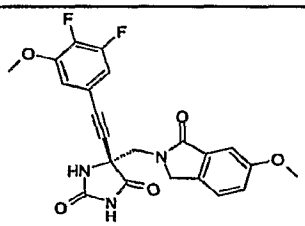
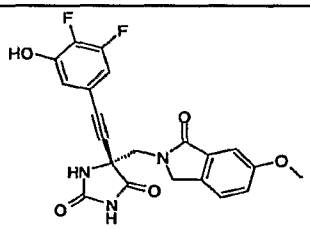
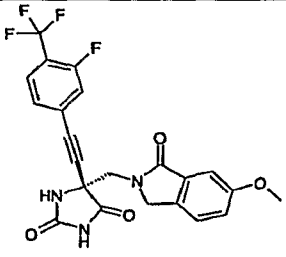
In another embodiment, the compound of Formula (I) is selected from the group consisting of compounds listed in the table below, or a pharmaceutically acceptable salt, solvate, ester or isomer thereof. This table also lists the mass spectroscopy data and the Ki rating for each compound. Those compounds having a Ki value of less than 5 nM (<5 nM) are designated with letter "A"; those with a Ki value of from 5 to less than 25 nM (5 - <25 nM) are designated with letter "B"; those with a Ki value of from 25 to 100 nM are designated with letter "C"; and those with a Ki value of more than 100 nM (>100 nM) are designated with letter "D". The syntheis and characterization of these compounds is described hereinbelow in the "EXAMPLES" section of the present application.

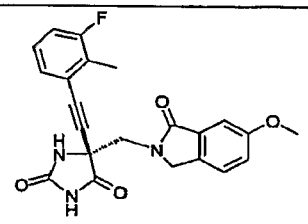
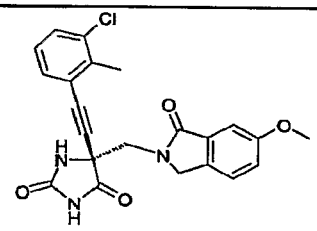
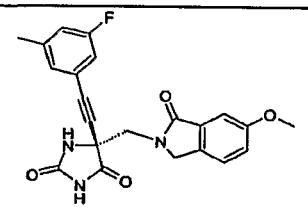
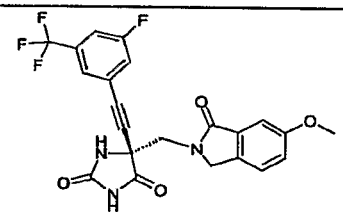
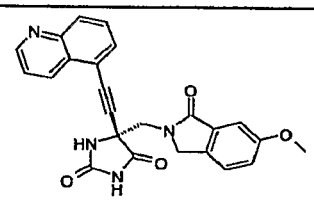
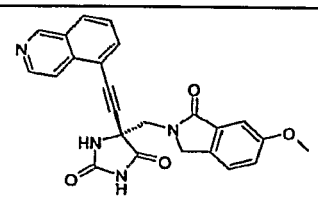
Table 1001

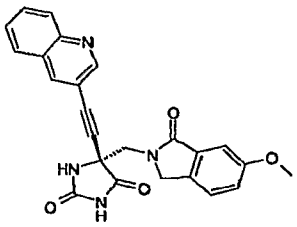
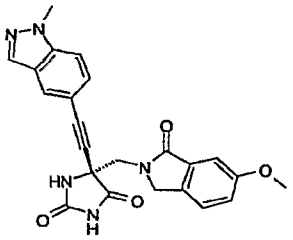
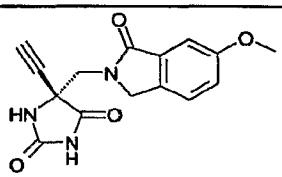
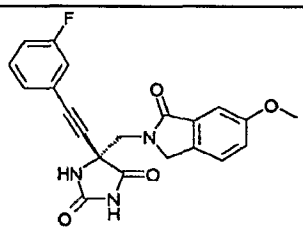
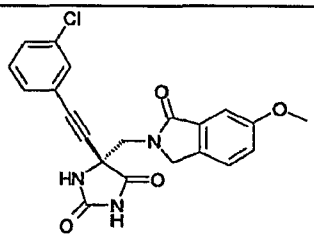
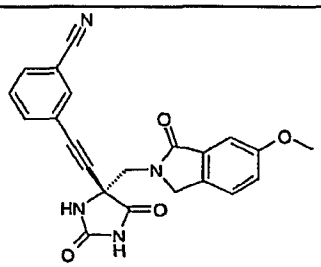
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315		393.11	394.1[M+H]$^+$	A
312		376.12	377[M+H]$^+$	A

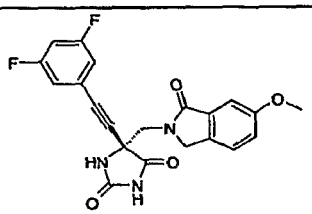
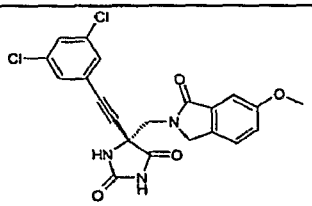
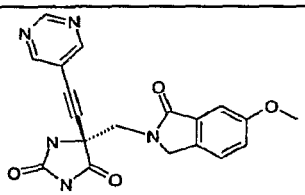
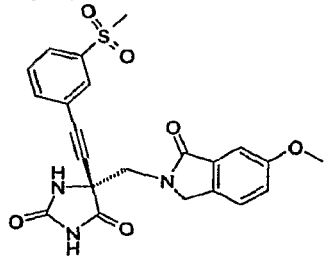
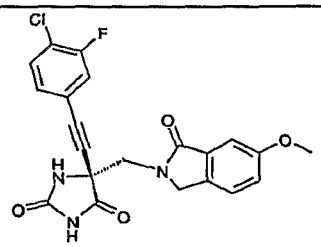
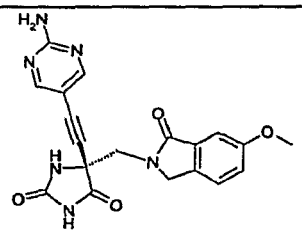
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
312B		379.13	380[M+H]$^+$	A
421		429.14	430.1[M+H]$^+$	A
422		440.15	441.1[M+H]$^+$	A
423		429.14	430.1[M+H]$^+$	A
424		429.14	430.1[M+H]$^+$	A
425		426.13	427.1[M+H]$^+$	A

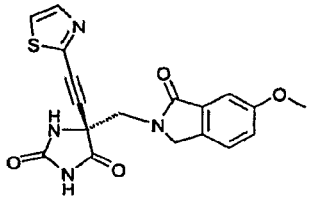
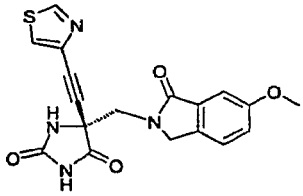
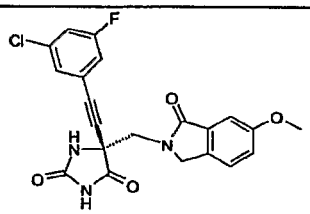
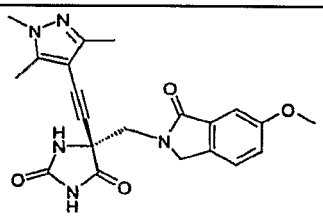
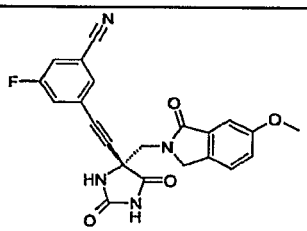
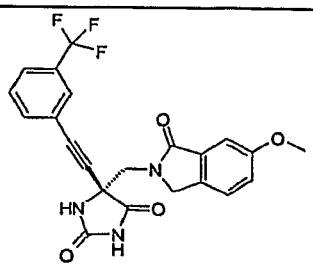
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
426		461.10	462.1[M+H]$^+$	A
427		407.13	408.1[M+H]$^+$	A
428		423.10	424.1[M+H]$^+$	A
429		459.10	460.1[M+H]$^+$	A
430		394.11	395.0[M+H]$^+$	A

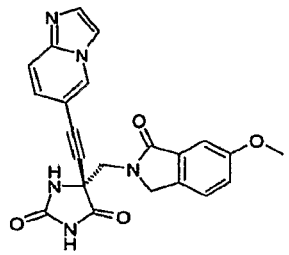
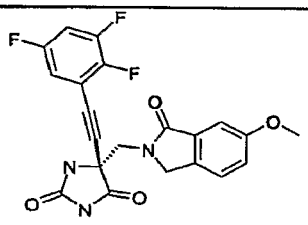
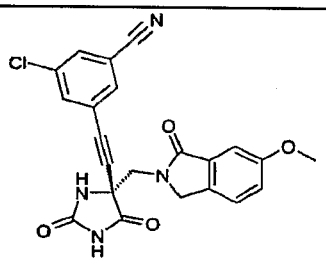
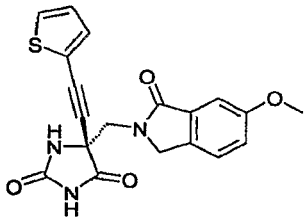
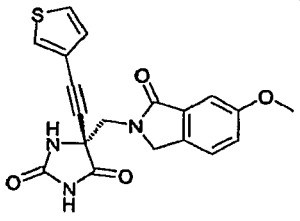
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
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433		427.07	428.0[M+H]$^+$	A
434		441.11	442.1[M+H]$^+$	A
435		427.10	428.0[M+H]$^+$	A
436		461.10	462.1[M+H]$^+$	A

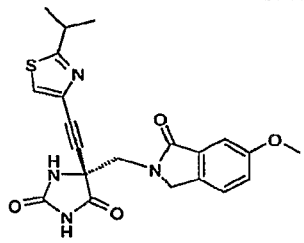
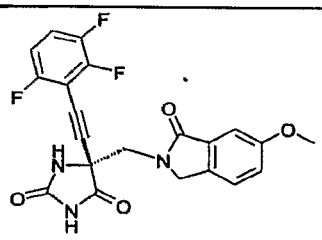
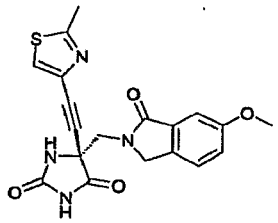
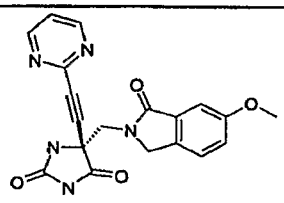
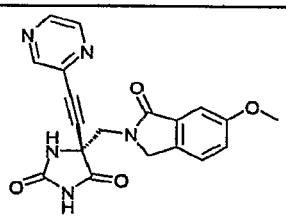
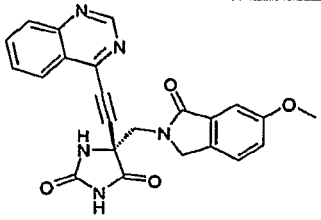
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
437		407.13	408.1[M+H]$^+$	A
438		423.10	424.1[M+H]$^+$	A
439		407.13	408.1[M+H]$^+$	A
440		461.10	462.1[M+H]$^+$	A
441		426.13	427.1[M+H]$^+$	A
442		426.13	427.1[M+H]$^+$	A

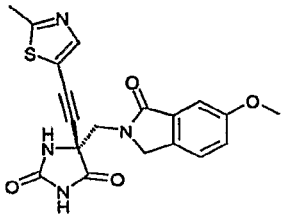
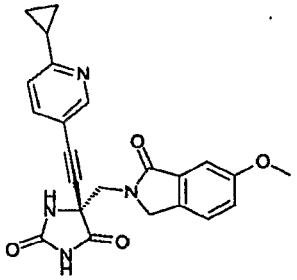
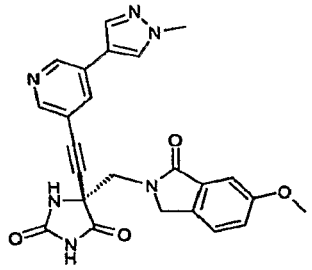
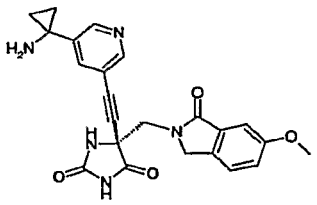
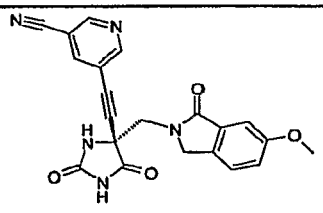
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
443		426.13	427.0[M+H]$^+$	A
444		429.14	430.1[M+H]$^+$	A
401		299.09	300.1[M+H]$^+$	A
445		393.11	394.1[M+H]$^+$	A
446		409.08	410.0[M+H]$^+$	A
447		400.12	401.1[M+H]$^+$	A

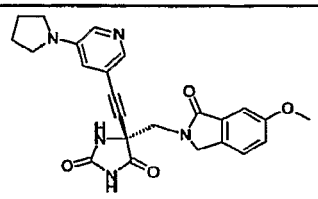
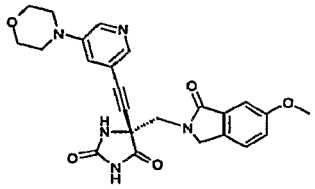
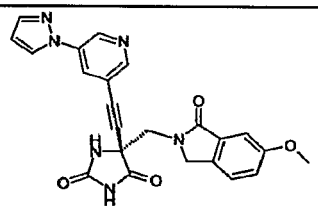
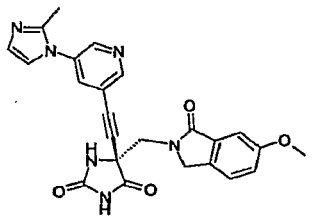
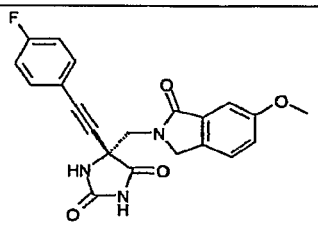
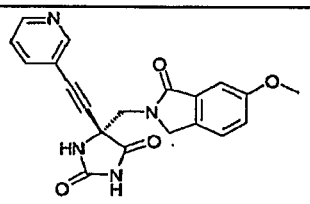
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
448		411.10	412.1[M+H]$^+$	A
449		443.04	444.1[M+H]$^+$	A
450		377.11	378.1[M+H]$^+$	A
451		453.10	454.1[M+H]$^+$	A
452		427.07	428.0[M+H]$^+$	A
453		392.12	393.1[M+H]$^+$	A

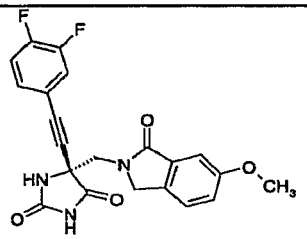
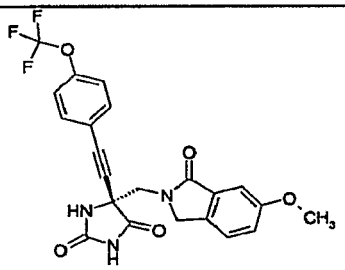
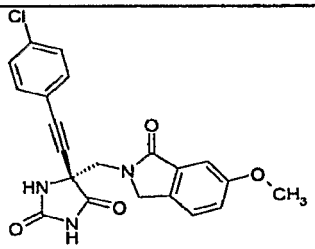
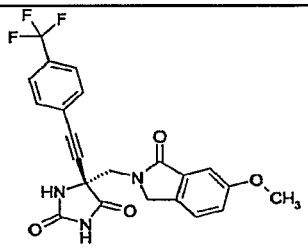
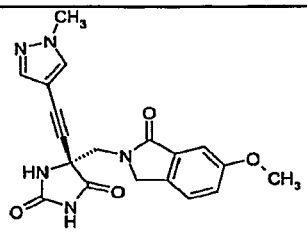
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
454		382.07	383.0[M+H]$^+$	A
455		382.07	383.0[M+H]$^+$	A
456		427.07	428.0[M+H]$^+$	A
457		407.16	408.1[M+H]$^+$	A
458		418.11	419.0[M+H]$^+$	A
459		443.11	444.1[M+H]$^+$	A

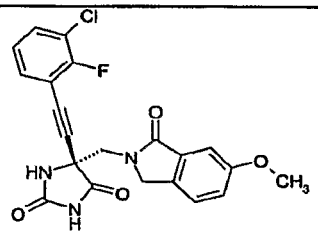
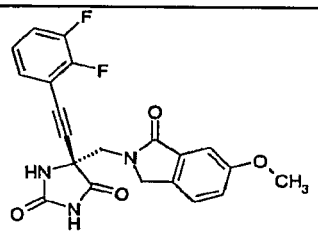
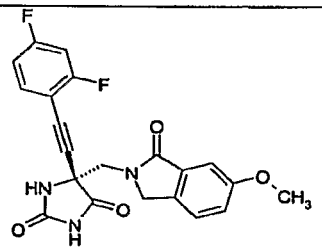
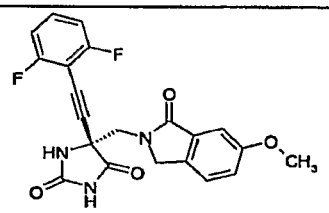
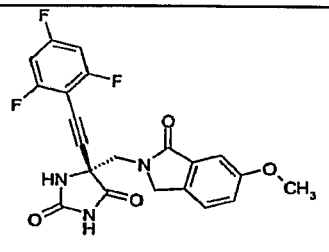
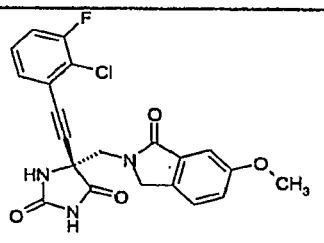
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
460		415.13	416.1[M+H]$^+$	A
461		429.09	430.1[M+H]$^+$	A
462		434.08	435.1[M+H]$^+$	A
463		381.08	382.1[M+H]$^+$	A
464		381.08	382.1[M+H]$^+$	A

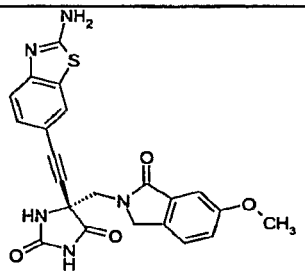
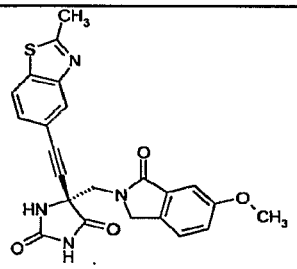
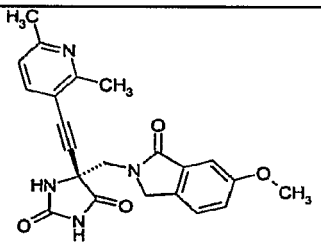
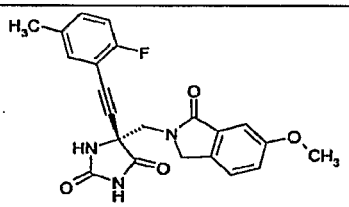
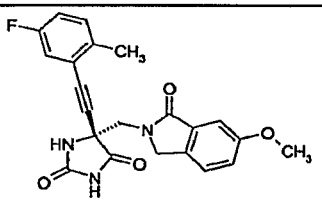
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
465		424.12	425.1[M+H]$^+$	A
466		429.09	430.1[M+H]$^+$	A
467		396.09	397.1[M+H]$^+$	A
468		377.11	378.1[M+H]$^+$	A
469		377.11	378.1[M+H]$^+$	A
470		427.13	428.0[M+H]$^+$	A

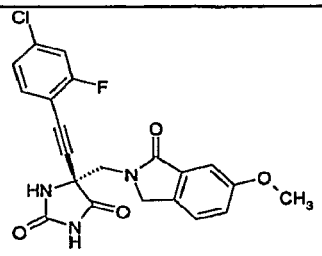
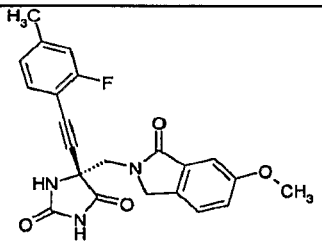
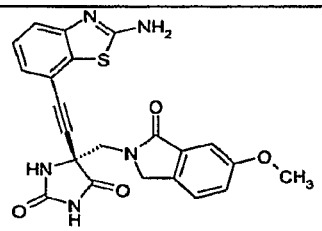
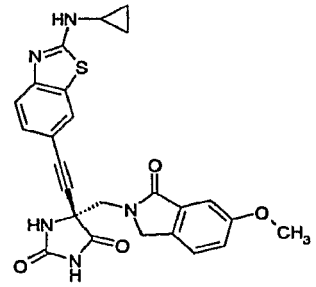
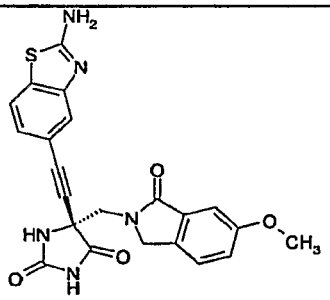
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
471		396.09	397.1[M+H]$^+$	A
472		416.15	417.2[M+H]$^+$	A
409C		456.15	457.1[M+H]$^+$	A
480		431.16	432.2[M+H]$^+$	A
481		401.11	402.1[M+H]$^+$	A

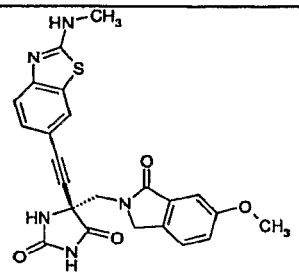
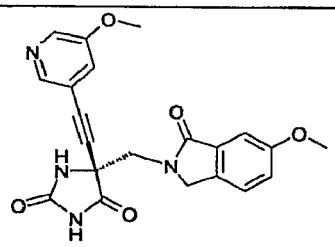
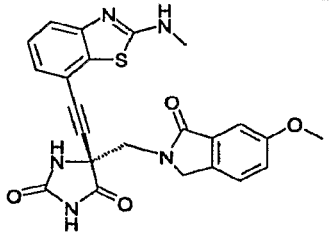
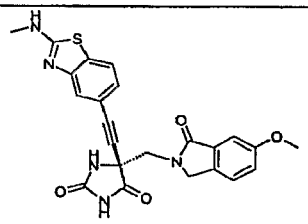
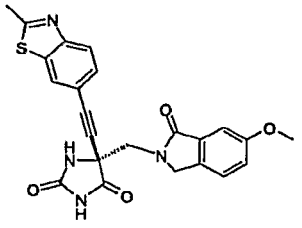
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
410B		445.18	446.2[M+H]$^+$	A
482		461.17	462.3[M+H]$^+$	A
482B		442.14	443.2[M+H]$^+$	A
482C		456.15	457.1[M+H]$^+$	A
411		393.37	394.1[M+H]$^+$	A
400B		376.37	377.0[M+H]$^+$	A

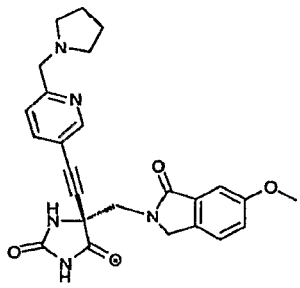
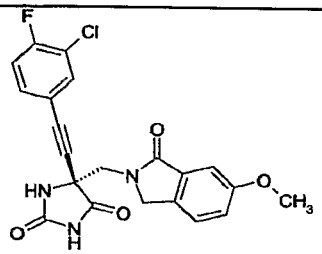
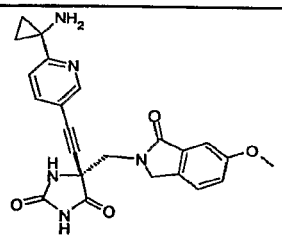
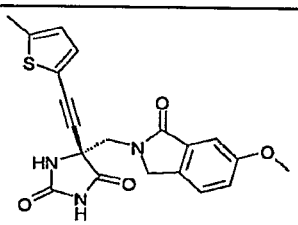
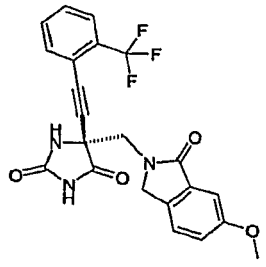
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
483		411.36	412.1[M+H]$^+$	A
484		459.37	460.1[M+H]$^+$	A
485		409.82	410.0[M+H]$^+$	A
486		443.38	444.1[M+H]$^+$	A
487		379.37	380.2[M+H]$^+$	A

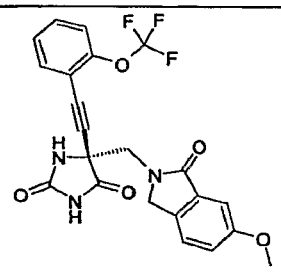
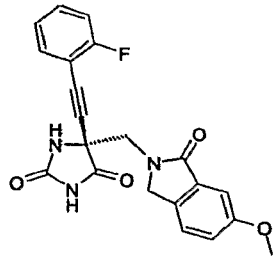
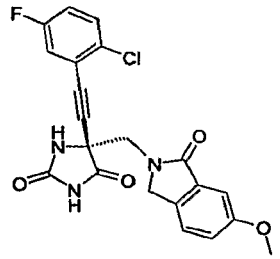
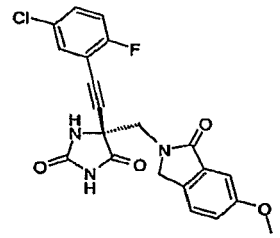
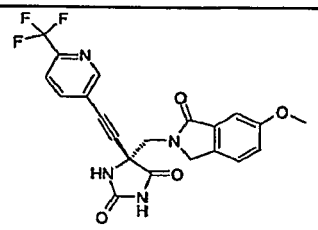
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
488		427.81	428.0[M+H]$^+$	A
489		411.36	412.1[M+H]$^+$	A
490		411.36	412.1[M+H]$^+$	A
491		411.36	412.0[M+H]$^+$	A
492		429.35	430.0[M+H]$^+$	A
493		427.81	428.0[M+H]$^+$	A

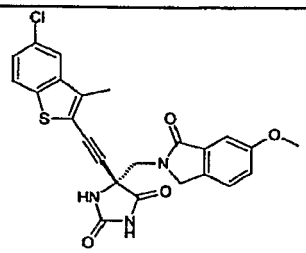
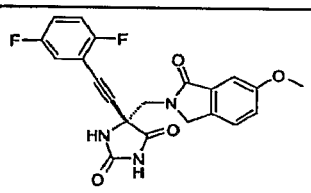
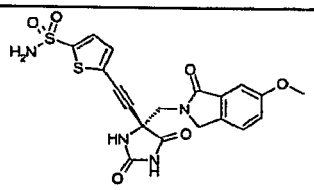
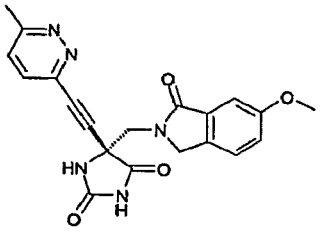
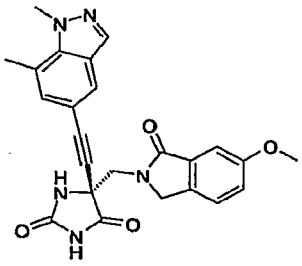
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
494		447.47	448.1[M+H]$^+$	A
495		446.48	447.1[M+H]$^+$	A
496		404.42	405.1[M+H]$^+$	A
497		407.39	408.1[M+H]$^+$	A
498		407.39	408.1[M+H]$^+$	A

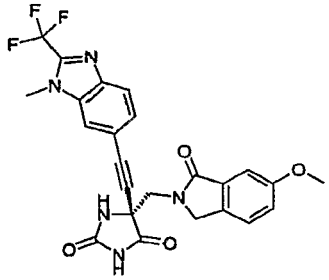
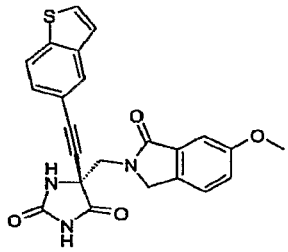
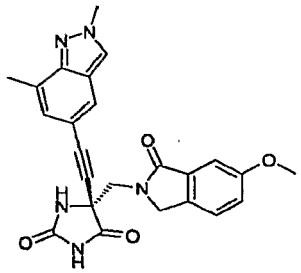
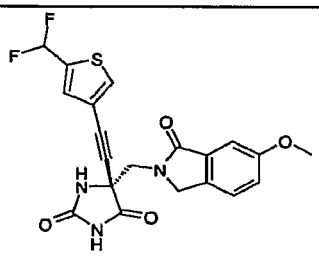
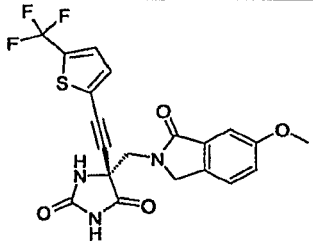
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
499		427.81	428.0[M+H]$^+$	A
500		407.39	408.1[M+H]$^+$	A
503		447.47	448.1[M+H]$^+$	A
504		487.53	488.0[M+H]$^+$	A
505		447.47	448.1[M+H]$^+$	A

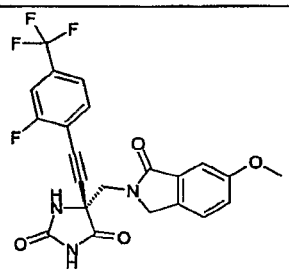
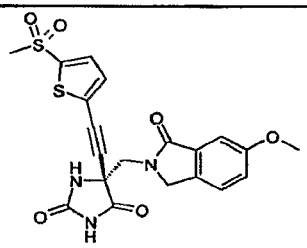
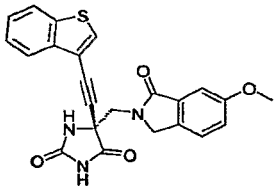
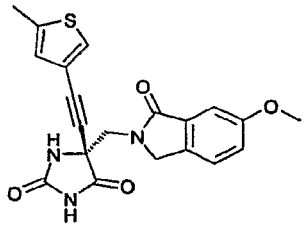
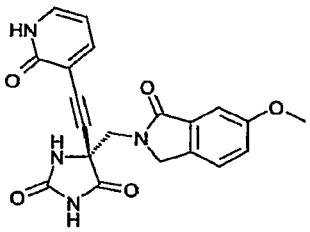
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
412D		461.49	462.1[M+H]$^+$	A
506		406.39	407.0[M+H]$^+$	A
507		461.49	462.1[M+H]$^+$	A
508		461.49	462.1[M+H]$^+$	A
509		446.48	447.1[M+H]$^+$	A

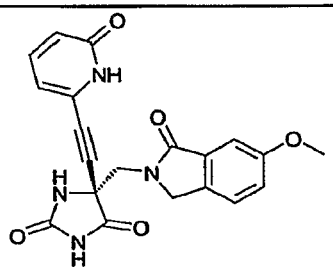
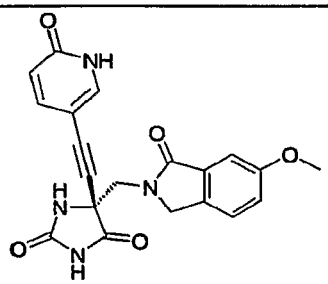
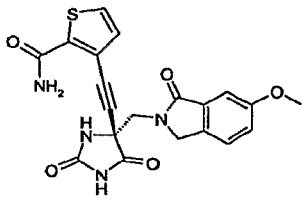
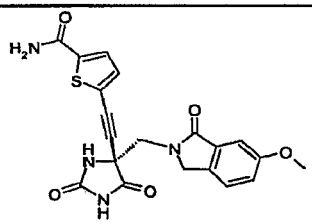
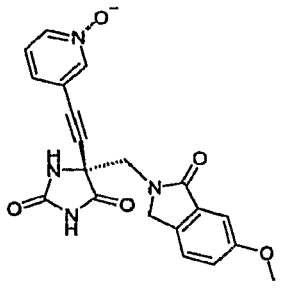
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
413D		459.50	460.2[M+H]$^+$	A
510		427.81	428.1[M+H]$^+$	A
414B		431.44	432.1[M+H]$^+$	B
513		395.09	396.1[M+H]$^+$	A
514		443.11	444.1[M+H]$^+$	A

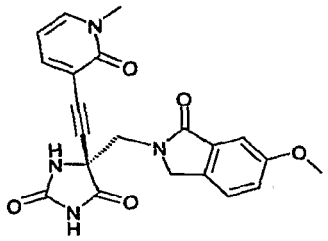
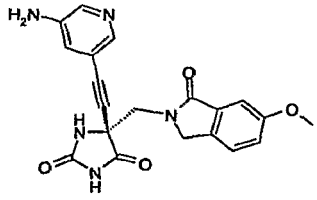
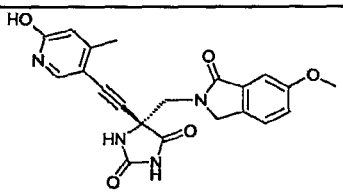
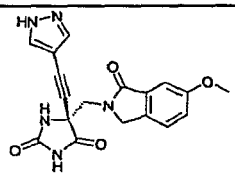
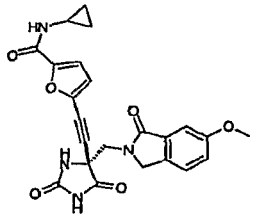
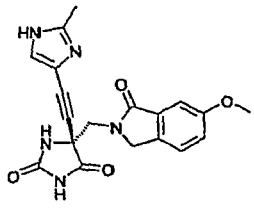
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
515		459.10	460.1[M+H]$^+$	A
516		393.11	394.1[M+H]$^+$	A
517		427.07	428.0[M+H]$^+$	A
518		427.07	428.0[M+H]$^+$	A
519		444.10	445.1[M+H]$^+$	A

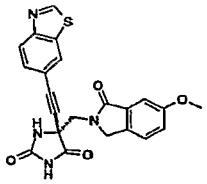
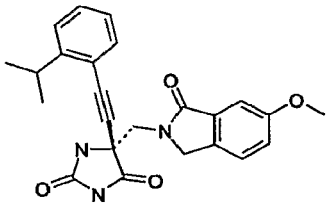
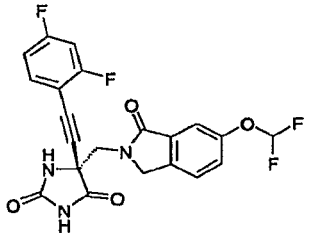
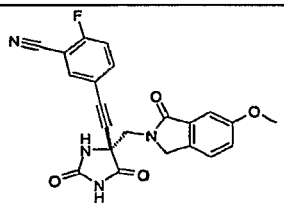
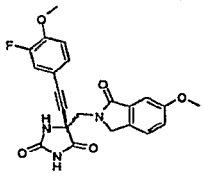
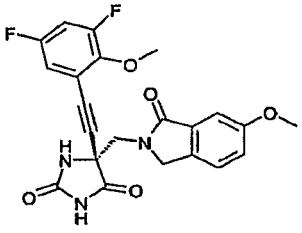
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
520		479.07	480.0[M+H]$^+$	A
521		411.10	412.0[M+H]$^+$	A
522		460.05	461.0[M+H]$^+$	A
523		391.13	392.2[M+H]$^+$	A
524		443.16	444.1[M+H]$^+$	A

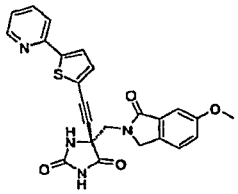
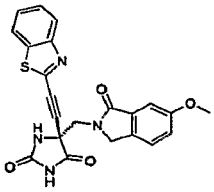
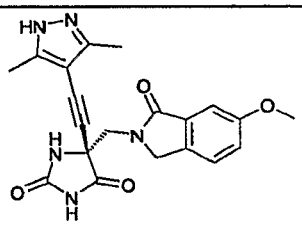
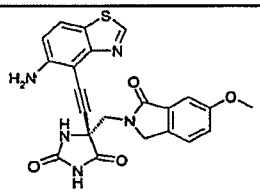
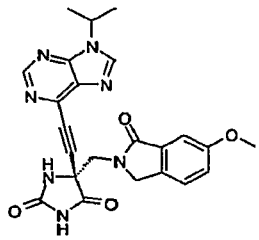
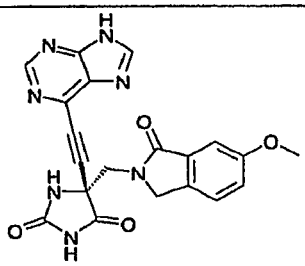
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
525		497.13	498.1[M+H]$^+$	A
526		431.09	432.1[M+H]$^+$	A
527		443.16	444.1[M+H]$^+$	A
528		431.08	432.1[M+H]$^+$	A
529		449.07	450.1[M+H]$^+$	A

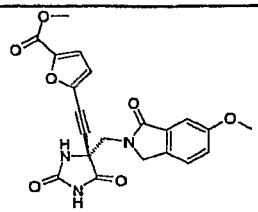
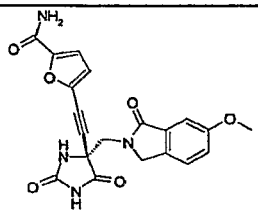
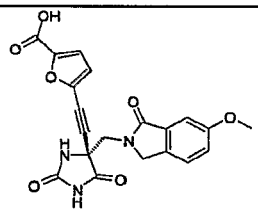
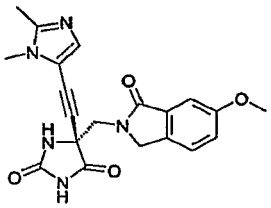
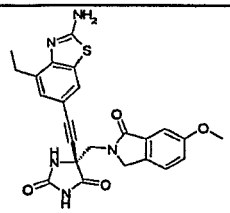
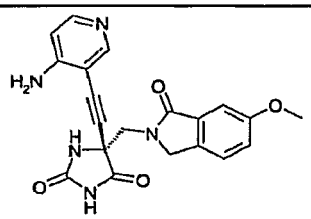
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
530		461.10	462.1[M+H]$^+$	A
531		459.06	460.0[M+H]$^+$	A
532		431.09	432.1[M+H]$^+$	A
533		395.09	396.1[M+H]$^+$	A
417C		392.11	393.1[M+H]$^+$	A

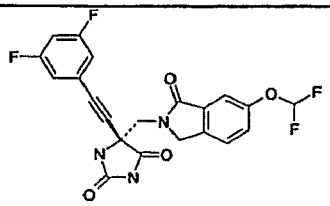
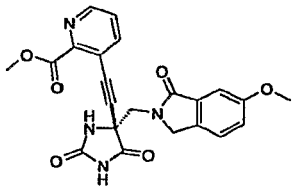
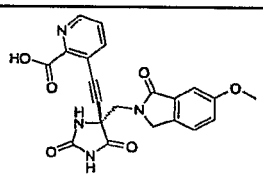
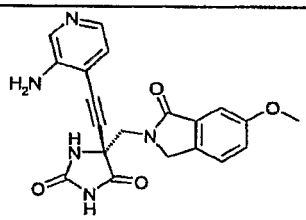
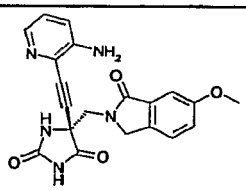
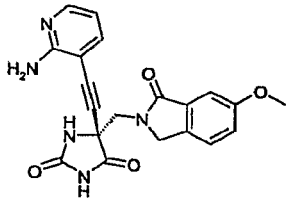
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
535		392.11	393.1[M+H]$^+$	A
536		392.11	393.1[M+H]$^+$	A
537		424.08	425.0[M+H]$^+$	A
538		424.08	425.0[M+H]$^+$	A
539		392.11	393.1[M+H]$^+$	A

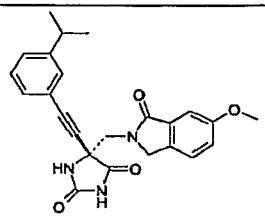
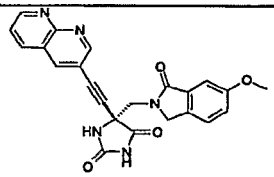
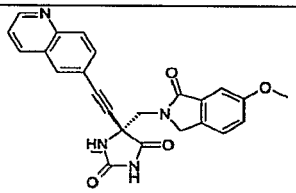
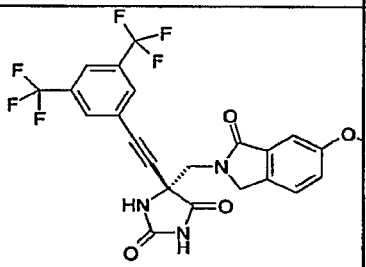
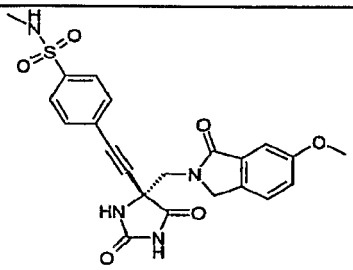
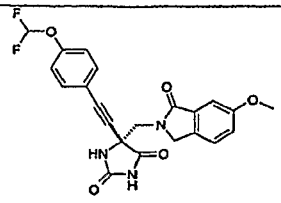
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
540		406.13	407.2[M+H]$^+$	A
554		391.13	392.2[M+H]$^+$	A
555		406.13	407.1[M+H]$^+$	A
900		365.11	366.2[M+H]$^+$	A
901		448.14	449.2[M+H]$^+$	A
902		379.13	380.2[M+H]$^+$	A

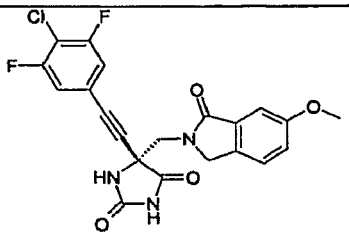
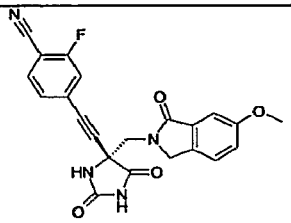
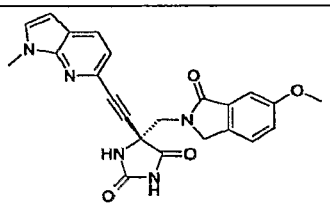
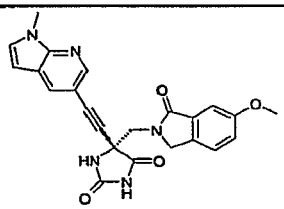
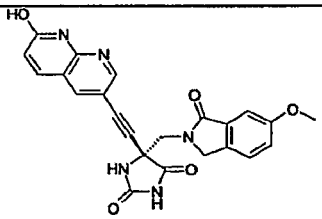
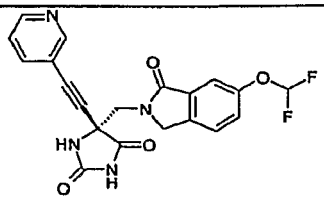
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
903		432.09	433.2[M+H]$^+$	A
904		417.17	418.2[M+H]$^+$	A
905		447.08	448.2[M+H]$^+$	A
906		418.11	419.2[M+H]$^+$	A
907		423.12	424.2[M+H]$^+$	A
908		441.11	442.2[M+H]$^+$	A

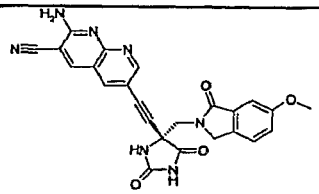
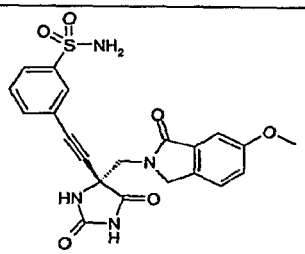
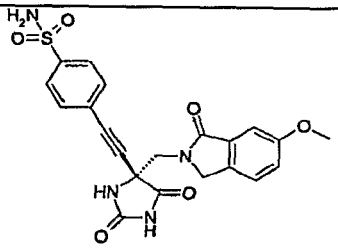
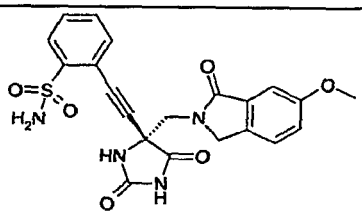
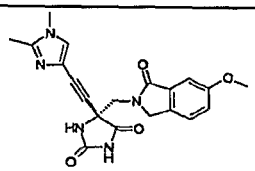
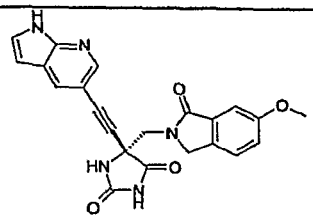
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
909		458.10	459.3[M+H]$^+$	A
910		432.09	433.2[M+H]$^+$	A
911		393.14	394.2[M+H]$^+$	A
912		447.10	448.2[M+H]$^+$	A
913		459.17	460.3[M+H]$^+$	A
914		417.12	418.2[M+H]$^+$	A

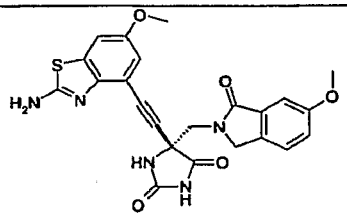
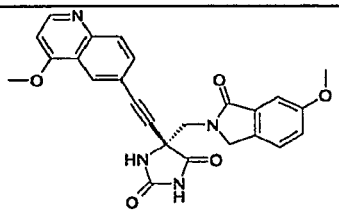
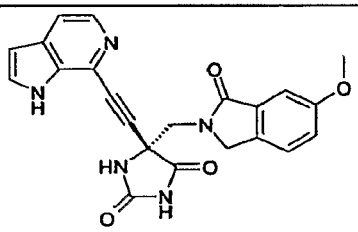
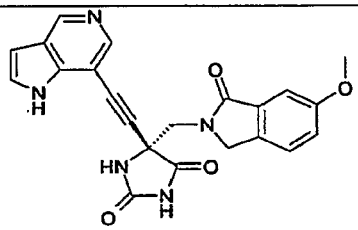
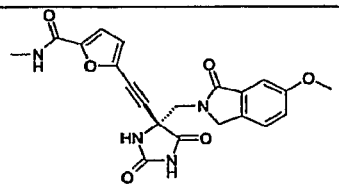
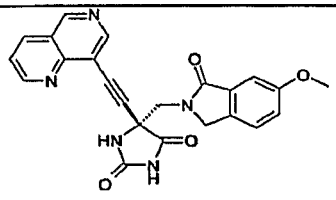
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
915		423.11	424.2[M+H]$^+$	A
916		408.11	409.2[M+H]$^+$	A
917		409.09	410.2[M+H]$^+$	A
918		393.14	394.2[M+H]$^+$	A
919		475.13	476.3[M+H]$^+$	A
920		391.13	392.2[M+H]$^+$	A

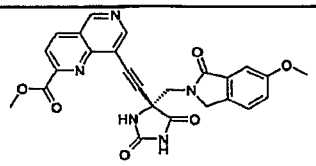
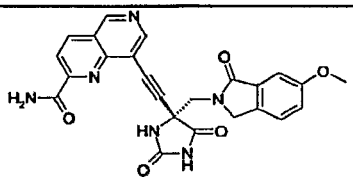
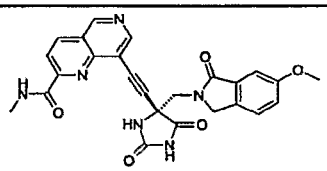
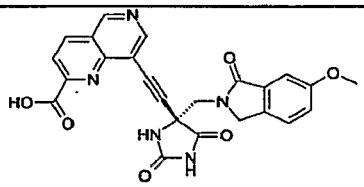
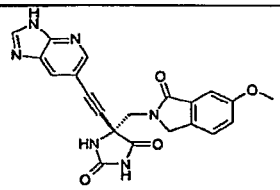
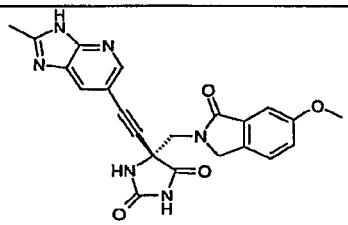
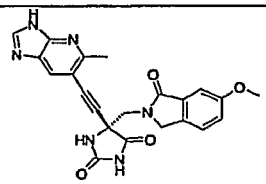
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
922		447.08	448.2[M+H]$^+$	A
924		434.12	435.2[M+H]$^+$	A
925		421.11	421.2 M$^+$	A
926		391.13	392.2[M+H]$^+$	A
928		391.13	392.2[M+H]$^+$	B
930		392.14	392.2[M+H]$^+$	A

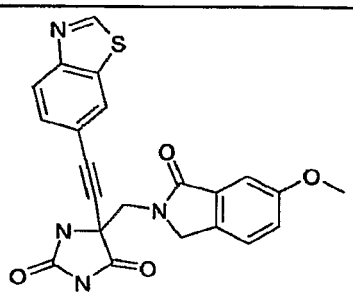
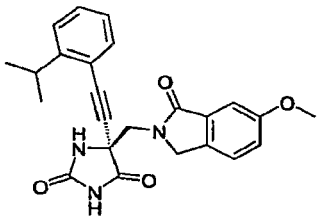
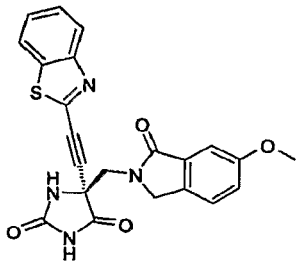
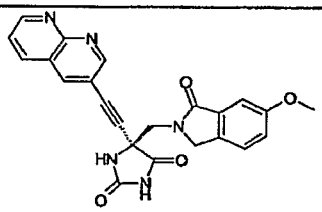
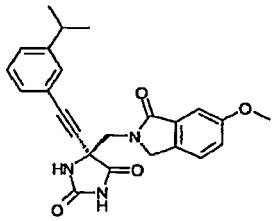
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
931		417.17	418.2[M+H]$^+$	A
932		427.13	428.2[M+H]$^+$	A
933		426.13	427.2[M+H]$^+$	A
934		511.10	512.3[M+H]$^+$	A
935		482.13	483.3[M+H]$^+$	A
937		441.11	442.2[M+H]$^+$	A

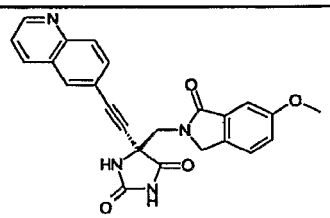
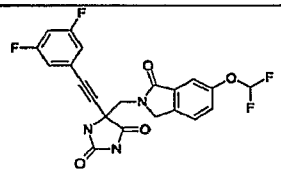
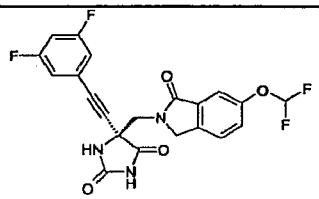
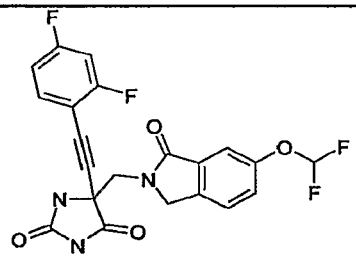
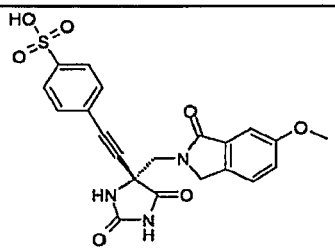
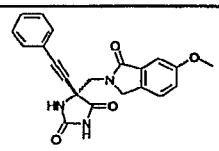
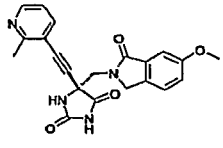
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
938		445.06	446.2[M+H]$^+$	A
939		418.11	419.2[M+H]$^+$	A
940		429.14	430.2[M+H]$^+$	A
941		429.14	430.2[M+H]$^+$	A
942		443.12	444.2[M+H]$^+$	A
943		412.10	413.2[M+H]$^+$	A

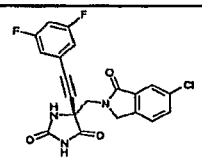
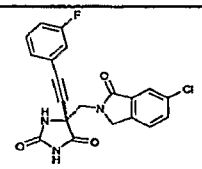
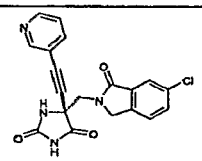
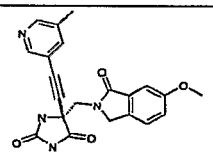
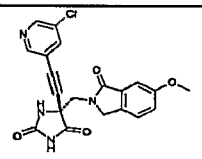
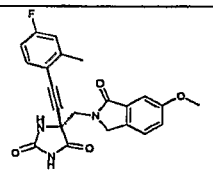
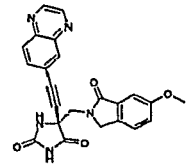
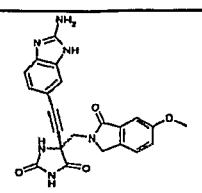
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
944		467.13	468.3[M+H]$^+$	A
945		454.09	455.3[M+H]$^+$	A
946		454.09	455.3[M+H]$^+$	A
947		454.09	455.3[M+H]$^+$	A
948		393.14	394.2[M+H]$^+$	A
949		415.13	416.2[M+H]$^+$	A

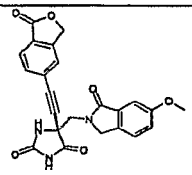
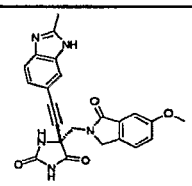
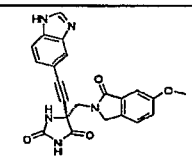
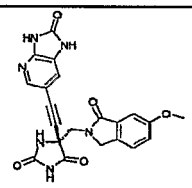
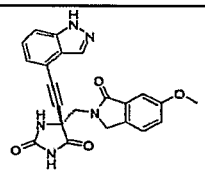
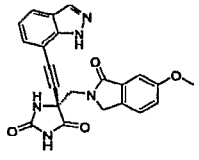
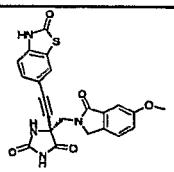
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
950		477.11	478.3[M+H]$^+$	A
951		456.14	457.3[M+H]$^+$	A
952		415.13	416.2[M+H]$^+$	A
953		415.13	416.2[M+H]$^+$	A
954		422.12	423.2[M+H]$^+$	A
955		427.13	428.2[M+H]$^+$	A

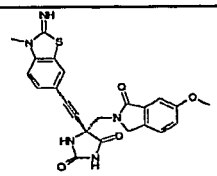
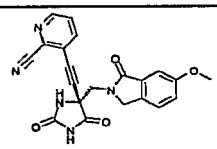
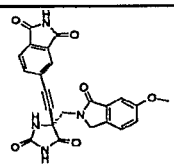
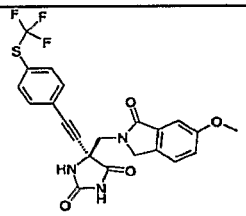
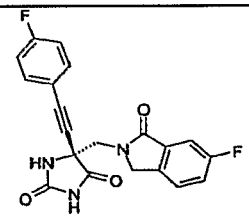
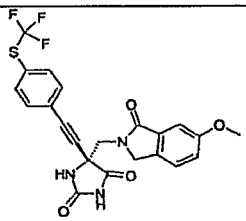
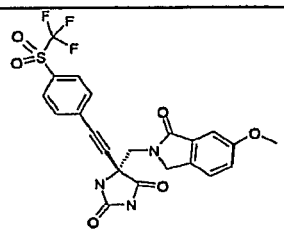
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
956		485.13	485.3[M+H]$^+$	A
957		470.13	471.3[M+H]$^+$	A
958		484.15	485.3[M+H]$^+$	A
959		471.12	472.3[M+H]$^+$	A
960		416.39	417.2[M+H]$^+$	A
961		430.14	431.2[M+H]$^+$	A
962		430.14	431.2[M+H]$^+$	A

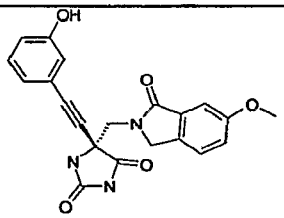
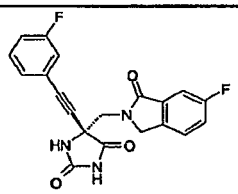
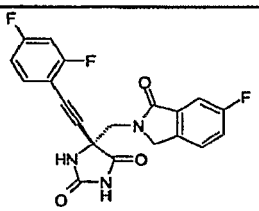
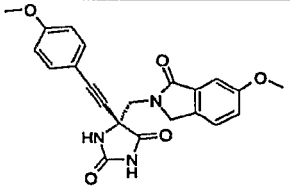
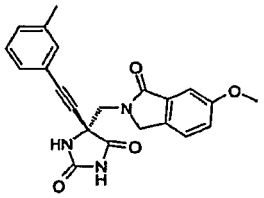
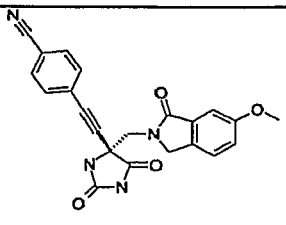
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
963		432.09	433.2[M+H]$^+$	A
964		417.17	418.2[M+H]$^+$	B
965		432.09	433.2[M+H]$^+$	C
966		427.13	428.2[M+H]$^+$	C
967		417.17	418.2[M+H]$^+$	C

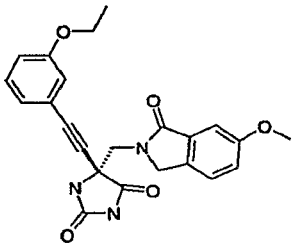
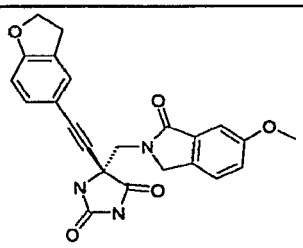
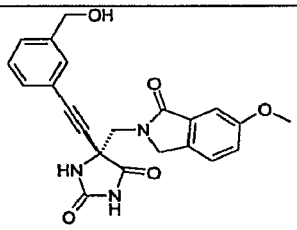
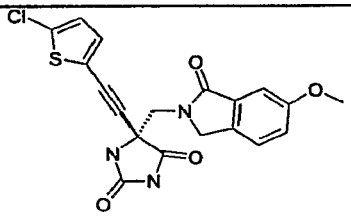
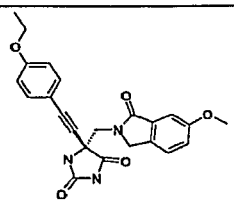
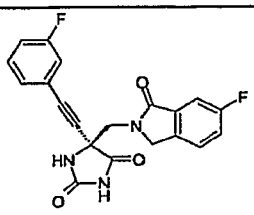
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
968		426.13	427.2[M+H]$^+$	C
969		447.08	448.2[M+H]$^+$	A
970		447.08	448.2[M+H]$^+$	D
971		447.08	448.2[M+H]$^+$	A
973		455.08	456.3[M+H]$^+$	A
1002		375.12	376.2 [M+H]$^+$	A
1003		390.13	391.2 [M+H]$^+$	A

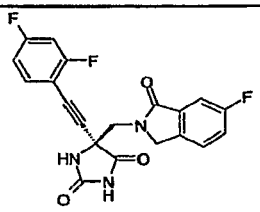
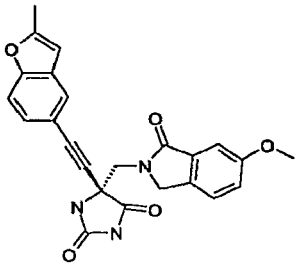
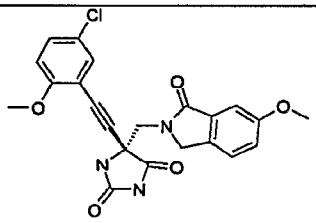
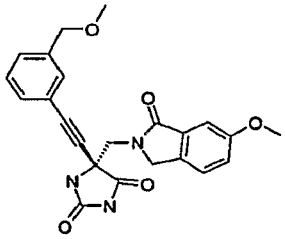
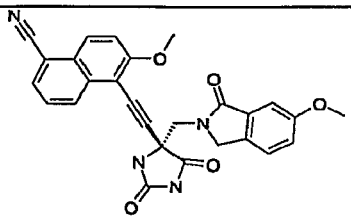
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1003B		415.05	416.2 $[M+H]^+$	A
1003C		397.06	398.2 $[M+H]^+$	A
1004		380.07	381.2 $[M+H]^+$	A
1005		390.13	391.2 $[M+H]^+$	A
1006		410.08	411.2 $[M+H]^+$	A
1007		407.13	408.2 $[M+H]^+$	A
1008		427.13	428.2 $[M+H]^+$	A
1009		430.14	431.2 $[M+H]^+$	A

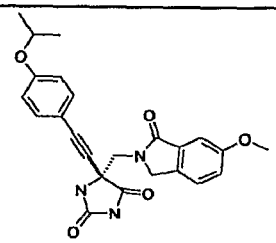
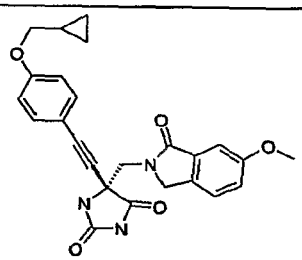
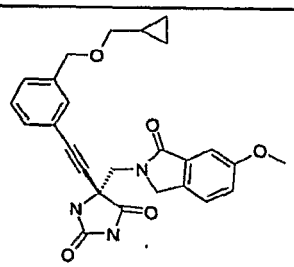
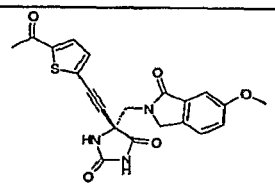
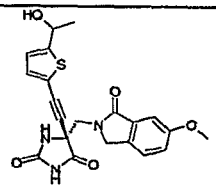
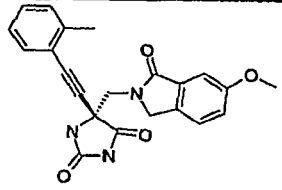
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1010		431.11	432.2 $[M+H]^+$	A
1011		429.14	430.2 $[M+H]^+$	A
1012		415.13	416.2 $[M+H]^+$	A
1013		432.12	433.2 $[M+H]^+$	A
1014		415.13	416.2 $[M+H]^+$	A
1015		415.13	416.2 $[M+H]^+$	A
1016		448.08	449.2 $[M+H]^+$	A

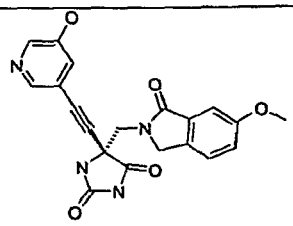
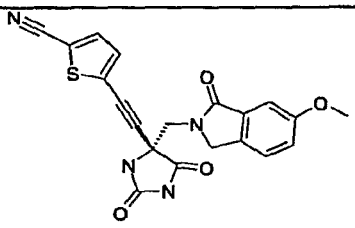
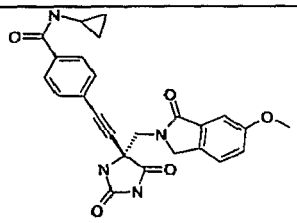
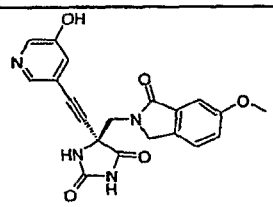
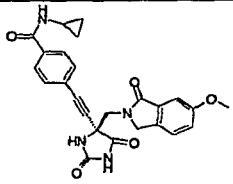
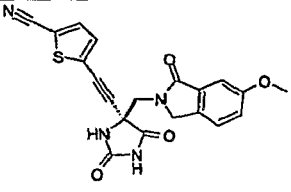
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1017		461.12	462.3 $[M+H]^+$	A
1018		401.11	402.2 $[M+H]^+$	A
1019		444.11	445.2 $[M+H]^+$	A
1036		475.44	476.3 $[M+H]^+$	D
1037		381.33	382.3 $[M+H]^+$	A
1038		475.44	476.3 $[M+H]^+$	A
1039		507.44	508.3 $[M+H]^+$	B

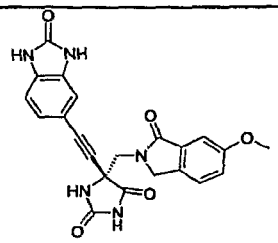
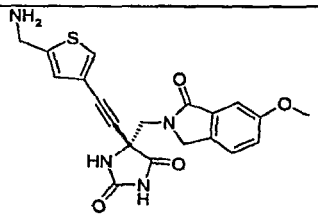
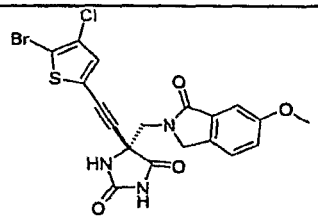
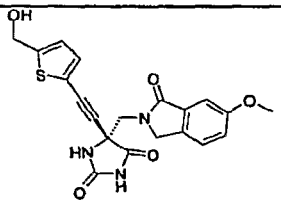
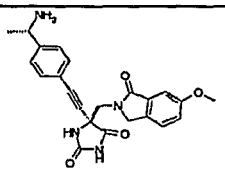
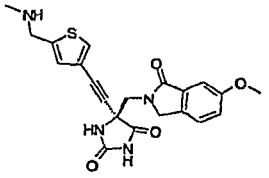
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1040		391.38	392.2 $[M+H]^+$	A
1041		381.33	382.2 $[M+H]^+$	A
1042		399.32	400.2 $[M+H]^+$	A
1043		405.40	406.2 $[M+H]^+$	A
1044		389.40	390.2 $[M+H]^+$	A
1045		400.39	401.2 $[M+H]^+$	A

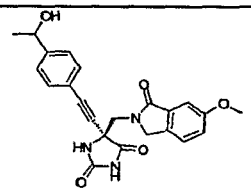
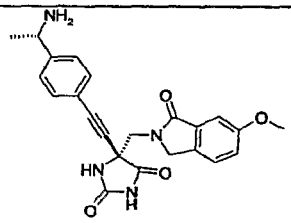
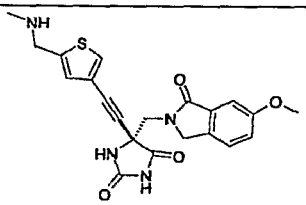
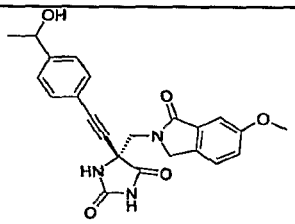
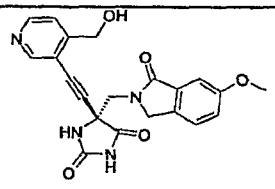
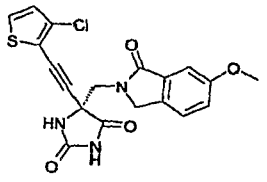
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1046		419.43	420.2 $[M+H]^+$	A
1047		417.41	418.2 $[M+H]^+$	A
1048		405.40	406.2 $[M+H]^+$	A
1049		415.85	416.2 $[M+H]^+$	A
1050		419.43	420.2 $[M+H]^+$	A
1051		381.33	382.2 $[M+H]^+$	C

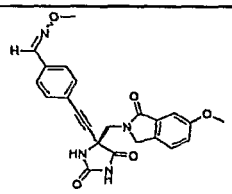
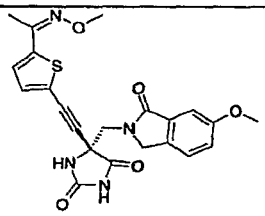
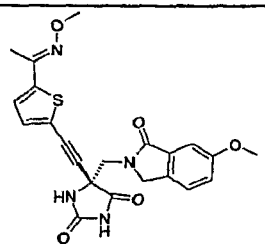
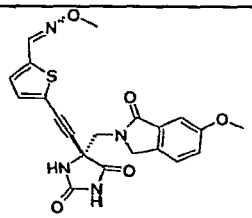
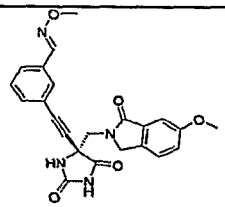
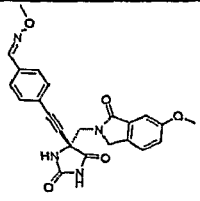
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1052		399.32	400.2 $[M+H]^+$	C
1053		429.42	430.2 $[M+H]^+$	A
1054		439.85	440.2 $[M+H]^+$	A
1055		419.43	420.2 $[M+H]^+$	A
1056		480.47	481.3 $[M+H]^+$	A

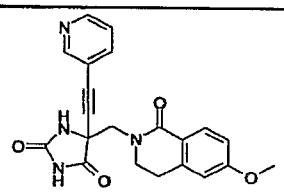
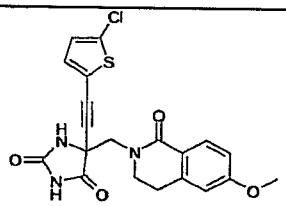
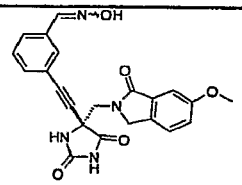
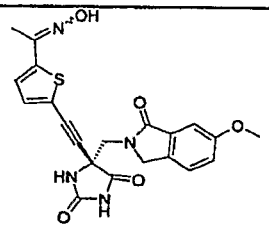
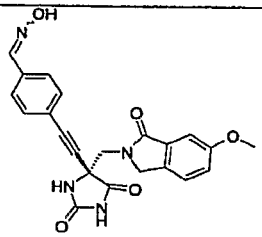
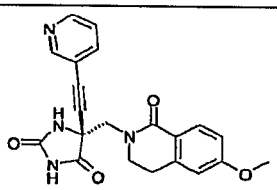
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1057		433.46	434.2 $[M+H]^+$	A
1058		445.47	446.2 $[M+H]^+$	A
1059		459.49	460.3 $[M+H]^+$	A
1060		423.44	424.2 $[M+H]^+$	A
1061		425.46	426.2 $[M+H]^+$	A
1062		389.40	390.2 $[M+H]^+$	A

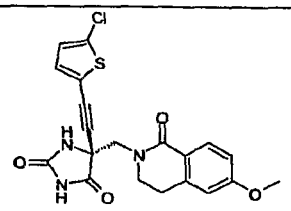
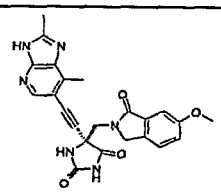
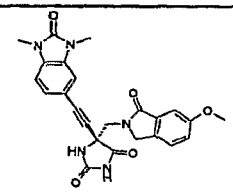
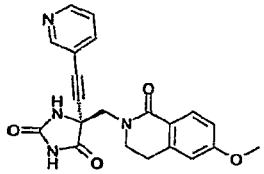
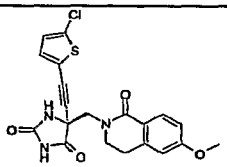
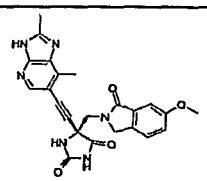
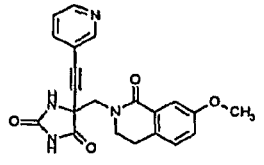
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1063		392.36	393.2 $[M+H]^+$	A
1064		406.41	407.2 $[M+H]^+$	A
1065		458.47	459.3 $[M+H]^+$	A
1066		392.36	393.2 $[M+H]^+$	D
1067		458.47	459.3 $[M+H]^+$	D
1068		406.41	407.2 $[M+H]^+$	D

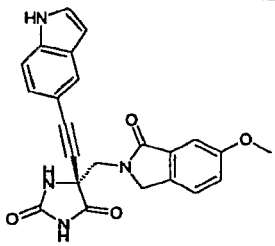
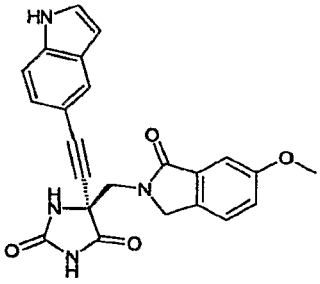
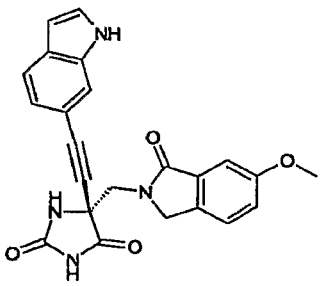
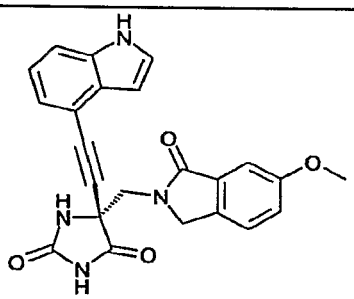
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1069		431.40	432.2 $[M+H]^+$	A
1070		410.45	411.2 $[M+H]^+$	A
1071		494.95	496.3 $[M+H]^+$	A
1072		411.43	412.2 $[M+H]^+$	A
1073		418.45	419.2 $[M+H]^+$	D
1074		424.47	425.2 $[M+H]^+$	D

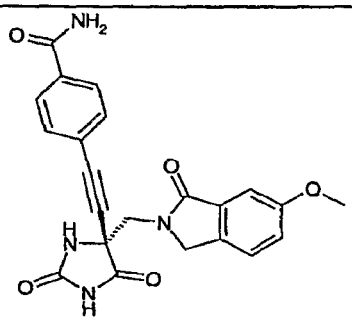
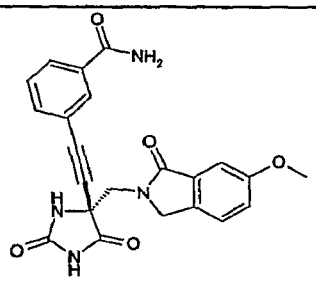
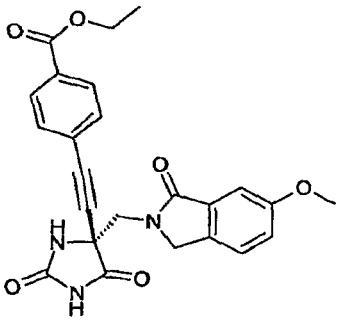
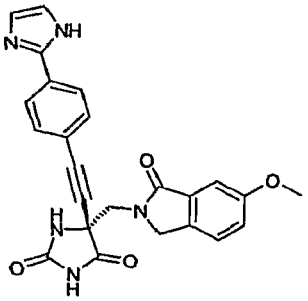
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1075		419.43	420.2 $[M+H]^+$	D
1076		418.45	419.2 $[M+H]^+$	A
1077		424.47	425.2 $[M+H]^+$	A
1078		419.43	420.2 $[M+H]^+$	A
1079		406.39	407.2 $[M+H]^+$	A
1080		415.85	416.2 $[M+H]^+$	A

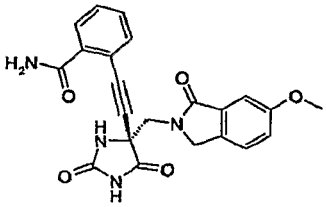
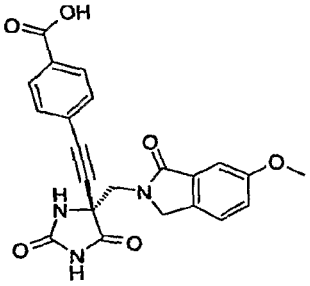
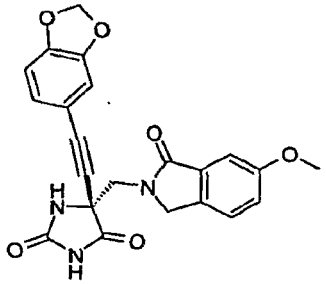
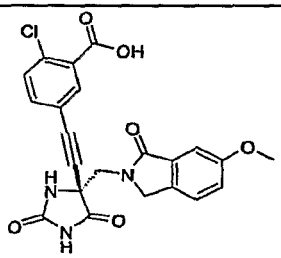
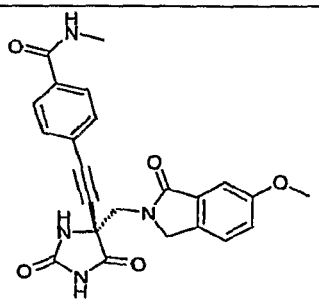
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1081		432.43	433.2 $[M+H]^+$	D
1082		452.48	453.2 $[M+H]^+$	A
1083		452.48	453.2 $[M+H]^+$	A
1084		438.46	439.2 $[M+H]^+$	A
1085		432.43	433.2 $[M+H]^+$	A
1086		432.43	433.2 $[M+H]^+$	A

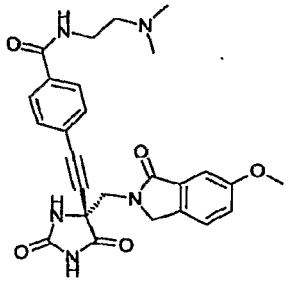
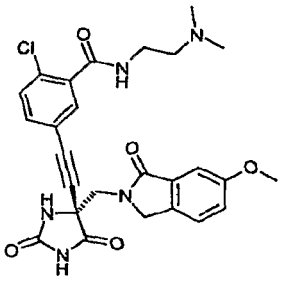
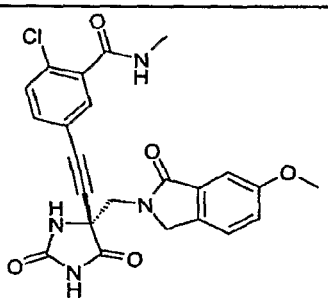
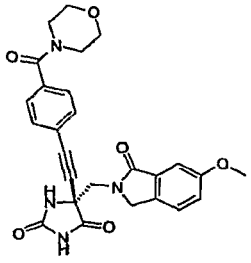
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1087		390.39	391.2 $[M+H]^+$	A
1088		429.88	430.2 $[M+H]^+$	B
1089		418.40	419.2 $[M+H]^+$	A
1090		438.46	439.2 $[M+H]^+$	A
1091		418.40	419.2 $[M+H]^+$	A
1092		390.39	391.2 $[M+H]^+$	A

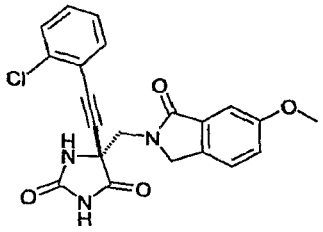
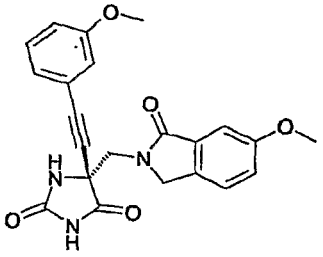
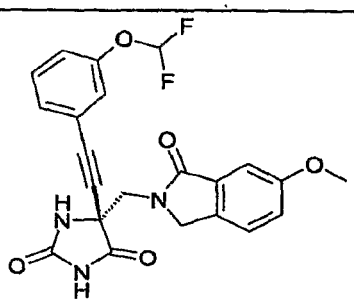
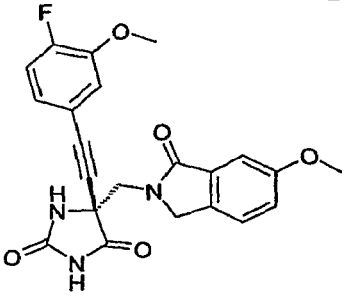
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1093		429.88	430.2 $[M+H]^+$	A
1094		444.44	445.2 $[M+H]^+$	D
1095		459.45	460.3 $[M+H]^+$	A
1096		390.39	391.2 $[M+H]^+$	D
1097		429.88	430.2 $[M+H]^+$	D
1098		444.44	445.2 $[M+H]^+$	A
1099		390.39	391.2 $[M+H]^+$	n/a

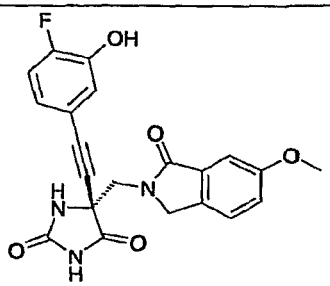
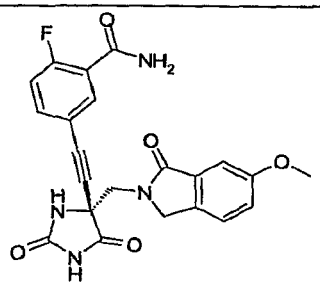
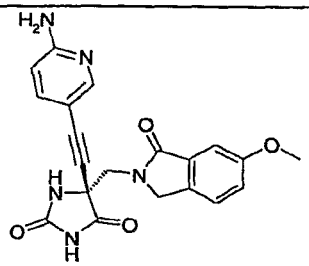
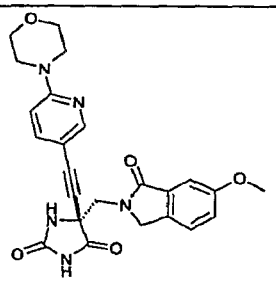
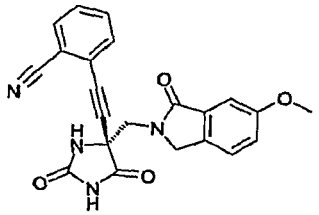
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1129		414.1	415.2[M+H]$^+$	A
1130		414.1	415.2[M+H]$^+$	B
1131		414.1	415.2[M+H]$^+$	A
1132		414.1	415.2[M+H]$^+$	A

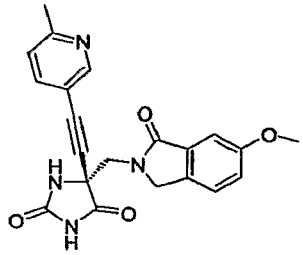
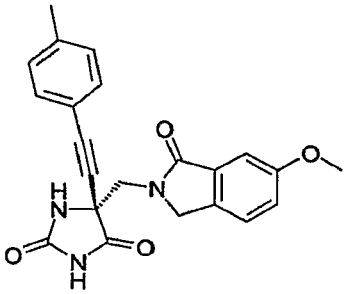
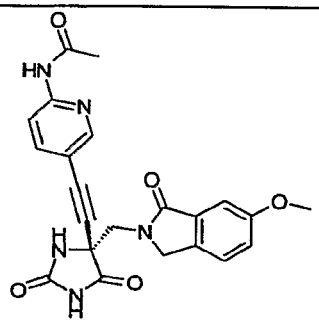
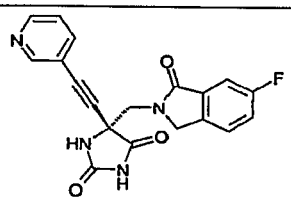
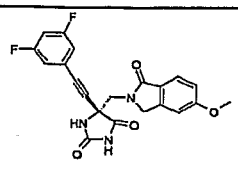
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1133		418.13	419.2[M+H]$^+$	A
1134		418.13	419.2[M+H]$^+$	A
1135		447.14	448.2[M+H]$^+$	A
1136		441.1	442.2[M+H]$^+$	A

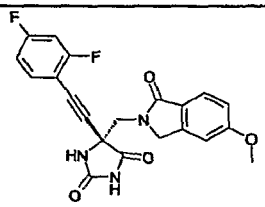
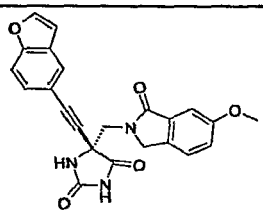
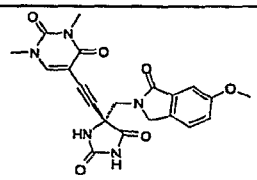
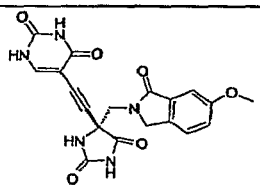
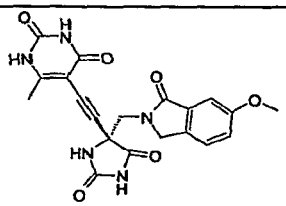
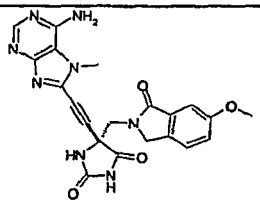
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1137		418.1	419.2[M+H]$^+$	A
1138 1380269		419.1	420.2[M+H]$^+$	A
1139		419.1	420.2[M+H]$^+$	A
1140		453.1	454.2[M+H]$^+$	A
1141		432.1	433.2[M+H]$^+$	A

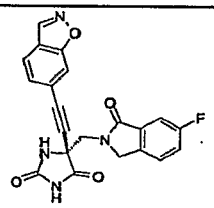
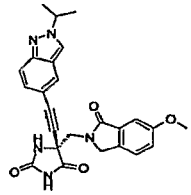
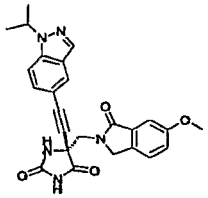
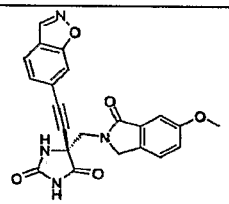
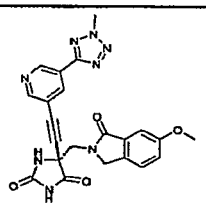
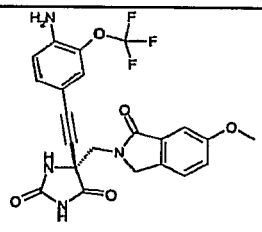
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1142		489.2	490.3[M+H]$^+$	A
1143		523.2	524.3[M+H]$^+$	A
1144		466.1	467.3[M+H]$^+$	A
1145		488.2	489.3[M+H]$^+$	A

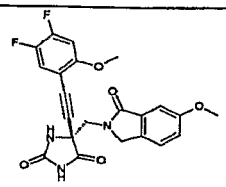
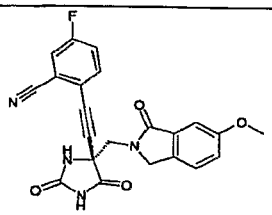
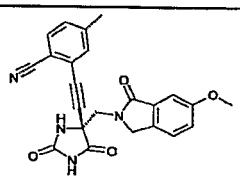
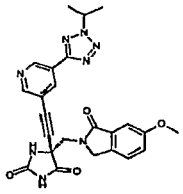
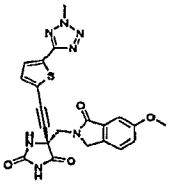
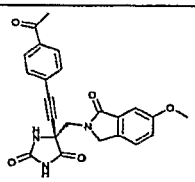
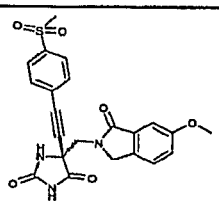
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1146		409.1	410.2[M+H]$^+$	A
1147		405.1	406.2[M+H]$^+$	A
1148		441.1	442.2[M+H]$^+$	A
1149		423.1	424.2[M+H]$^+$	A

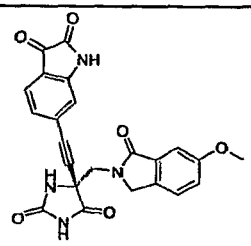
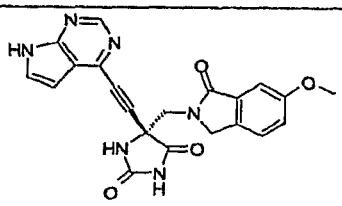
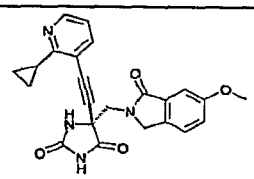
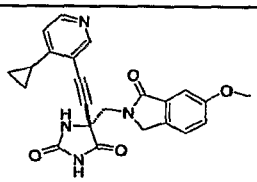
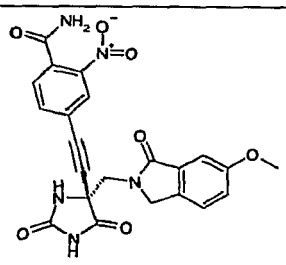
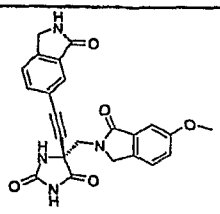
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1150		409.1	410.2[M+H]$^+$	A
1151		436.1	437.2[M+H]$^+$	A
1152		391.1	392.2[M+H]$^+$	A
1153		461.2	462.3[M+H]$^+$	A
1154		400.1	401.2[M+H]$^+$	A

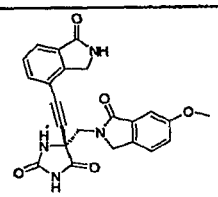
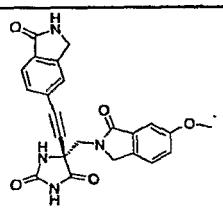
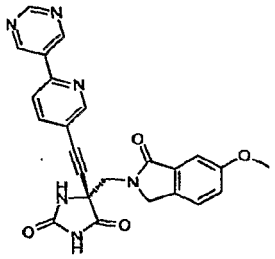
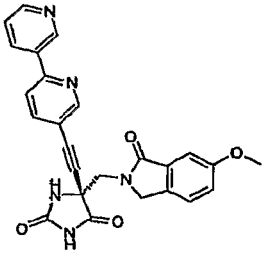
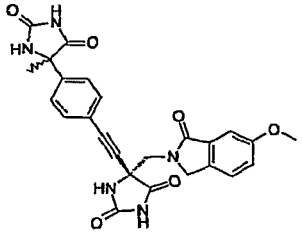
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1155		390.1	391.2[M+H]$^+$	A
1156		389.1	390.2[M+H]$^+$	A
1157		433.1	434.2[M+H]$^+$	A
1200		364.3	365.2[M+H]$^+$	A
1201		411.4	412.2[M+H]$^+$	A

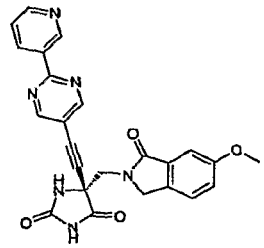
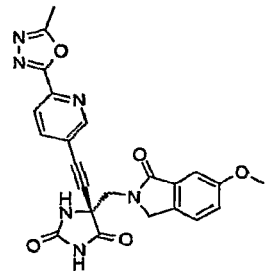
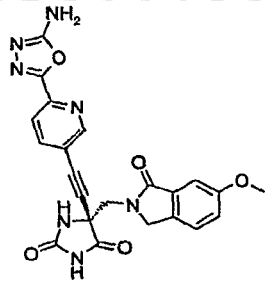
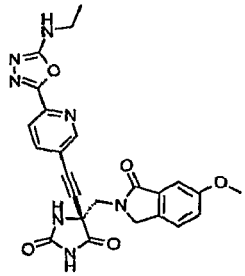
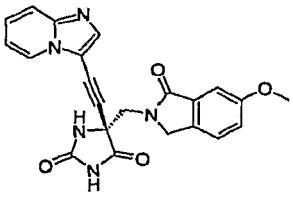
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1202		411.4	412.2[M+H]$^+$	A
1203		415.4	416.2[M+H]$^+$	A
1204		437.4	438.2[M+H]$^+$	A
1205		409.4	410.2[M+H]$^+$	A
1206		495.5	496.2[M+H]$^+$	A
1208		446.4	447.3[M+H]$^+$	A

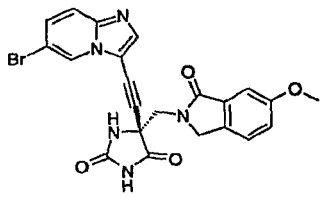
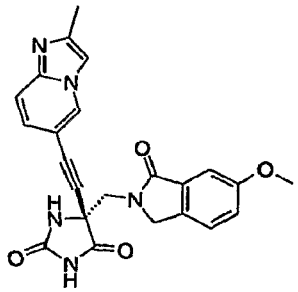
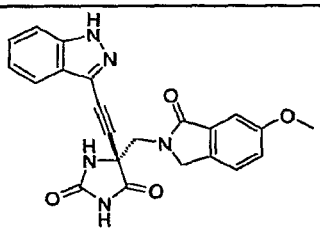
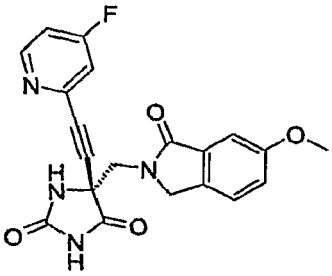
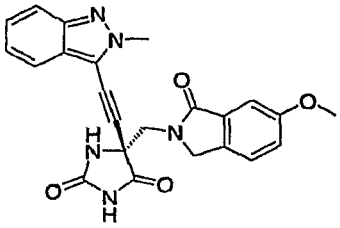
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1211		404.4	405.2[M+H]$^+$	A
1212		457.5	458.3[M+H]$^+$	A
1213		457.5	458.3[M+H]$^+$	A
1214		416.4	417.3[M+H]$^+$	A
1215		458.4	459.3[M+H]$^+$	A
1216		474.4	475.3[M+H]$^+$	A

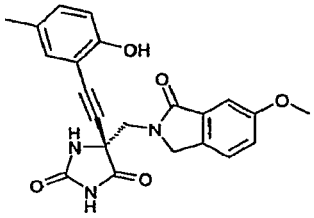
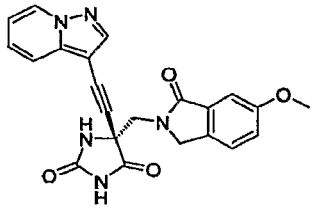
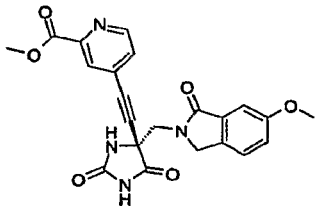
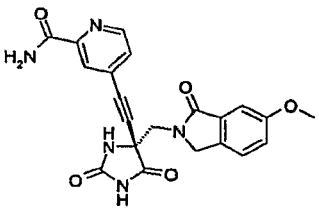
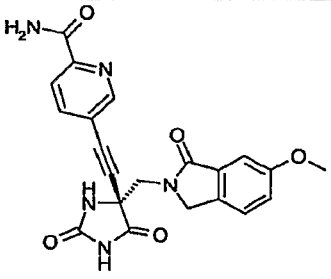
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1217		441.4	442.2[M+H]$^+$	A
1218		418.4	419.2[M+H]$^+$	A
1219		414.4	415[M+H]$^+$	A
1220		486.5	487.5[M+H]$^+$	A
1220A		463.5	464.5[M+H]$^+$	A
1220B		417.4	418.4[M+H]$^+$	A
1220C		453.5	454.5[M+H]$^+$	D

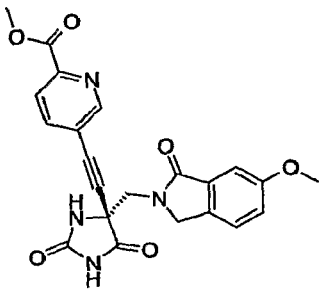
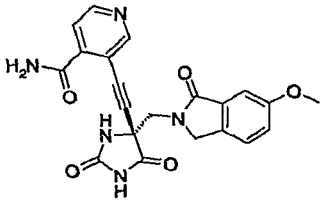
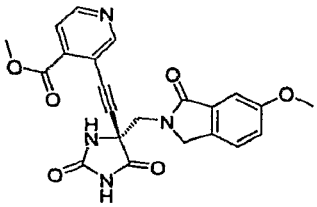
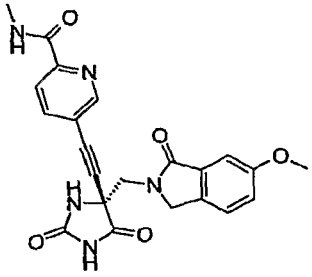
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1220D		444.11	445.2 $[M+H]^+$	A
1220E		416.12	417.2 $[M+H]^+$	A
1221		416.15	417.2 $[M+H]^+$	A
1222		416.15	417.2 $[M+H]^+$	A
1250		463.11	464.3 $[M+H]^+$	A
1251		430.13	431.2 $[M+H]^+$	A

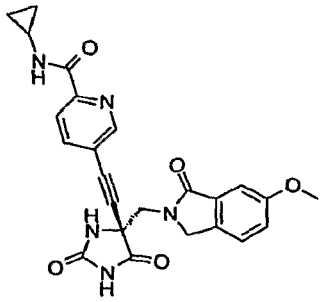
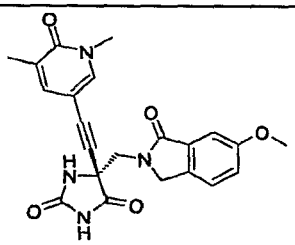
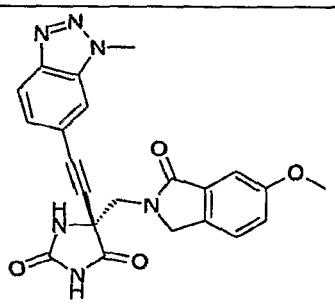
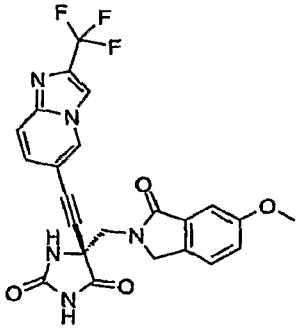
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1252		430.13	431.2 $[M+H]^+$	A
1253		430.13	431.2 $[M+H]^+$	A
1254		454.14	455.3 $[M+H]^+$	A
1255		453.14	454.2 $[M+H]^+$	0.75
1256		487.15	488.3 $[M+H]^+$	0.03

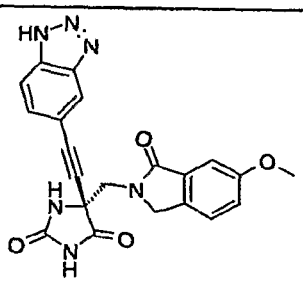
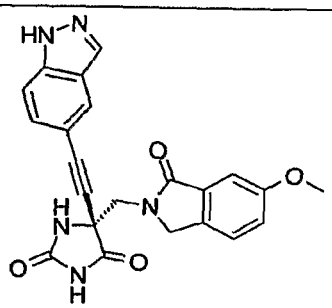
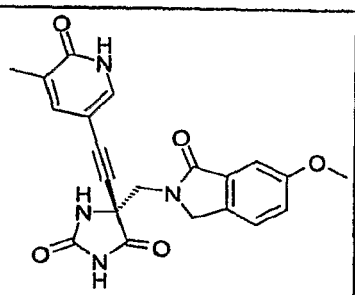
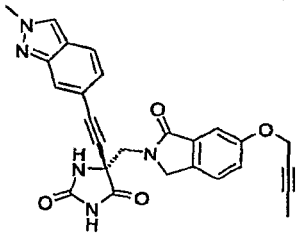
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1256C		454.14	455.2 $[M+H]^+$	A
1500		458.42	459.4$[M+H]^+$	A
1501		459.41	460.5$[M+H]^+$	A
1502		487.46	488.5$[M+H]^+$	A
1503		415.40	416.5$[M+H]^+$	A

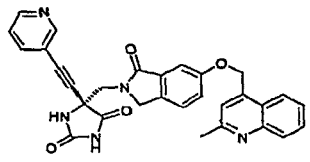
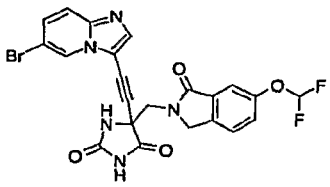
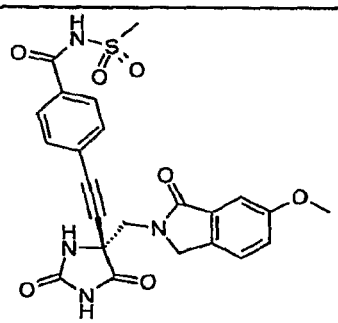
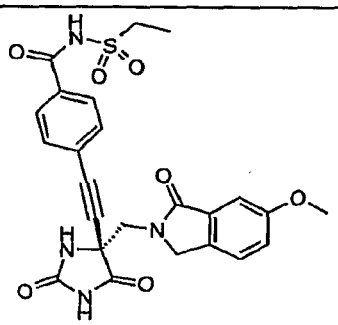
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1504		494.29	495.4[M+H]$^+$	A
1505		429.42	430.5[M+H]$^+$	A
1506		415.40	416.4[M+H]$^+$	A
1507		394.35	395.4[M+H]$^+$	A
1508		429.42	430.4[M+H]$^+$	A

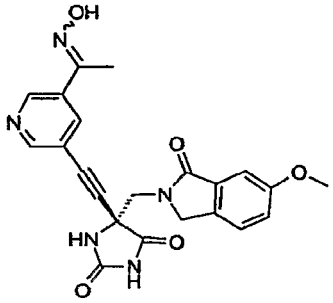
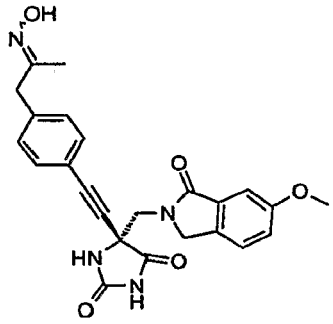
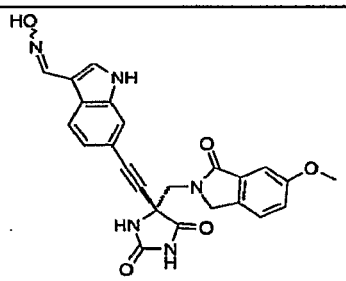
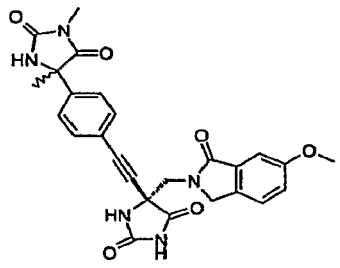
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1509		405.40	406.4[M+H]$^+$	A
1510		415.40	416.5[M+H]$^+$	A
1511		434.40	435.5[M+H]$^+$	A
1512		419.39	420.4[M+H]$^+$	A
1513		419.39	420.4[M+H]$^+$	A

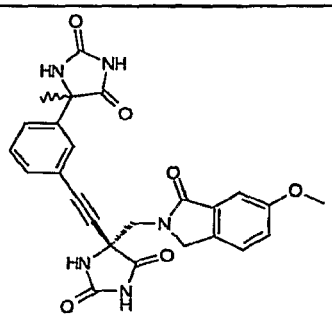
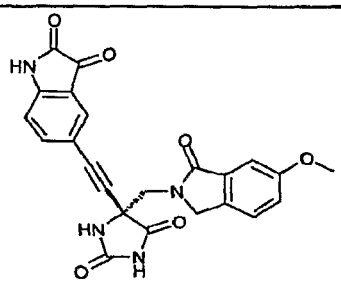
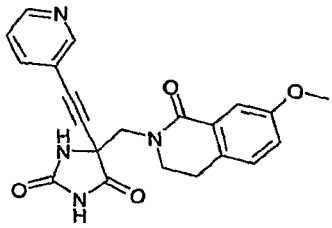
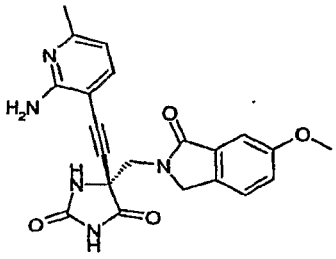
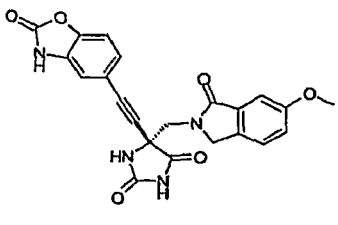
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1514		434.40	435.5[M+H]$^+$	A
1515		419.39	420.4[M+H]$^+$	A
1516		434.40	435.5[M+H]$^+$	A
1517		433.41	434.4[M+H]$^+$	A

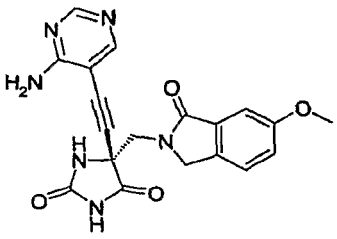
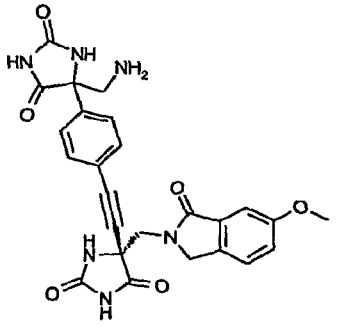
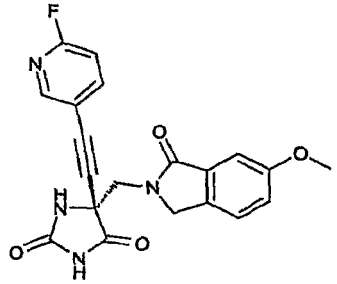
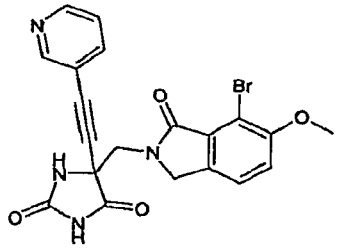
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1518		459.45	460.5[M+H]$^+$	A
1519		420.41	421.4[M+H]$^+$	A
1520		430.41	431.4[M+H]$^+$	A
1521		483.4	484.4[M+H]$^+$	A

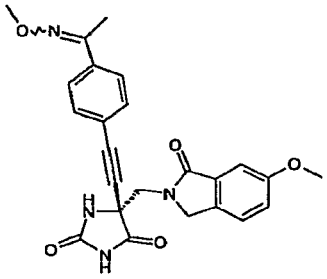
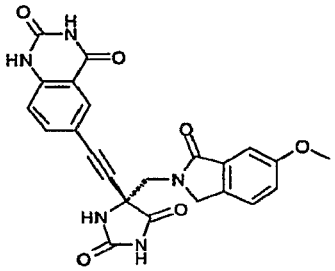
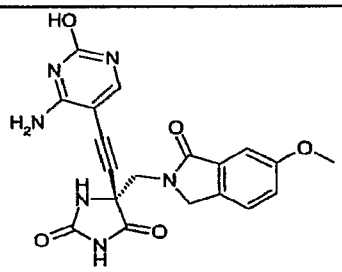
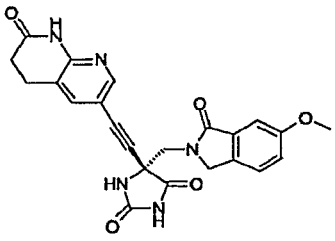
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1522		416.38	417.5[M+H]$^+$	A
1523		415.40	416.4[M+H]$^+$	A
1524		406.39	407.4[M+H]$^+$	A
1533		467.47	468.5[M+H]$^+$	A

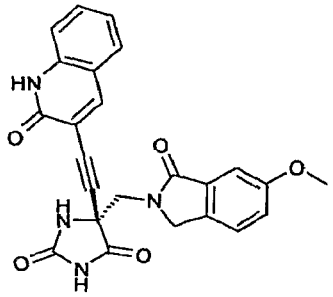
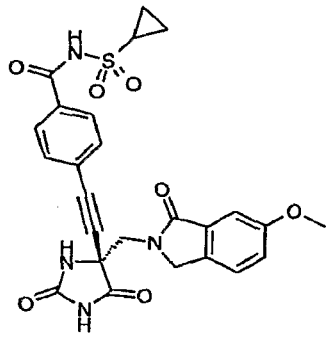
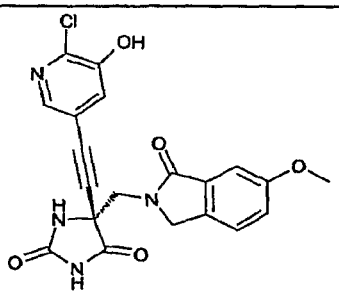
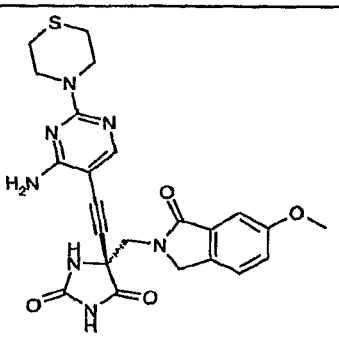
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1534		517.53	518.5[M+H]$^+$	A
1535		530.28	531.4[M+H]$^+$	B
1550		496.11	497.3 [M+H]$^+$	B
1551		510.12	511.3 [M+H]$^+$	A

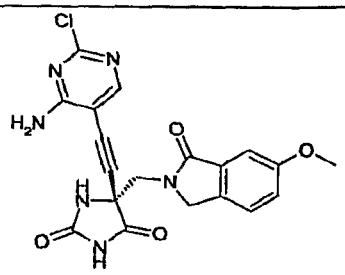
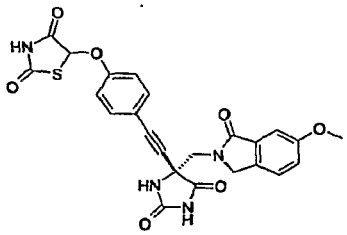
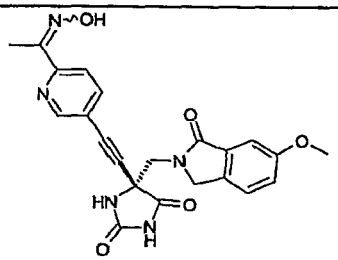
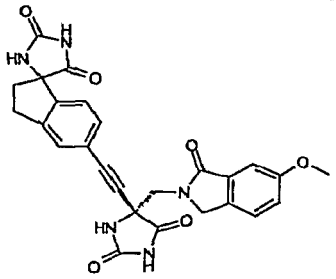
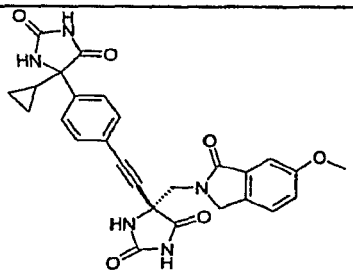
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1552		433.14	434.2 $[M+H]^+$	A
1553		446.16	447.2 $[M+H]^+$	A
1554		457.14	458.3 $[M+H]^+$	A
1555		501.16	502.3$[M+H]^+$	A

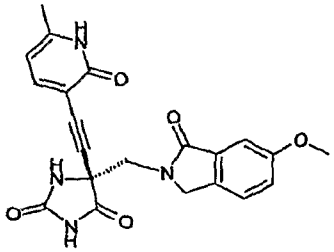
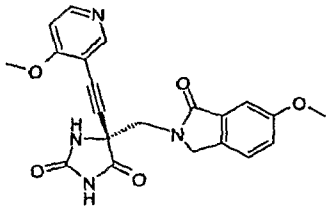
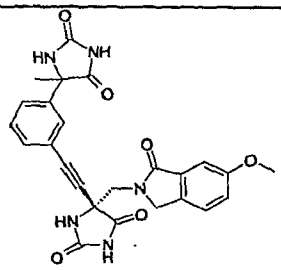
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1556		487.15	488.3[M+H]$^+$	A
1557		444.11	445.2[M+H]$^+$	A
1558		390.13	391.2 [M+H]$^+$	B
1559		405.14	406.2[M+H]$^+$	A
1560		432.11	433.2[M+H]$^+$	A

Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1561		392.12	393.2[M+H]$^+$	A
1562		502.16	503.3[M+H]$^+$	A
1563		394.35	395.2[M+H]$^+$	A
1564		455.26	455.3[M+H]$^+$	B

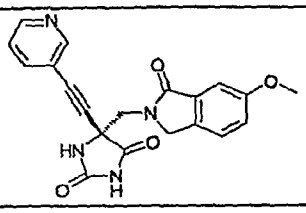
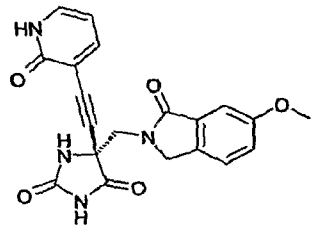
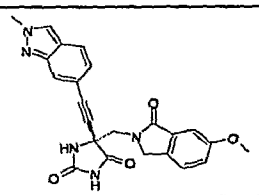
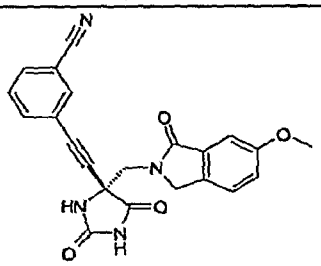
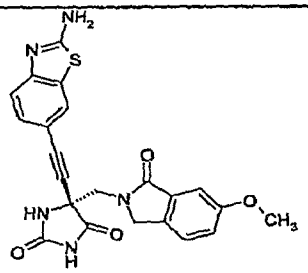
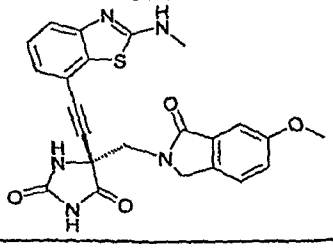
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1565		446.45	447.2[M+H]$^+$	A
1566		459.12	460.3[M+H]$^+$	A
1567		408.12	409.2[M+H]$^+$	A
1568		445.14	446.2[M+H]$^+$	A

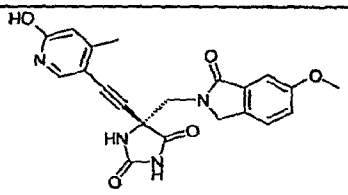
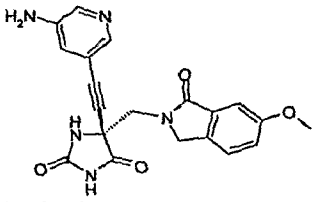
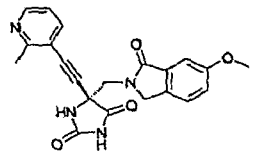
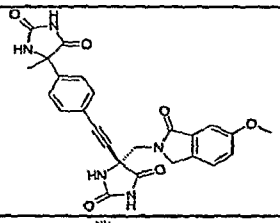
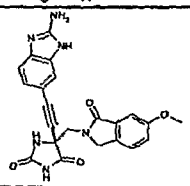
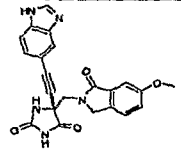
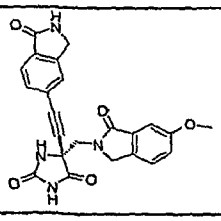
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1569		442.13	443.2[M+H]$^+$	A
1570		522.12	523.3 [M+H]$^+$	A
1571		426.80	427.2 [M+H]$^+$	A
1572		493.15	494.3[M+H]$^+$	A

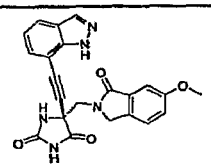
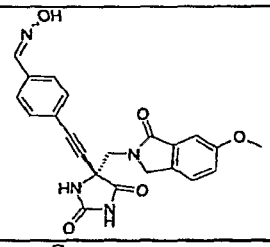
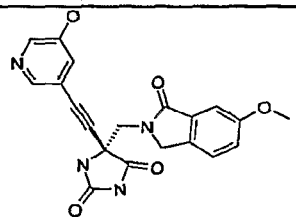
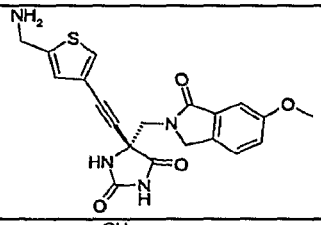
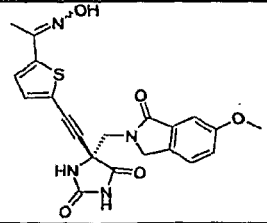
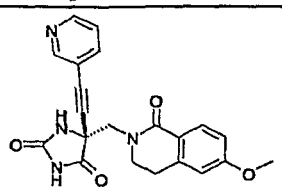
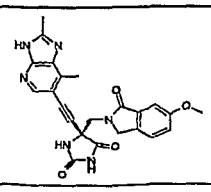
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1573		426.08	427.2[M+H]$^+$	A
1574		506.09	507.3[M+H]$^+$	A
1575		433.14	434.2[M+H]$^+$	A
1576		499.15	500.3[M+H]$^+$	A
1577		513.16	514.3[M+H]$^+$	A

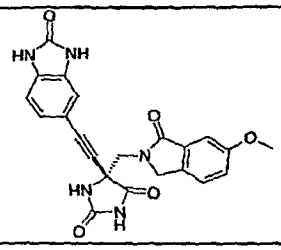
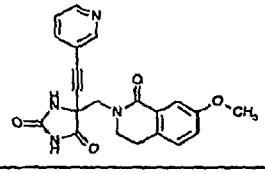
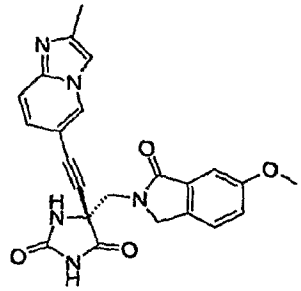
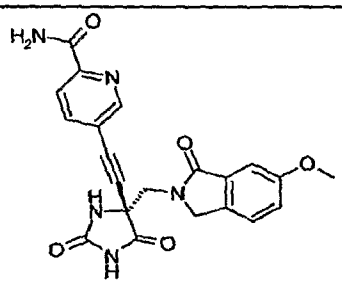
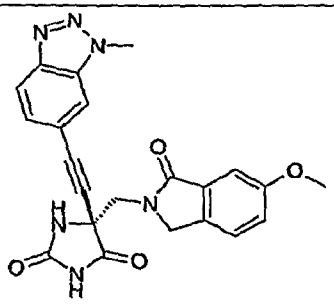
Compound ID	Structures	Exact Mass	Mass Obsvd	Ki Rating
1578		406.13	407.1[M+H]$^+$	A
1579		406.13	407.0[M+H]$^+$	A
1580		487.15	488.3[M+H]$^+$	A

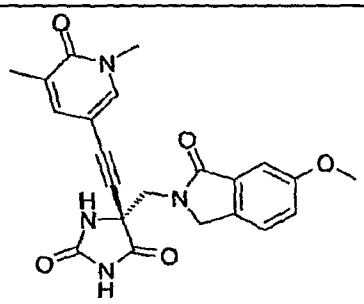
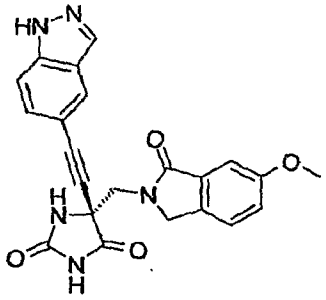
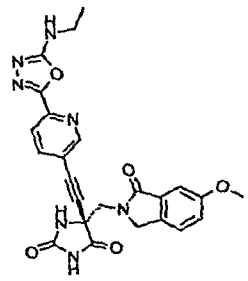
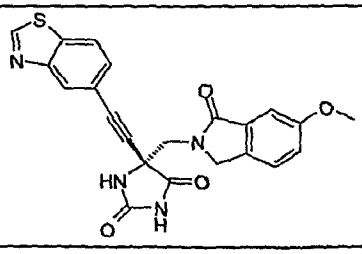
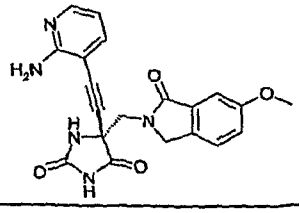
In another embodiment, the compounds of Formula (I) are selected from the group consisting of;

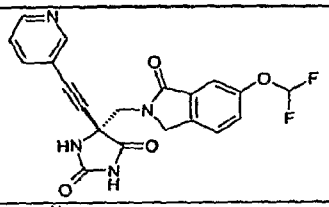
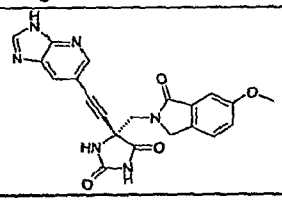
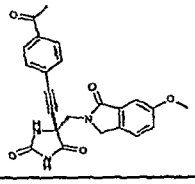
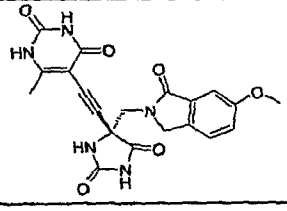
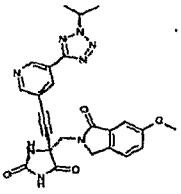
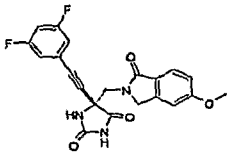
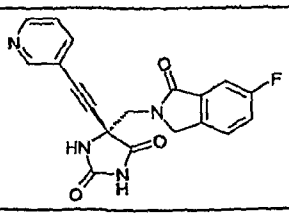
Compound ID	Structures
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417C	
424	
447	
494	
507	

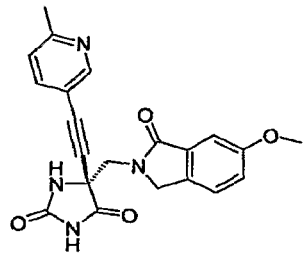
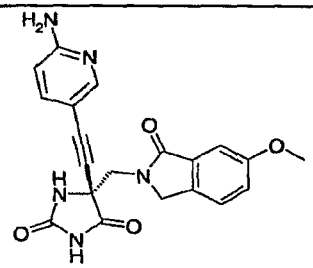
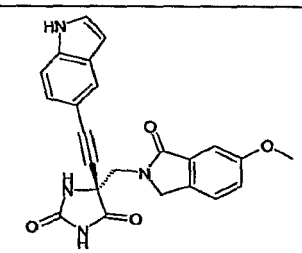
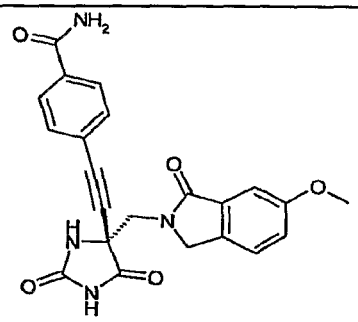
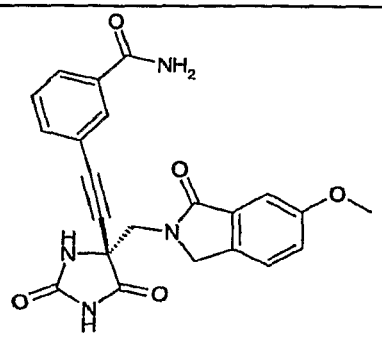
Compound ID	Structures
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554	
1003	
1256	
1009	
1012	
1253	

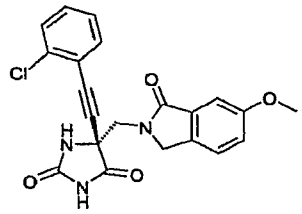
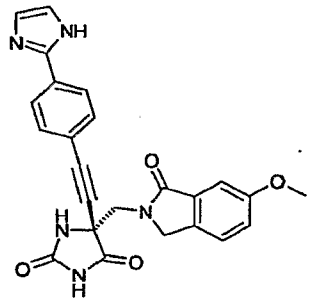
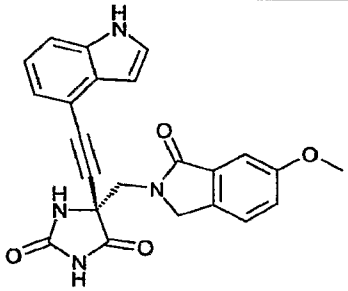
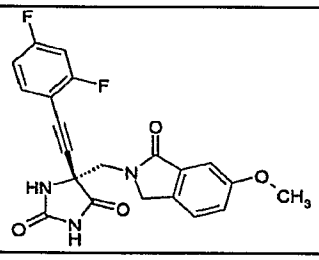
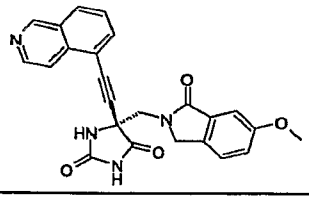
Compound ID	Structures
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1091	
1063	
1070	
1090	
1092	
1098	

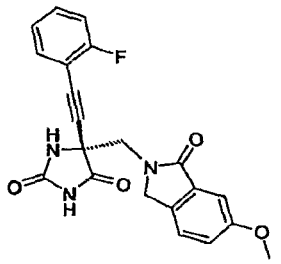
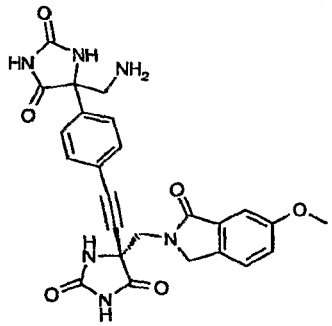
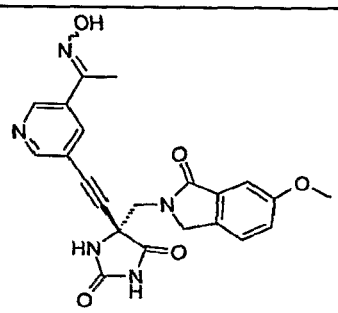
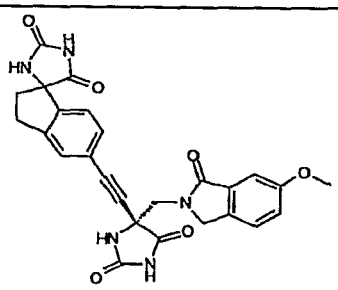
Compound ID	Structures
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1099	
1505	
1513	
1520	

Compound ID	Structures
1519	
1523	
1502	
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930	

Compound ID	Structures
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960	
1220B	
1206	
1220	
1201	
1200	

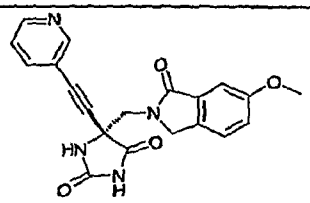
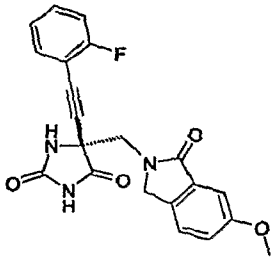
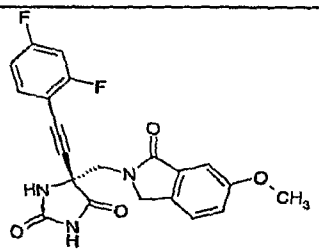
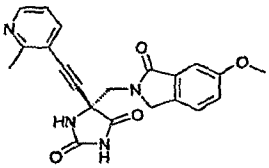
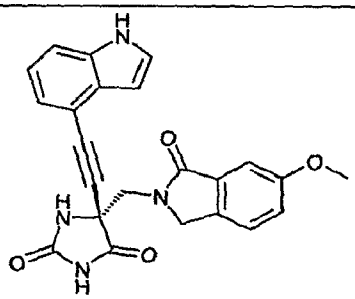
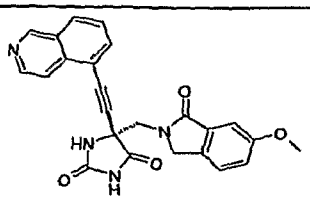
Compound ID	Structures
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1134	

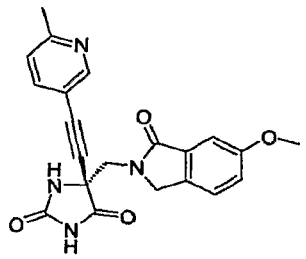
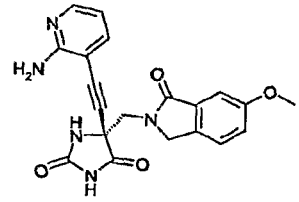
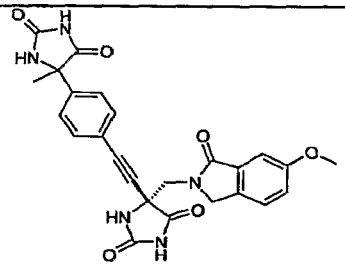
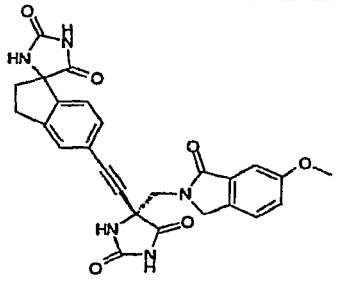
Compound ID	Structures
1146	
1136	
1132	
490	
442	

Compound ID	Structures
516	
1562	
1552	
1576	

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

In another embodiment, the compounds of Formula (I) are selected from the group consisting of:

Compound ID	Structures
400B	
516	
490	
1003	
1132	
442	

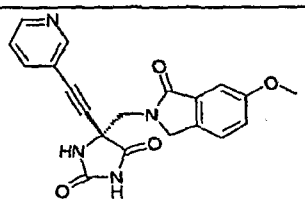
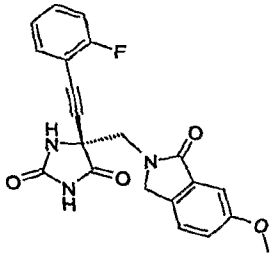
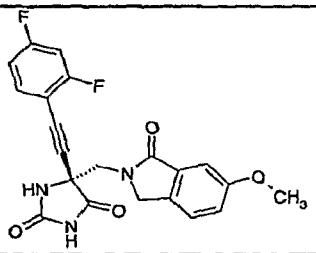
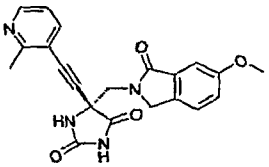
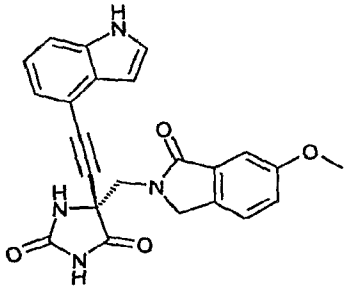
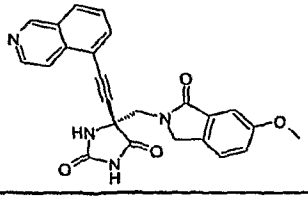
Compound ID	Structures
1155	
930	
1256	 and
1576	 ;

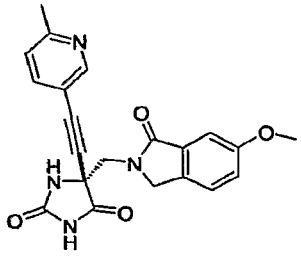
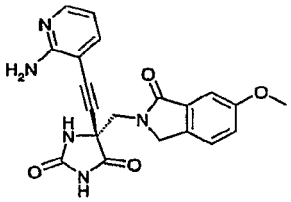
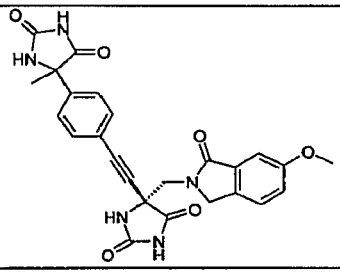
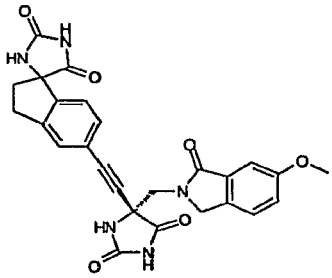
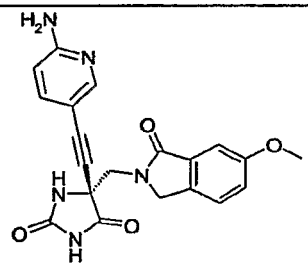
or a pharmaceutically acceptable salt, solvate, or ester thereof.

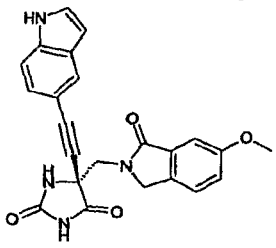
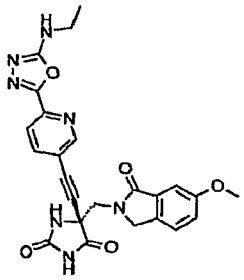
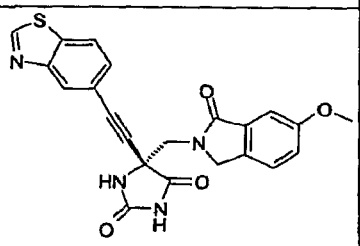
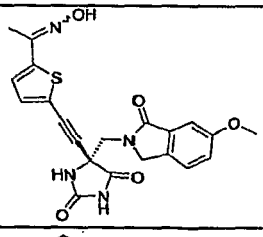
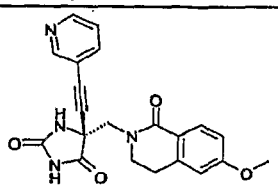
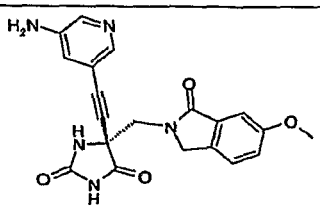
Specific TACE inhibitory activity (Ki values) of some representative compounds of the present invention are set forth below.

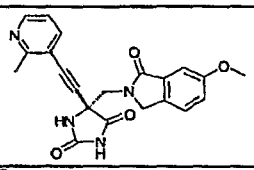
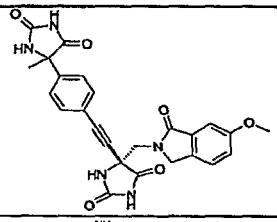
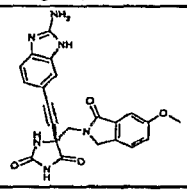
Table 1002

Compound ID	Structures	Exact Mass	Mass Obsvd	Ki (nM)

Compound ID	Structures	Exact Mass	Mass Obsvd	Ki (nM)
400B		376.37	377.0[M+H]$^+$	0.44
516		393.11	394.1[M+H]$^+$	0.13
490		411.36	412.1[M+H]$^+$	0.23
1003		390.13	391.2 [M+H]$^+$	0.11
1132		414.1	415.2[M+H]$^+$	1.8
442		426.13	427.1[M+H]$^+$	0.11

Compound ID	Structures	Exact Mass	Mass Obsvd	Ki (nM)
1155		390.1	391.2[M+H]$^+$	0.41
930		392.14	392.2[M+H]$^+$	0.56
1256		487.15	488.3 [M+H]$^+$	0.03
1576		499.15	500.3[M+H]$^+$	0.27
1152		391.1	392.2[M+H]$^+$	0.03

Compound ID	Structures	Exact Mass	Mass Obsvd	Ki (nM)
1129		414.1	415.2[M+H]$^+$	0.17
1502		487.46	488.5[M+H]$^+$	0.094
972		432.09	433.2[M+H]$^+$	0.12
1090		438.46	439.2 [M+H]$^+$	0.3
1092		390.39	391.2 [M+H]$^+$	0.37
554		391.13	392.2[M+H]$^+$	0.31

Compound ID	Structures	Exact Mass	Mass Obsvd	Ki (nM)
1003		390.13	391.2 $[M+H]^+$	0.11
1256		487.15	488.3 $[M+H]^+$	0.03
1009		430.14	431.2 $[M+H]^+$	1.33

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.

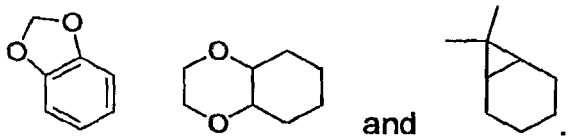
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents"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

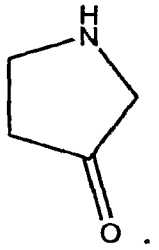
"Halogen" (or "halo") means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"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 -

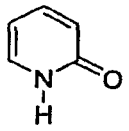
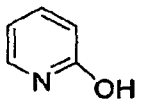
$SO_2NG_1G_2$, wherein G_1 and G_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon 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 1001** 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. β-methasone; and anti-TNF-α compound, e.g. Enbrel® or Remicade®; a PDE IV inhibitor, or other classes of compounds indicated for the treatment of RA.

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

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

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

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

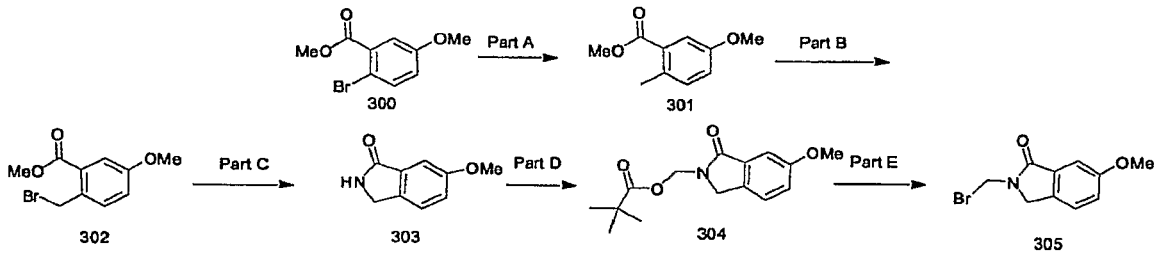
The following abbreviations may be used in the procedures and schemes:

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 ionization
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
HPLC	High pressure liquid chromatography
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
M	Molar
mmol	milimolar
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mg	Milligrams
MHZ	Megahertz
mL	Milliliter
MPLC	Medium Pressure Liquid Chromatography
NMR	Nuclear Magnetic Resonance
MS	Mass Spectroscopy
NBS	N-Bromosuccinimide
NMM	N-Methylmorpholine
NMP	1-methyl-2-pyrrolidone
ON	Overnight
PCC	Pyridinium Chlorochromate
PTLC	Preparative thin layer chromatography
PyBrOP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Pyr	Pyridine
RT	Room temperature
sgc	Silica gel 60 chromatography
tBOC	tert-Butoxycarbonyl

TACE	TNF-alpha converting enzyme
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

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%).

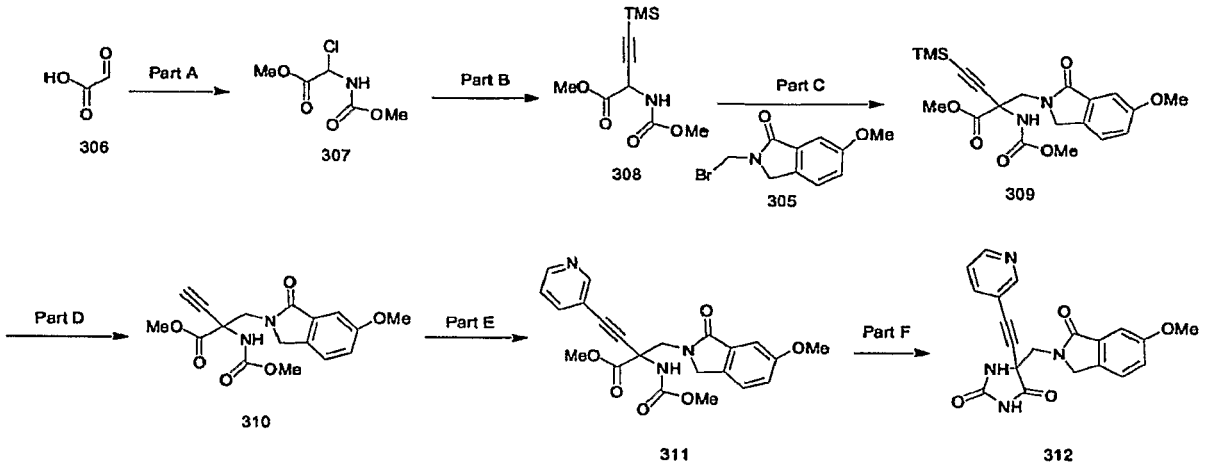
Part D:

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 300B



Part A:

Compound **307** was prepared from compound **306** using the procedure found in *Tetrahedron* **1975**, 31, 863-866.

Part B:

Compound **308** was prepared from compound **307** using the procedure found in *J. Med. Chem.* **1981**, 24, 16-20. HPLC-MS t_R = 1.839 min (ELSD); mass calculated for formula $C_{10}H_{17}NO_4Si$ 243.09, observed LCMS m/z 244.1 (M+H).

Part C:

Diisopropylamine (0.80 mL, 5.8 mmol) and HMPA (2.3 mL) were dissolved in THF (10 mL) and cooled to -78 °C. A solution of n-BuLi (2.5 M, 2.0 mL, 5 mmol) was added to the reaction dropwise and stirred for 20 minutes. Compound **308** (425 mg, 1.66 mmol) was dissolved in THF (5 mL) and added dropwise. After 20 minutes, compound **305** (470 mg, 1.83 mmol) in THF (10 mL) was added dropwise and the reaction was stirred for 2 hours at the same temperature. 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** (0.360 g, 52%). HPLC-MS

t_R = 1.904 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 D:

Compound **309** (100 mg, 0.23 mmol) was dissolved in THF (5 mL) and cooled to 0°C. Tetrabutylammonium fluoride (1 M in THF, 0.3 mL, 0.3 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 **310** (70 mg, 88%). The product was used without purification.

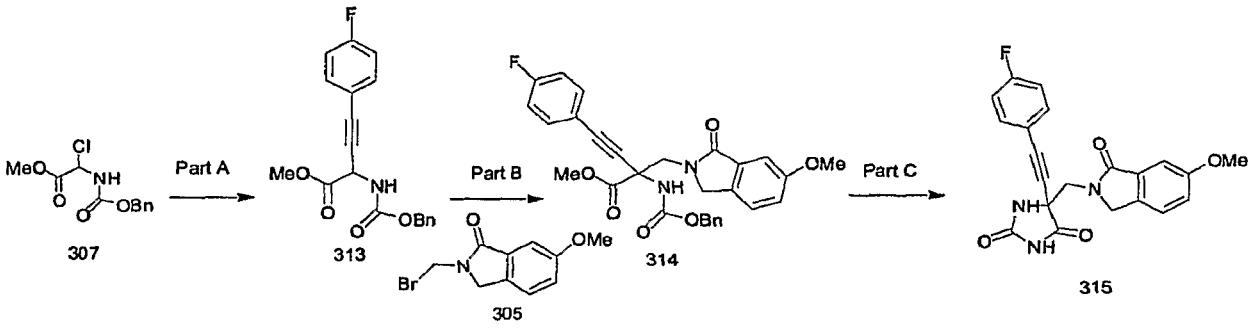
Part E:

Compound **310** (627 mg, 1.87 mmol) was combined with 3-iodopyridine (561 mg, 2.8 mmol), $Pd(dppf)Cl_2$ (76 mg, 0.093 mmol), X-PHOS (88 mg, 0.186 mmol), piperidine (321 mg, 3.74 mmol) in acetonitrile (20 mL) and stirred overnight at 80 °C. The reaction mixture was cooled to room temperature and concentrated. Purification by column chromatography (SiO_2, ethyl acetate to 2% methanol/ethyl acetate) afforded the desired product **311** (0.630 g, 80%). HPLC-MS t_R = 1.389 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{21}N_3O_6$ 423.14, observed LCMS m/z 424.1 (M+H).

Part F:

Compound **311** (60 mg, 0.14 mmol) was dissolved in 7 M ammonia in methanol solution (5 mL) and stirred in a sealed pressure tube at 90 °C overnight. The reaction mixture was cooled to room temperature and concentrated. Trituration with ethyl acetate provided the desired product **312** (49.5 mg, 93%). HPLC-MS t_R = 1.086 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{16}N_4O_4$ 376.11, observed LCMS m/z 377.0 (M+H).

Example 300C



Part A:

Compound **313** was prepared using the procedure found in *J. Org. Chem.* **1990**, 55, 4657-4663.

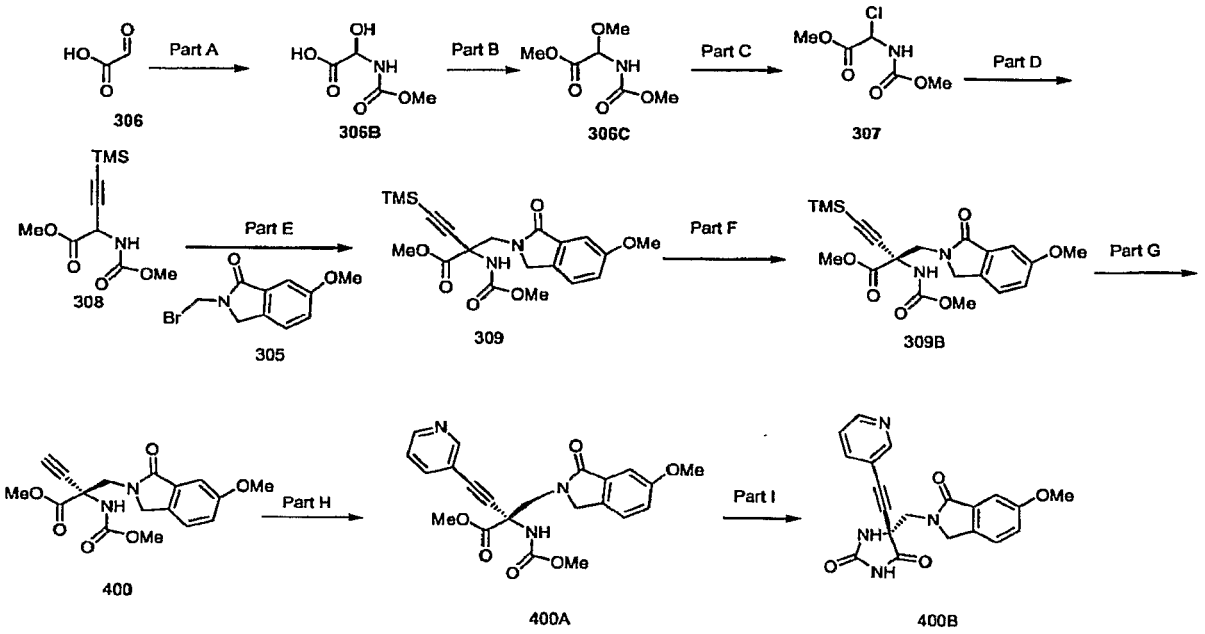
Part B:

Compound **314** was prepared using a procedure found in Part C of Example 300B.

Part C:

Compound **314** (100 mg, 0.23 mmol) was dissolved in 7 M ammonia in methanol solution (5 mL) and stirred in a sealed pressure tube at 90°C overnight. The reaction mixture was cooled to room temperature and concentrated. Trituration with ethyl acetate provided the desired product (57 mg, 63%). HPLC-MS t_R = 1.533 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{16}N_3O_4F$ 393.1, observed LCMS m/z 394.1 (M+H).

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).

The synthesis for compound **305** was described in **Example 300A**.

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:

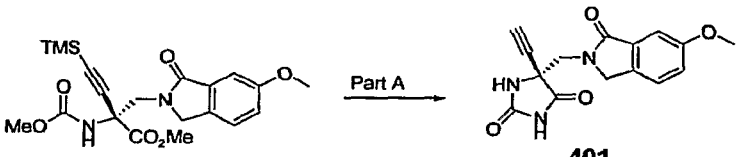
Compound **400** (500 mg, 1.45 mmol) was combined with 3-iodopyridine (434 mg, 2.16 mmol), $Pd(PPh_3)_2Cl_2$ (50 mg, 0.072 mmol), CuI (14 mg, 0.072 mmol), diisopropylamine (0.4 mL, 2.9 mmol) in DMF (5 mL) and stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, ethyl acetate to 2% methanol/ethyl acetate) afforded the desired product **400A** (0.520 g, 84%). HPLC-MS t_R = 1.39 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{21}N_3O_6$ 423.14, observed LCMS m/z 424.1 (M+H).

Part I:

Compound **400A** (480 mg, 1.13 mmol) was dissolved in 7 M ammonia solution (5 mL) and stirred in a sealed pressure tube at 90 °C overnight. The

reaction mixture was cooled to room temperature and concentrated. The residue was treated with 1M HCl (2 mL) and then diluted with acetonitrile (10 mL) and water (3 mL). The solvent was removed by lyophilization to provide compound **400B** as the HCl salt (437.4 mg, 93%). HPLC-MS t_R = 1.09 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{16}N_4O_4$ 376.11, observed LCMS m/z 377.0 (M+H).

Example 401:

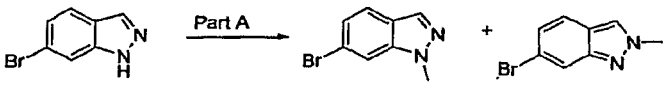


309B **401**

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 402:



402A **402B** **402C**

Part A:

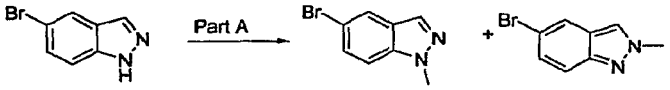
To 6-bromoindazole (402A) (5.0 g, 25.4 mmol) in THF (50 mL) was added sodium hydride (95%, 672 mg, 26.6 mmol) with ice bath cooling. The mixture was stirred for 30 minutes. Methyl iodide (6.36 mL, 102 mmol) was added at room temperature. The reaction mixture was quenched with ammonium chloride solution and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, ethyl acetate/hexane gradient) afforded 1-methyl-6-

bromoindazole (402B) (2.71 g, 51%) as a yellow oil and 2-methyl-6-bromoindazole (402C) (2.28 g, 43%) as a yellow crystalline solid.

402B: HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_7BrN_2$ 209.98, observed LCMS m/z 211.0 (M+H).

402C: HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_7BrN_2$ 209.98, observed LCMS m/z 211.0 (M+H).

Example 403:



403A **403B** **403C**

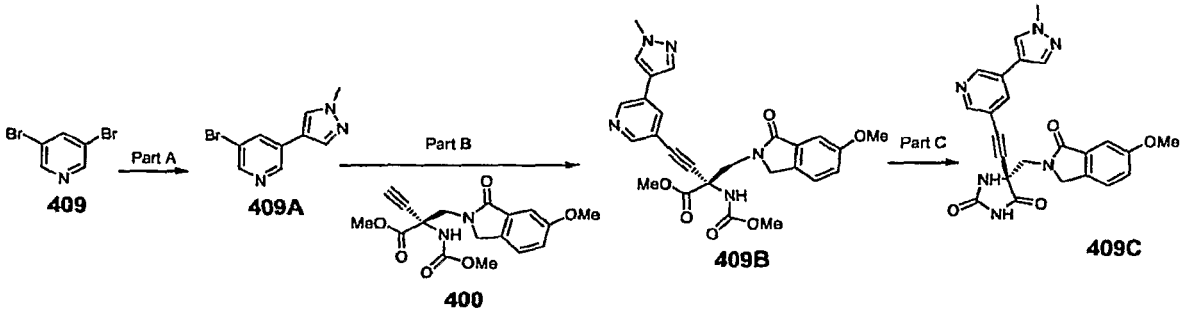
Part A:

Using the procedure described in Example 402 403B (53%) and 403C (39% were prepared.

403B: HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_7BrN_2$ 209.98, observed LCMS m/z 211.0 (M+H).

403C: HPLC-MS t_R = 1.46 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_7BrN_2$ 209.98, observed LCMS m/z 211.0 (M+H).

Example 409:



409 **409A** **400** **409B** **409C**

Part A:

Compound **409** (545 mg, 2.3 mmol) was combined with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (526 mg, 2.53 mmol), $PdCl_2dppf.CH_2Cl_2$ (94 mg, 0.11 mmol) and K_3PO_4 (1.46 g, 6.9 mmol) in 1,4-dioxane (10 mL) and heated overnight at 80 °C. The reaction mixture was

diluted with ethyl acetate and filtered through Celite. The organic filtrate was concentrated and purified by column chromatography (SiO_2, 50% to 80% ethyl acetate/hexane to ethyl acetate) to afford desired product **409A** (0.250 g, 46%) as a yellow solid. HPLC-MS t_R = 1.24 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_8BrN_3$ 236.99, observed LCMS m/z 238.1, 240.0 (M+H, Br isotope).

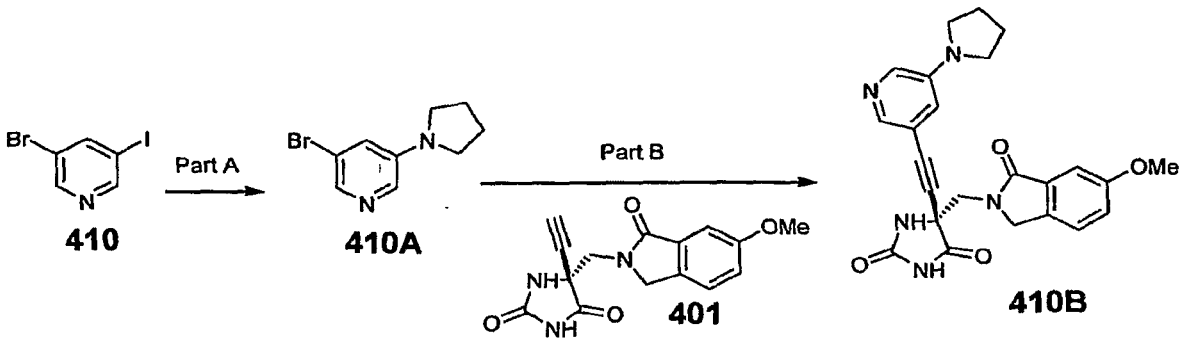
Part B:

Compound **409B** was prepared using procedures described in Example 400, part H. Purification by column chromatography (SiO_2, ethyl acetate to 5% methanol/ethyl acetate) afforded the desired product **409B** (0.1 g, 59%). HPLC-MS t_R = 1.38 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{25}N_5O_6$ 503.18, observed LCMS m/z 504.2 (M+H).

Part C:

Compound **409C** was prepared using procedures described in Example 400, part I. Purification by reverse-phase prepLC afforded the desired product **409C** (46 mg, 50%). HPLC-MS t_R = 1.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{20}N_6O_4$ 456.15, observed LCMS m/z 457.1 (M+H).

Example 410:



Part A:

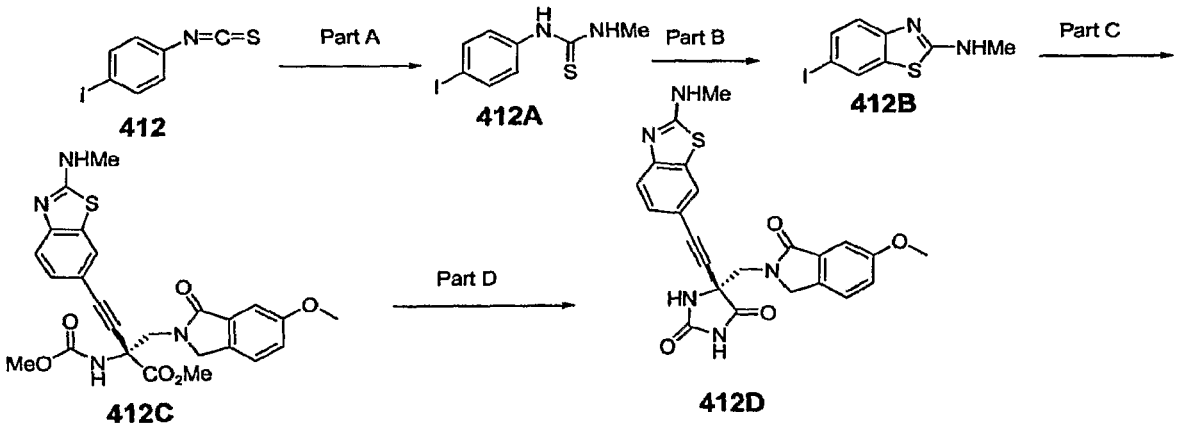
According to a modification of a procedure by Xue, C-B *et. al.* (WO 2006/004741) a mixture of compound **410** (1.0 g, 3.52 mmol), pyrrolidine

(0.31 mL, 3.7 mmol), CuI (67 mg, 0.35 mmol), K_3PO_4 (1.57 g, 7.4 mmol) and ethylene glycol (0.4 mL, 7.04 mmol) in isopropanol (10 mL) was heated at 85 °C in a sealed tube for 60 h. The reaction mixture was diluted with ethyl acetate and filtered through Celite. The organic filtrate was concentrated and purified by column chromatography (SiO_2, 10% to 30% ethyl acetate/hexane) to afford desired product **410A** (0.39 g, 49%) as a white solid. HPLC-MS t_R = 1.26 min ($UV_{254\ nm}$); mass calculated for formula $C_9H_{11}BrN_2$ 226.01, observed LCMS m/z 227.1, 229.1 (M+H, Br isotope).

Part B:

Compound **410B** was prepared using procedures described in Example 400, part H. Purification by reverse-phase prepLC afforded the desired product **410B** (54 mg, 24%). HPLC-MS t_R = 1.11 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{23}N_5O_4$ 445.18, observed LCMS m/z 446.2 (M+H).

Example 412:



Part A:

Compound **412** (500 mg, 1.92 mmol) was dissolved in methylene chloride (15 mL) and triethylamine (0.53 mL, 3.84 mmol). Methylamine hydrochloride (186 mg, 2.3 mmol) was added and the solution was stirred for two hours. The

reaction mixture was washed with water and the organic layer was dried over sodium sulfate and concentrated to provide compound **412A** (430 mg, 77%).

Part B:

Compound **412A** (430 mg, 1.47 mmol) was dissolved in acetic acid (10 mL) and bromine (0.091 mL, 1.76 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The solvent was removed and the residue was dissolved in ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated to provide the desired product (230 mg, 43%). HPLC-MS t_R = 1.53 min ($UV_{254\ nm}$); mass calculated for formula $C_8H_7IN_2S$ 290.12, observed LCMS m/z 291.0 (M+H).

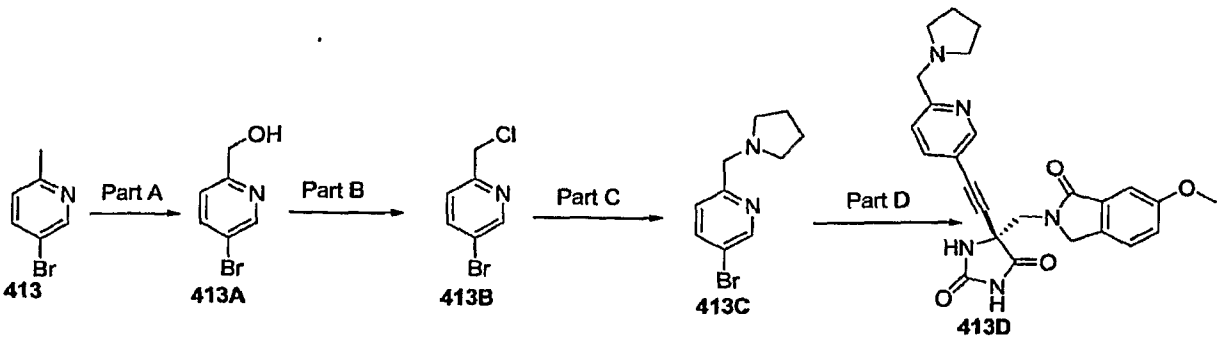
Part C:

See Example 400, Part H for similar experimental procedure. HPLC-MS t_R = 1.47 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{24}N_4O_6S$ 508.55, observed LCMS m/z 509.1 (M+H).

Part D:

See Example 400, Part I for similar experimental procedure. HPLC-MS t_R = 1.19 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{19}N_5O_4S$ 461.49, observed LCMS m/z 462.1 (M+H).

Example 413:



Part A:

Compound **413** (3.5 g, 20.7 mmol) was dissolved in methylene chloride (100 mL) and m-CPBA (4.95 g, 28.9 mmol) was added. The reaction mixture was stirred for two hours and then quenched with saturated sodium carbonate and stirred overnight. The organic layer was dried over sodium sulfate and the concentrated to provide a yellow solid (3.8 g). The solid was placed under argon and trifluoroacetic anhydride (15 mL) was added slowly. The reaction was stirred for 30 minutes at room temperature and then refluxed for 30 minutes. The reaction was cooled to room temperature and quenched slowly with saturated sodium bicarbonate. Methylene chloride was added and the organic layer was washed dried over sodium sulfate and concentrated. Column chromatography (2 to 1 ethyl acetate/hexanes) provided the desired product (3.0 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, 1H), 7.8 (m, 1H), 7.2 (d, 1H), 4.7 (s, 2H).

Part B:

Compound **413A** (500 mg, 2.7 mmol) was dissolved in methylene chloride (5 mL) and cooled in an ice bath. Thionyl chloride (480 mg, 4.05 mmol) was added dropwise and stirred at room temperature for 3 hours. The reaction was quenched with saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated to provide the desired product (510 mg, 92%).

Part C:

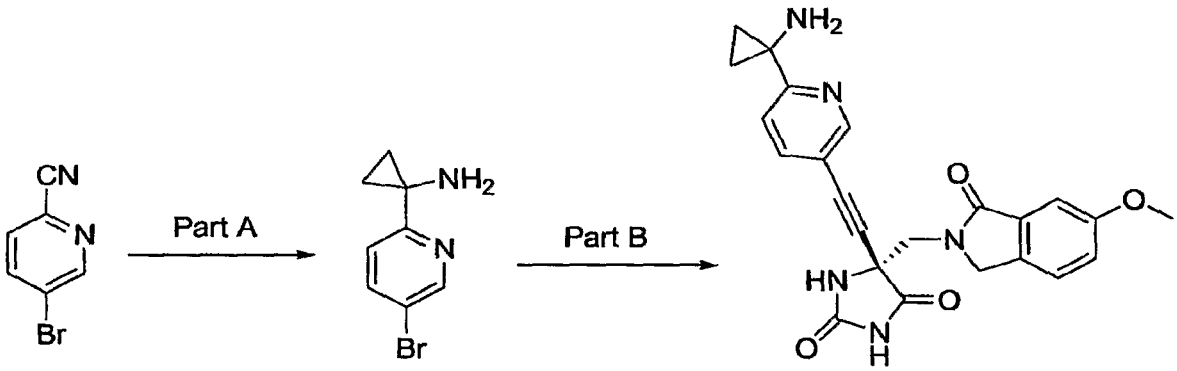
Compound **413B** (255 mg, 1.25 mmol) was dissolved in DMF (8 mL) and cesium carbonate (812 mg, 2.5 mmol) and pyrrolidine (108 mg, 1.5 mmol) added. The reaction mixture was stirred at 80°C for one hour. The reaction was diluted with ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated to provide the desired product (250 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.6 (d, 1H), 7.8 (m, 1H), 7.35 (d, 1H), 3.75 (s, 2H), 2.55 (m, 2H), 1.8 (m, 2H).

Part D:

Compound **401** (100 mg, 0.334 mmol), **413C** (104 mg, 0.43 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.021 mmol), CuI (8 mg, 0.041 mmol), diisopropylamine (0.1 mL) and DMF (1 mL) were stirred overnight at 80 °C. The solvent was evaporated and the residue was washed with ethyl acetate and water. The remaining residue was purified by reverse phase HPLC to provide the desired product (50 mg, 32%). HPLC-MS t_R = 0.981 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}N_5O_4$ 459.50, observed LCMS m/z 460.2 (M+H).

Example 414:



414 **414A** **414B**

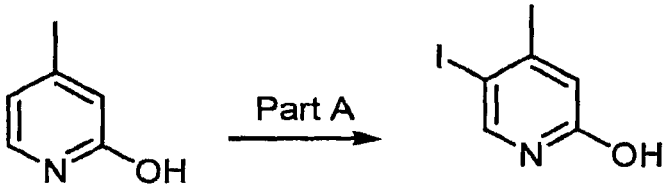
Part A:

Compound **414** (1.0 g, 5.46 mmol) was suspended in diethylether (30 mL) and cooled to -78 °C. Titanium (IV) isopropoxide (1.7 mL, 6.01 mmol) was added dropwise and stirred for 5 minutes. Ethyl magnesium bromide (3M in diethylether, 4.0 mL) was added dropwise and stirred for 30 minutes at the same temperature and 1 hour at room temperature. Boron trifluoride dietherate (1.55 g, 10.92 mmol) was added dropwise and the reaction was stirred for 2 hours. The reaction was quenched with 1M hydrochloric acid and the aqueous layer was washed with diethyl ether. The aqueous layer was

made basic (pH = 10) and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Column chromatography (1:1 hexanes/ethyl acetate) provided the desired product (350 mg, 30%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (d, 1H), 7.7 (m, 1H), 7.3 (d, 1H), 1.25 (m, 2H), 1.15 (m, 2H).

Part B:
See Example 413, Part D for similar experimental. HPLC-MS t_R = 0.85 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{21}N_5O_4$ 431.44, observed LCMS m/z 432.1 (M+H).

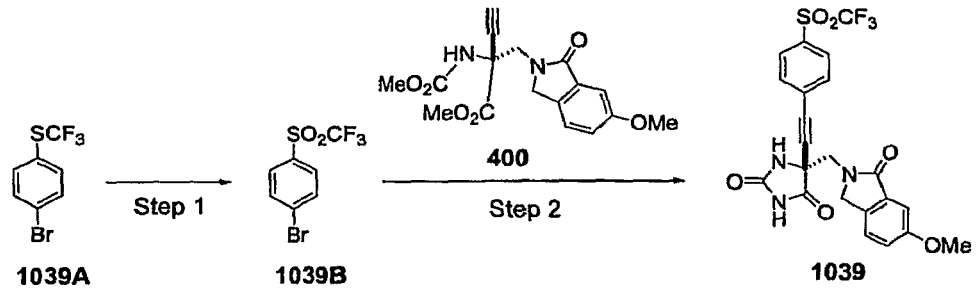
Example 555:



555A 555B

Part A:
Compound **555B** was prepared according to a modification of a procedure described in WO-9846609. A mixture of 2-hydroxy-4-methylpyridine **555A** (1.50 g, 13.7 mmol), iodine (3.68 g, 13.7 mmol) and sodium carbonate (3.06 g, 28.9 mmol) in water (70 mL) was heated at 70 °C overnight. The mixture was acidified with concentrated HCl to pH=3, and the resulting brown solid residue was washed twice with ethyl acetate, and then taken in hot ethanol. The solid which did not dissolve (diiodo byproduct) was filtered off, and the ethanol filtrate was concentrated to give the desired product **555B** as a white solid (0.67 g, 21%); HPLC-MS t_R = 1 min ($UV_{254\ nm}$); mass calculated for formula C_6H_6INO 234.95, observed LCMS m/z 236.0.

Example 1039



1039A **1039B** **1039**

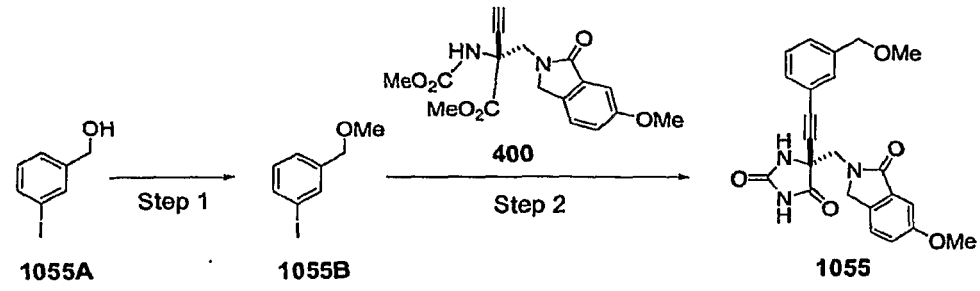
Step 1

mCPBA (3.49 g, 77%, 15.6 mmol) was added to an ice-cold solution of Compound **1039A** (1 g, 3.9 mmol) in CH_2Cl_2 (19 mL). The reaction mixture was allowed to warm to rt, and was stirred overnight. The mixture was diluted with CH_2Cl_2 and was washed sequentially with saturated aq sodium bicarbonate and brine. The organic solution was dried over $MgSO_4$, filtered and concentrated. The resulting crude product was purified by sgc (0-50% EtOAc–hexanes gradient) to afford Compound **1039B** (787 mg, 70%).

Step 2

Compounds **1039B** and **400** were converted to Compound **1039** by applying the procedure described for Examples **300A** and **300B**.

Example 1055



1055A **1055B** **1055**

Step 1

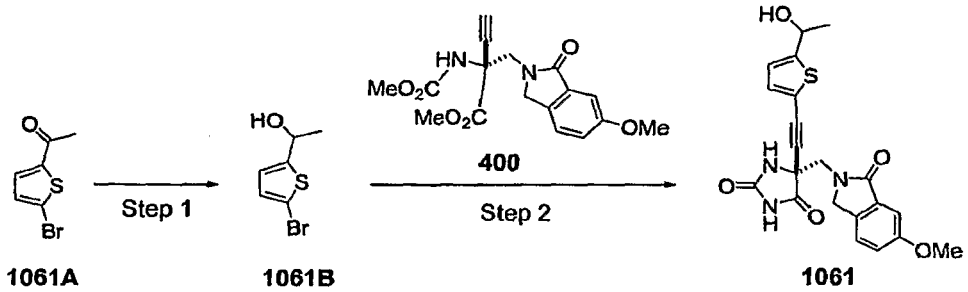
A solution of Compound **1055A** (300 mg, 1.28 mmol) in DMF (4.3 mL) was treated with solid cesium carbonate (835 mg, 2.56 mmol) followed by iodomethane (0.09 mL, 218 mg, 1.54 mmol). The reaction mixture was stirred overnight at rt. The reaction mixture was diluted with EtOAc, then washed sequentially with water (3x) and brine. The organic layer was dried over anhydrous MgSO4, filtered, and concentrated. The residue was purified by sgc (0-50% EtOAc–hexanes gradient) to afford Compound **1055B** (150 mg).

Step 2

Compounds **1055B** and **400** were converted to Compound **1055** by applying the procedure described for Examples **300A** and **300B**.

Compounds **1046**, **1050**, **1057**, **1058**, and **1059** were prepared using the same procedure as for Compound **1055**.

Example 1061



Step 1

Compound **1061A** (620 mg, 3.02 mmol) was dissolved in methanol (30 mL) and the solution was cooled to 0 °C. Solid sodium borohydride (230 mg, 6.04 mmol) was added in small portions. The resulting cloudy reaction mixture was stirred at 0 ° C for 40 min. The reaction was quenched by dropwise addition of glacial acetic acid (0.4 mL). Solvents were removed under reduced pressure, and the resulting white solid was partitioned between EtOAc (100 mL) and water (50 mL). The aqueous layer was extracted once

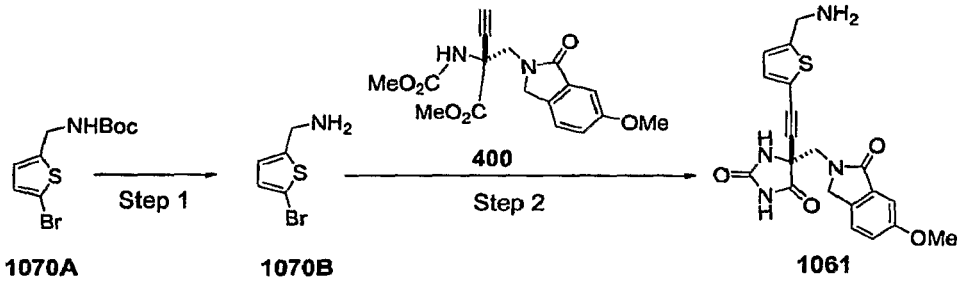
more with EtOAc (~25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a colorless oil. The crude product was purified by sgc (10-40% EtOAc–hexanes gradient) to give Compound **1061B** (591 mg, 95%) as a clear, colorless oil.

Step 2

Compounds **1061B** and **400** were converted to Compound **1061** by applying the procedure described for Examples **300A** and **300B**.

The same procedure was used for the preparation of Compounds **1075**, **1078** and **1079**.

Example 1070



1070A **1070B** **1061**

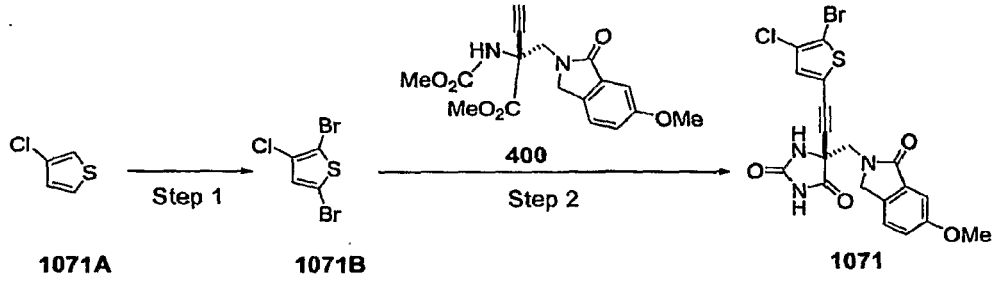
Step 1

HCl (17 mL, 4 M in dioxane, 68 mmol) was added to an ice-cold solution of Compound **1070A** in CH2Cl2 (27 mL). The reaction mixture was stirred at 0 °C for 30 min, and at rt for 18 h. The solvent was concentrated to dryness to give Compound **1070B** as an off-white solid (1.51 g).

Step 2

Compounds **1070B** and **400** were converted to Compound **1070** by applying the procedure described for Examples **300A** and **300B**.

Example 1071



1071A 1071B 1071

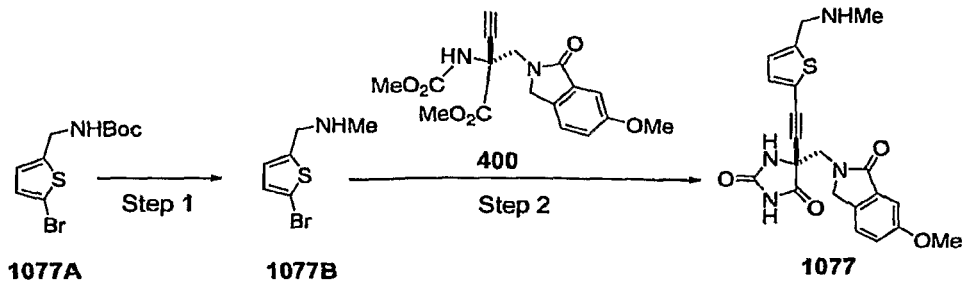
Step 1

Neat bromine (1.4 mL, 28 mmol, 1.1 eq) was added dropwise to a stirred solution of Compound **1071A** (3.0 g, 26 mmol) in dioxane (8 mL) at 0 °C. Upon completion of the addition, the reaction mixture was heated at 60 °C for 18 h. The reaction mixture was diluted with Et_2O (50 mL), and was washed sequentially with saturated aq sodium bicarbonate (50 mL) and brine (~50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The desired product, Compound **1071B**, was separated from the crude product by sgc (0-10% EtOAc–hexanes). Yield: 0.987 g, 15% yield.

Step 2

Compounds **1071B** and **400** were converted to Compound **1071** by applying the procedure described for Examples **300A** and **300B**.

Example 1077



1077A 1077B 1077

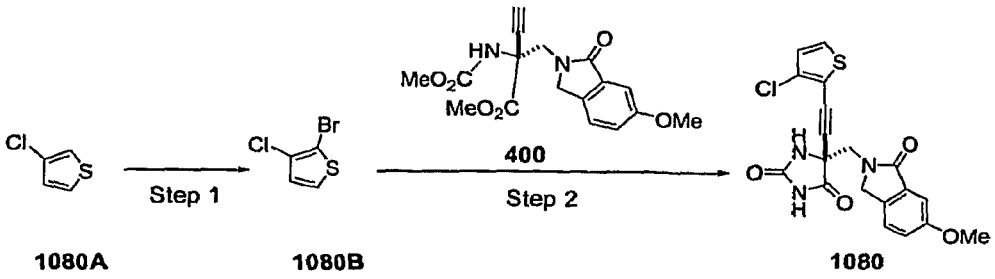
Step 1

A solution of Compound **1077A** (200 mg, 0.68 mmol) in DMF (3 mL) was treated with sodium hydride (41 mg, 60% dispersion in oil; 0.82 mmol) followed by iodomethane (0.05 mL, 117 mmol). The reaction mixture was stirred for 3 d. The reaction mixture was diluted with EtOAc and washed sequentially with water and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to afford an intermediate (191 mg). This intermediate was re-dissolved in CH_2Cl_2 and treated with HCl solution (0.78 mL). The solution was stirred at rt overnight, then concentrated to afford the desired product (152 mg, 100% yield (HCl salt)), which was used without further purification.

Step 2

Compounds **1077B** and **400** were converted to Compound **1077A** by applying the procedure described for Examples **300A** and **300B**.

Example 1080



1080A **1080B** **1080**

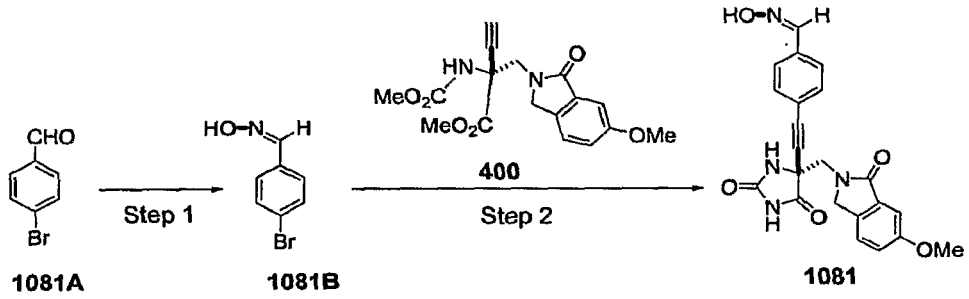
Neat bromine (0.8 mL, 24 mmol, 0.9 eq) was added dropwise over ~20 min to a stirred solution of Compound **1080A** (2.00 g, 0.026 mmol) in carbon tetrachloride (4 mL) at 0 °C. Upon completion of the addition, the reaction mixture was heated at 60 °C for 18 h. The reaction mixture was diluted with Et_2O (50 mL), and was washed sequentially with saturated aq sodium

bicarbonate (50 mL) and brine (~50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The desired product **1080B** was purified by sgc (100% hexanes, isocratic) to give Compound **1080B** as a clear, colorless liquid (1.78 g, 53%)

Step 2

Compounds **1080B** and **400** were converted to Compound **1080** by applying the procedure described for Examples **300A** and **300B**.

Example 1081



1081A **1081B** **1081**

Step 1

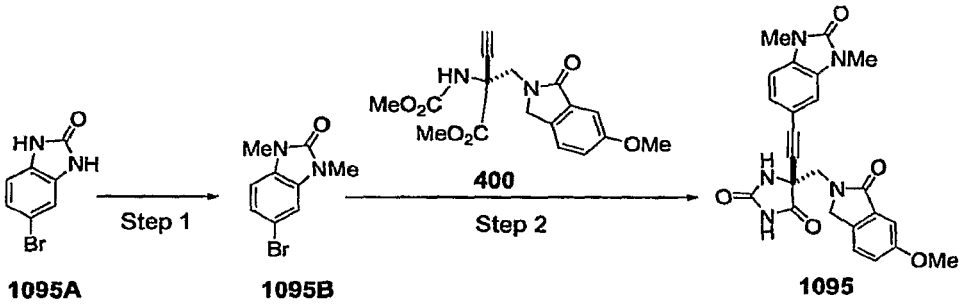
A pressure tube containing a mixture of Compound **1081A** (500 mg, 2.7 mmol) hydroxylamine hydrochloride (375 mg, 5.40 mmol), and sodium acetate (443 g, 5.6 mmol) in absolute ethanol (10 mL) was heated, with stirring, at 80 °C for 18 h. The mixture was allowed to cool, after which the solvent was removed. The residue was redissolved in EtOAc, and was washed with water and brine. The organic layer was dried over anhydrous MgSO4, filtered, and concentrated. The product was purified by PTLC (5% EtOAc–hexanes) to give Compound **1081B** (504 mg, 93%).

Step 2

Compounds **1081B** and **400** were converted to Compound **1081** by applying the procedure described for Examples **300A** and **300B**.

Analogous procedures were used for the preparation of Compounds **1082**, **1083**, **1084**, **1085**, **1086**, **1089**, **1090**, and **1091**.

Example 1095



1095A **1095B** **1095**

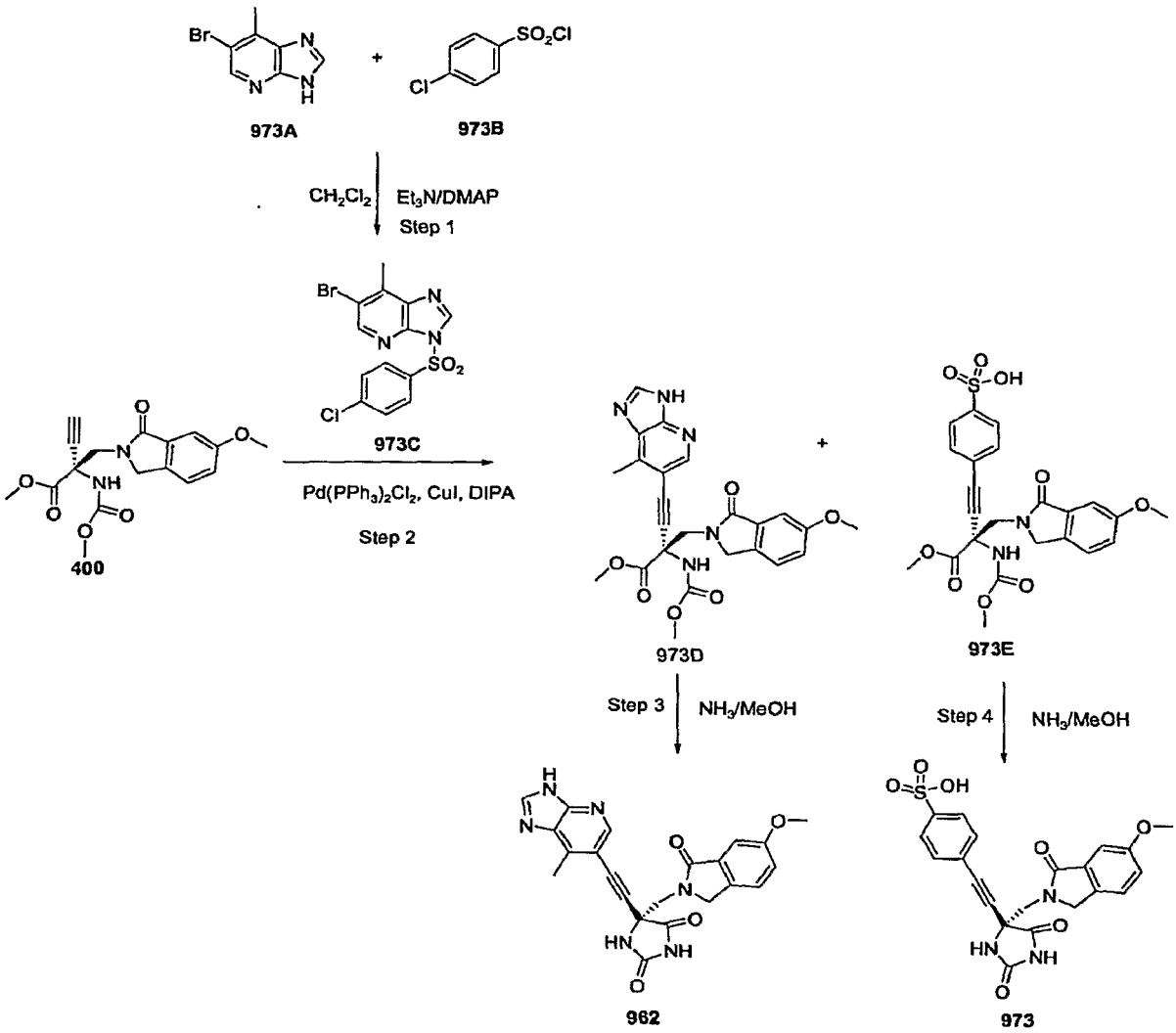
Step 1

A solution of Compound **1095A** in DMF (2 mL) was treated sequentially with sodium hydride (28 mg, 60% dispersion in oil, 0.70 mmol) and iodomethane (0.04 mL, 80 mg, 0.56 mmol). The reaction mixture was stirred overnight at rt. The reaction was quenched with water, diluted with EtOAc, and washed sequentially with water and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to give crude Compound **1095B** (37 mg, 68%), which was used without further purification.

Step 2

Compounds **1095B** and **400** were converted to Compound **1095** by applying the procedure described for Examples **300A** and **300B**.

Example 973



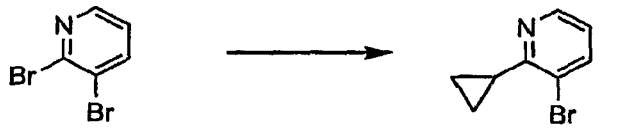
Step 1. To a solution of **973A** (320 mg, 1.62 mmol) in CH_2Cl_2 (10 mL) at rt was added Et_3N (0.45 mL, 3.2 mmol), **973B** (375 mg, 1.78 mmol) and DMAP (cat.) . After 30 min, the solvent was removed and the crude material was purified by column chromatography (SiO_2, 40% EtOAc/Hexanes) to afford **973C** (520 mg, 43%).

Step2. Compound **400** (100 mg, 0.29 mmol) was combined with compound **973C** (133 mg, 0.34 mmol), $Pd(PPh_3)_2Cl_2$ (2.2 mg, 0.003 mmol), CuI (5.5 mg, 0.03 mmol), diisopropylamine (0.05 mL, 0.36 mmol) in DMF (1 mL) and stirred overnight at 85°C. The reaction mixture was concentrated and the crude material was purified with TLC plates (SiO_2, 10% 7N NH_3 in methanol/CH_2Cl_2) afforded the desired product **973D** (20 mg, 15%) and **973E** (20 mg, 14%).

Step 3. Compound **973D** (20 mg, 0.042 mmol) was dissolved in 7 M NH_3 in MeOH solution (2 mL) and stirred in a sealed pressure tube at 90 °C overnight. The reaction mixture was cooled to room temperature and concentrated. The residue was purified with prepative TLC (SiO_2, 10% 7N NH_3 in methanol/CH_2Cl_2) afforded the desired product **962** (12 mg, 67%).

Step 4. Compound **973E** (20 mg, 0.04 mmol) was dissolved in 7 M ammonia solution (2 mL) and stirred in a sealed pressure tube at 90 °C overnight. The reaction mixture was cooled to room temperature and concentrated. The residue was purified with prepative TLC (SiO_2, 10% 7N NH_3 in methanol/CH_2Cl_2) afforded the desired product **973** (12 mg, 60%).

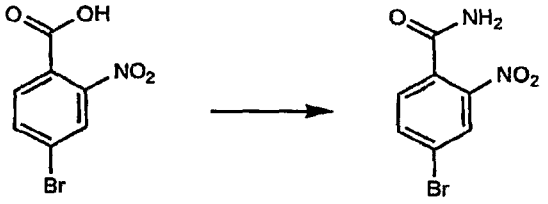
Example 1221



1221A 1221B

Compound **1221A** (1.0g, 4.22 mmol), cyclopropyl boronic acid (326 mg, 3.80 mmol) and [$PdCl_2$(dppf)]CH_2Cl_2 (150, 0.21 mmol) in CH_3CN (15 mL) was treated with potassium carbonate (5 mL, 5 mmol, 1M in H_2O). The mixture was subjected to vacuum and refilled with Nitrogen three times. The reaction mixture was stirred at 80 °C (oil bath) for 3 days. Additional [$PdCl_2$(dppf)]CH_2Cl_2 (150 mg) was added in day two. After cooling down, the water layer was separated and extracted with EtOAc (20 mL) once. The organic layers were combined, filtered through a Celite pad, and concentrated. The product was purified by silica gel chromatography (Hexane/EtOAc, 1:0 to 10:1 to 5:1) to give **1221B** (280 mg, 33.5%)

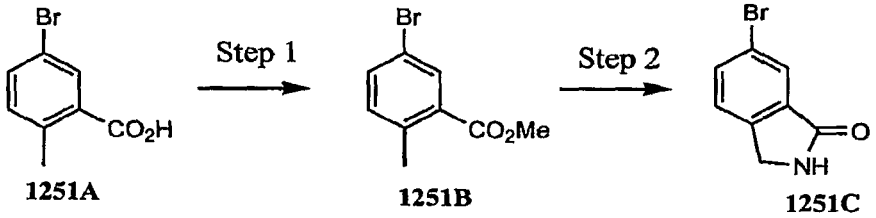
Example 1250



1250A **1250B**

Compound **1250A** (5.0 g, 20.3 mmol) was dissolved in thionyl chloride (40 mL) and stirred at reflux for two hours. After cooling down, thionyl chloride was removed by rotary evaporator. The residue was dissolved in CH_2Cl_2 and was added to NH_3-H_2O (conc. 50 mL) slowly with stirring. The solid was collected by filtration, washed with water, dried under vacuum for overnight to give compound **1250B**.

Example 1251



1251A **1251B** **1251C**

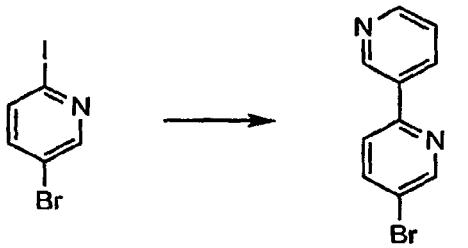
Step 1

Compound **1251A** (2.0 g), MeOH (20 mL), and H_2SO_4 (conc., 2mL) were stirred at RT for three days. Hexane (50 mL) was added. The organic layer was washed by water, dried over Na_2SO_4, concentrated by rotary evaporator. The product was purified by sgc (Hexane/EtOAc 10:1) to give compound **1251B** (1.219 g)

Step 2

Compound **1251B** (1.219g, 5.32 mmol) was dissolved in CCl_4 (30 mL). NBS (947 mg, 5.32 mmol) and benzoyl peroxide (66 mg, 0.27 mmol) was added. The solution was stirred at 85 °C for 2 hours. After cooling down, the solid was filtered and the organic layer was washed with water (10 mL). The organic layer was dried over Na_2SO_4, concentrated by rotary evaporator, dried under vacuum. The residue was then dissolved in NH_3-MeOH (7N, 10 mL) and transferred into a 75 mL pressure bottle. The solution was stirred at 90 °C for over night. The product was purified by C18 chromatography (CH_3CN/water: 5% to 90%, with addition of 0.1% HCO_2H) to give compound **1251C** (800mg, 71%).

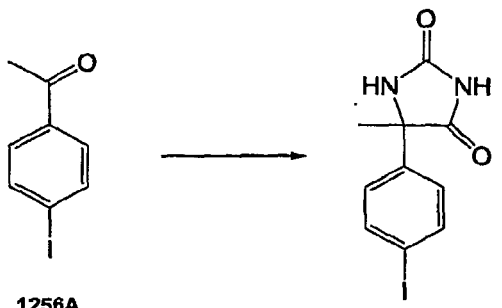
Example 1254



1254A **1254B**

Compound **1254A** (5.0 g, 17.61 mmol), 4-pyridine boronic acid (2.06 g, 16.73 mmol), and Pd(dppf)Cl_2-CH_2Cl_2 (644 mg, 0.88 mmol) were placed in a 500 mL flask. The flask was vacuumed for 1 minutes and then it was filled with N_2. This process was repeated twice. CH_3CN (200 mL) and K_2CO_3 (1M, 100 mL) were added. The solution was stirred in at 35 °C for two days. Additional Pd(dppf)Cl_2-CH_2Cl_2 (400mg) was added in the second day. The aqueous layer was separated and extracted with EtOAc (50 mL) once. The organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4. The solution was concentrated and purified by sgc (Hexane/EtOAc 3:1 to 2:1) to give compound **1254B** (3.1g, 74.9%).

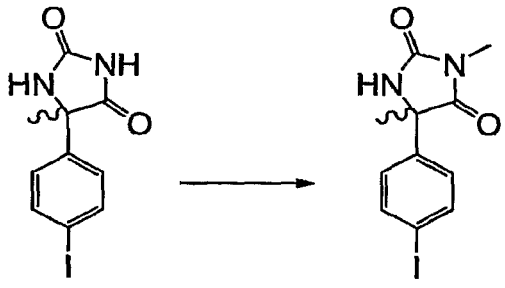
Example 1256



1256A 1256B

Compound **1256A** (5.00g, 20.3 mmol), KCN (1.59g, 24.4 mmol), and $(NH_4)_2CO_3$ (7.80 g, 81.3 mmol) were placed in a 150 mL pressure bottle. EtOH (30 mL) and water (30 mL) were added. The bottle was sealed and stirred at 80 °C oil bath for overnight. A white solid appeared. After cooling down, 30 mL water was added and the solid was collected by filtration. The solid was washed by water (20 mL) twice, dried under vacuum at 50 °C for overnight to give compound **1256B** (6.18 g, 96.2%).

Example **1555**

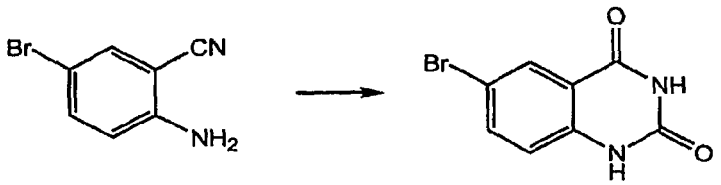


1555A **1555B**

Compound **1555A** (1.0g, 3.16 mmol) was dissolved in anhydrous DMF (20 mL). Methyl iodide (0.236 mL, 3.80 mL) and DIPEA (1.1 mL, 6.32 mL) was added and the solution was stirred at RT for two days. More methyl iodide (0.472 mL, 7.6 mL) was added in day two. The solvent was removed by

rotary evaporator. The product was purified by sgc (Hexane/EtOAc: 3:1 to 1:1) to give compound **1555B** (766 mg, 73.4%).

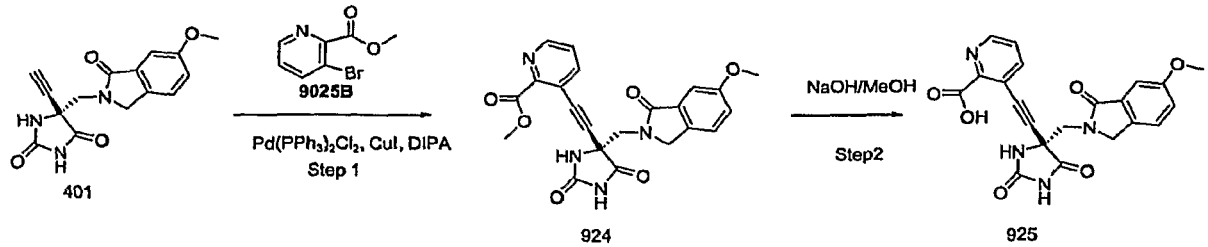
Example **1566**



1566A **1566B**

Compound **1566A** (200mg, 1.02 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 459 μl, 3.06 mmol) were dissolved in DMF (2 mL) in a two-neck flask. The mixture was subjected to vacuum and the atmosphere refilled with CO_2 supplied from the evaporation of dry ice at 23°C in a separate flask through a vacuum adapter. The mixture was allowed to stir at 23°C for overnight and the atmosphere of CO_2 was allowed to gradually escape through a pin hole in a septum. The solvent was removed and the remaining yellow oil was redissolved in THF (2 mL). 2M HCl (5 mL) was added dropwise with stirring. A cloudy white precipitate formed which was briefly sonicated. The solid was filtered, washed with THF (10 mL), and dried under reduced pressure to yield compound **1566B** (206.3 mg, 84.0%) as a white solid.

Example 925

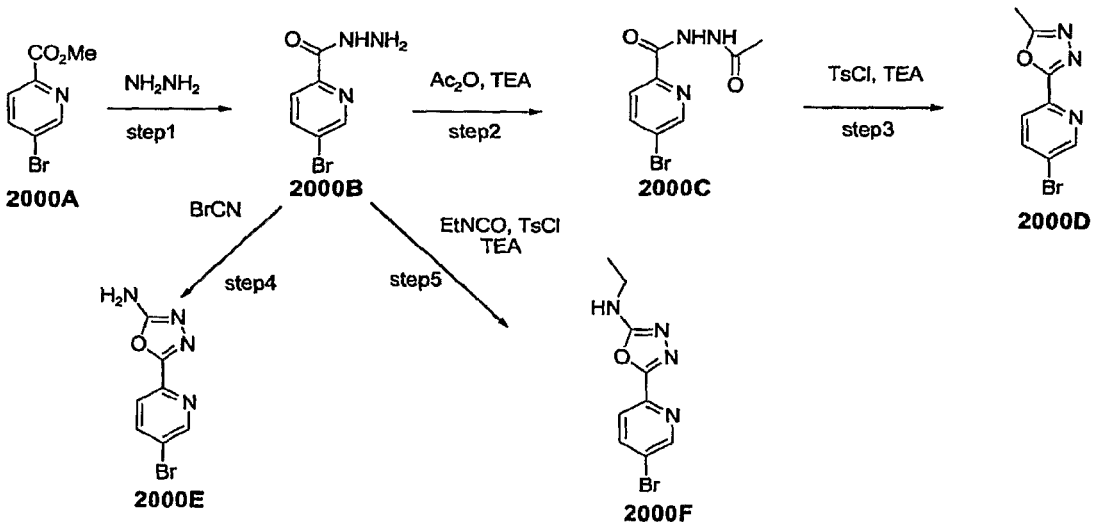


Step1. Compound **401** (130 mg, 0.43 mmol) was combined with compound **925B** (112 mg, 0.52 mmol), $Pd(PPh_3)_2Cl_2$ (6 mg, 0.009 mmol), CuI (12 mg, 0.06 mmol), diisopropylamine (0.1 mL, 0.71 mmol) in DMF (1 mL) and stirred

at 85°C for 2 h. The reaction mixture was purified on a Gilson reverse phase HPLC (0-40% acetonitrile with Formic acid 0.01% in H_2O with formic acid 0.01%) afforded the desired product **924**(107 mg, 57%).

Step 2. Compound **924** (100 mg, 0.23 mmol) was stirred in MeOH (5 mL) and LiOH (1N, aq., 5 mL) was added. The reaction was stirred at rt for 2 h. Solvent was removed and the crude material was purified on a Gilson reverse phase HPLC (0-40% acetonitrile in H_2O with 0.1% formic acid) afforded the desired product **925**(40 mg, 41%).

Example 2000



Step 1

To a solution of **2000A** (1 g, 4.6 mmol) in EtOH (12 mL) was added hydrazine (0.22 mL, 6.9 mmol) at 25 °C and the mixture was heated to reflux for 3 h. The reaction mixture was cooled to 0 °C and the resulting precipitate was filtered and washed with cold EtOH to afford **2000B** (0.86 g, 86% yield).

Step 2

To a suspension of **2000B** (300 mg, 1.39 mmol) and triethylamine (0.39 mL, 2.78 mmol) in CH_2Cl_2 (9 mL) was added acetic anhydride (0.15 mL, 1.53 mmol) at 25 °C. After stirring at the temperature for 1.5 h, the mixture was poured to a cold water and the resulting precipitate was collected by filtration. The white solid was washed with water and dried under reduced pressure to afford **2000C** (323 mg, 90% yield).

Step 3

A suspension of **2000C** (120 mg, 0.47 mmol) in CH_3CN (3 mL) and CH_2Cl_2 (3 mL) was treated with triethylamine (0.39 mL, 2.82 mmol) and TsCl (94 mg, 0.49 mmol) at 25 °C. The mixture was stirred at the temperature for 5 h and added to 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. The crude product was purified by SiO_2 column chromatography (0 to 5% MeOH in CH_2Cl_2) to afford **2000D** (80 mg, 71% yield).

Step 4

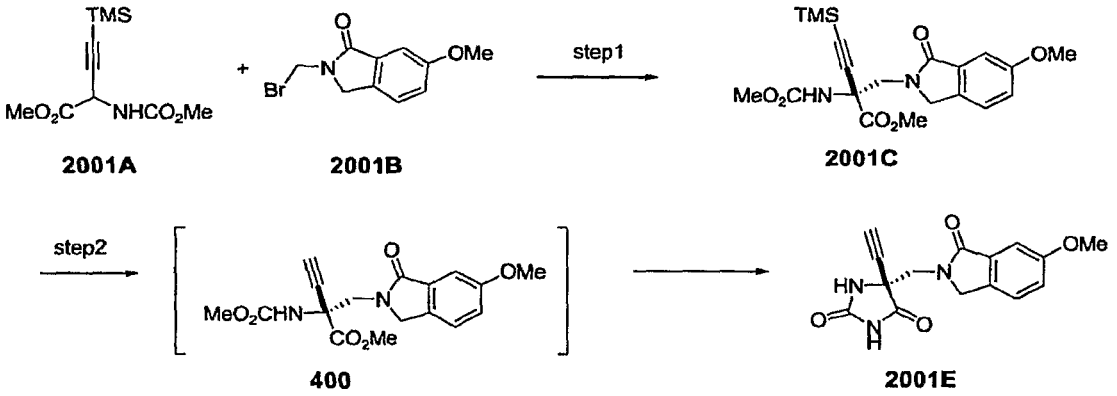
A suspension of **2000B** (100 mg, 0.46 mmol) in MeOH (3 mL) and 1,4-dioxane (1.5 mL) was treated with BrCN (3 M solution in CH_2Cl_2, 0.17 mL, 0.51 mmol) dropwisely at 25 °C. After stirring for 1 h at the temperature, $NaHCO_3$ (80 mg, 0.95 mmol) was added and the resulting suspension was continued stirring for 18 h. The white precipitate formed was filtered, washed with water, and dried in the air to afford **2000E** (95 mg, 86% yield).

Step 5

A suspension of **2000B** (100 mg, 0.46 mmol) in CH_2Cl_2 (6 mL) was treated with ethylisocyanate (0.04 mL, 0.50 mmol) at 0 °C and the mixture was stirred at 25 °C for 6 h. To this suspension were added triethylamine (0.32 mL, 2.2 mmol) and TsCl (95 mg, 0.50 mmol) and the mixture was stirred at the temperature for 18 h followed by addition to 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. The residue was purified by SiO_2 column chromatography (0 to 5% MeOH in CH_2Cl_2) to afford **2000F** (102 mg, 82% yield).

Example 2001



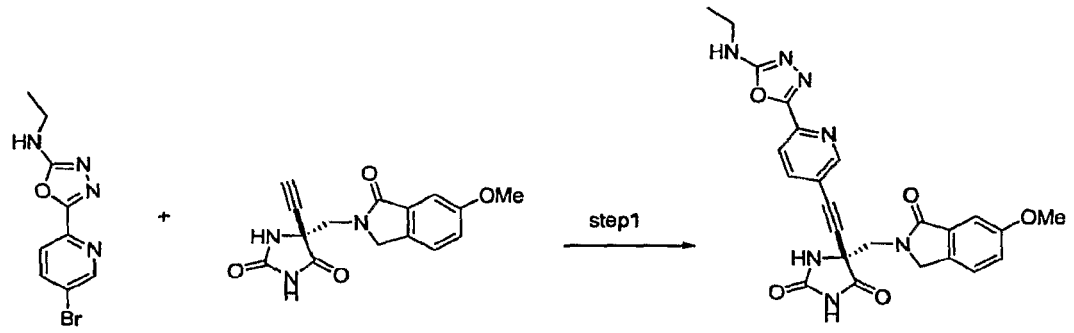
Step1

A solution of **2001A** (11.7 g, 48 mmol) and **2001B** (10.3 g, 40 mmol) in THF (400 mL) was cooled to -7~8 °C and treated with NaH (60% dispersion, 6 g, 150 mmol) portionwisely. The mixture was stirred for 2 h at the temperature and quenched by slow addition of acetic acid (15 mL). The mixture was poured to a mixture of cold aqueous $NaHCO_3$ solution and EtOAc. After stirring for 0.5 h, 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. The oily residue was solidified in EtOAc/hexane (1:1 mixture) to afford racemic **2001C** (8.5 g) as a white solid after filtration. The filtrate was concentrated and the residue was purified by SiO_2 column chromatography (EtOAc : hexane = 1:2) to afford **2001C** (1.5 g, 60% combined yield). The active chiral isomer **2001C** (0.32 g from racemic 0.8 g per loading) was obtained by HPLC separation using preparative chiral OD column (EtOH : hexane = 1:4).

Step 2

A solution of **2001C** (3 g, 7.16 mmol) in THF (30 mL) was treated with TBAF (1 M solution in THF, 10 mL, 10 mmol) at 0 °C. The mixture was stirred for 1.5 h at the temperature and poured to a mixture of ice-water and EtOAc. 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 provide crude **400**. The crude **400** was placed in a pressure vessel and dissolved in ammonia in MeOH (7 N solution, 60 mL). The solution was heated to 80 °C for 14 h and cooled to 25 °C followed by concentration. The residue was treated with CH_2Cl_2 in an ice bath and the resulting solid was filtered to afford **2001E** (1.38 g) and the filtrate was concentrated and the residue was solidified in CH_2Cl_2 and hexane to afford **2001E** (0.24 g, 76% combined yield).

Example 2002



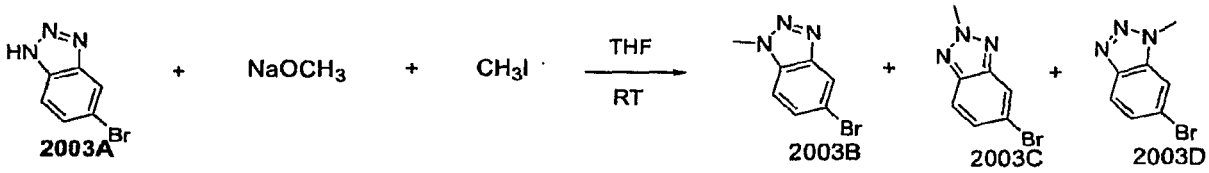
2000F 2001E 1502

Step1

A mixture of **2001E** (52 mg, 0.17 mmol), **2000F** (68 mg, 0.26 mmol), $Pd(PPh_3)_2Cl_2$ (2.4 mg, 3.4 μmol), CuI (3.2 mg, 17 μmol), and diisopropylethylamine (65 μL, 0.37 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

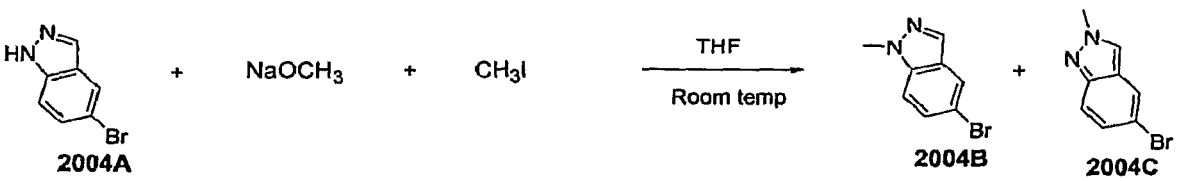
(0.01%HCO_2H in water/0.01% HCO_2H in CH_3CN) to afford compound **1502** (47 mg, 57% yield).

Example 2003



Compound **2003A** (400 mg, 2.0 mmol) was dissolved in 10 mL of THF and reacted with sodium methoxide (4 mL, 2.0 mmol). After 30 min iodomethane (0.5 mL, 8.0 mmol) was added. Reaction mixture was stirred for 4 hours at room temp, then it was added to ethyl acetate and water. The aqueous layer was extracted with ethyl acetate twice. All the organic layers were combined, washed with brine solution and dried over sodium sulfate. The solvent was removed by rotary evaporator and further purified by SiO_2 column chromatography to give **2003B** (105 mg, 25% yield), **2003C** (110 mg, 26% yield) and **2003D** (106 mg, 25% yield).

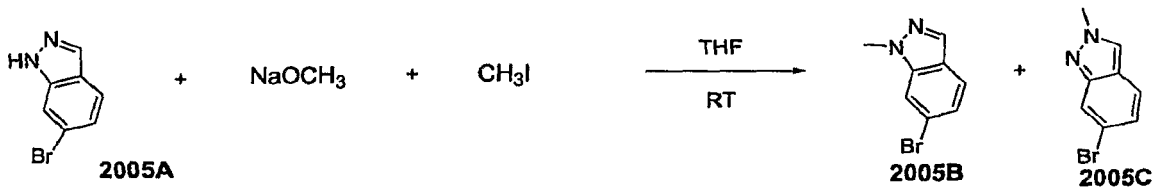
Example 2004



Compound **2004A** (1 g, 5.07 mmol) was dissolved in 20 mL of THF and reacted with sodium methoxide (10 mL, 5.07 mmol). After 30 min, iodomethane (1.3 mL, 20.3 mmol) was added. Reaction mixture was stirred

for 5 hours at room temp, then it was added to ethyl acetate and water. The aqueous layer was extracted with ethyl acetate twice. All the organic layers were combined, washed with brine solution and dried over sodium sulfate. The solvent was removed by rotary evaporator and further purified by SiO_2 column chromatography to give **2004B** (470 mg, 44% yield) and **2004C** (450 mg, 42% yield).

Example 2005



Compound **2005A** (400 mg, 2.03 mmol) was dissolved in 10 mL of THF and reacted with sodium methoxide (4 mL, 2.03 mmol). After 30 min iodomethane (0.5 mL, 8.12 mmol) was added. Reaction mixture was stirred for 3 hours at room temp, then it was added to ethyl acetate and water. The aqueous layer was extracted with ethyl acetate twice. All the organic layers were combined, washed with brine solution and dried over sodium sulfate. The solvent was removed by rotary evaporator and further purified by SiO_2 column chromatography to give **2005B** (200 mg, 47% yield), **2005C** (150 mg, 35% yield).

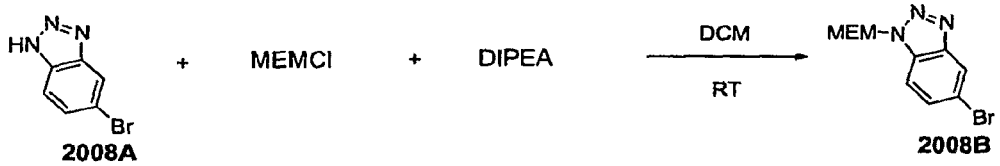
Example 2007



2007A **2007B**

Compound **2007A** (200 mg, 1.01 mmol) was dissolved in 10 mL of CH_2Cl_2 and reacted with DIPEA (0.5 ml, 3.04 mmol), followed by addition of MEMCl (0.15 mL, 1.31 mmol). The reaction mixture was stirred for 5 hours at room temp, then it was added to CH_2Cl_2 and sodium bicarbonate aqueous solution. The organic layers were extracted with CH_2Cl_2, combined and dried over sodium sulfate. The solvent was removed by rotary evaporator to yield compound **2007B** (205 mg, 71% yield).

Example 2008



2008A **2008B**

Compound **2008A** (200 mg, 1.02 mmol) was dissolved in 10mL of CH_2Cl_2 and reacted with DIPEA (0.53 ml, 3.03 mmol), followed by addition of MEMCl (0.15 mL, 1.31 mmol). The reaction mixture was stirred for 16 hours at room temp, then it was added to CH_2Cl_2 and sodium bicarbonate aqueous solution. The organic layers were extracted with CH_2Cl_2, combined and dried over sodium sulfate. The solvent was removed by rotary evaporator to yield compound **2008B** (210 mg, 72% yield).

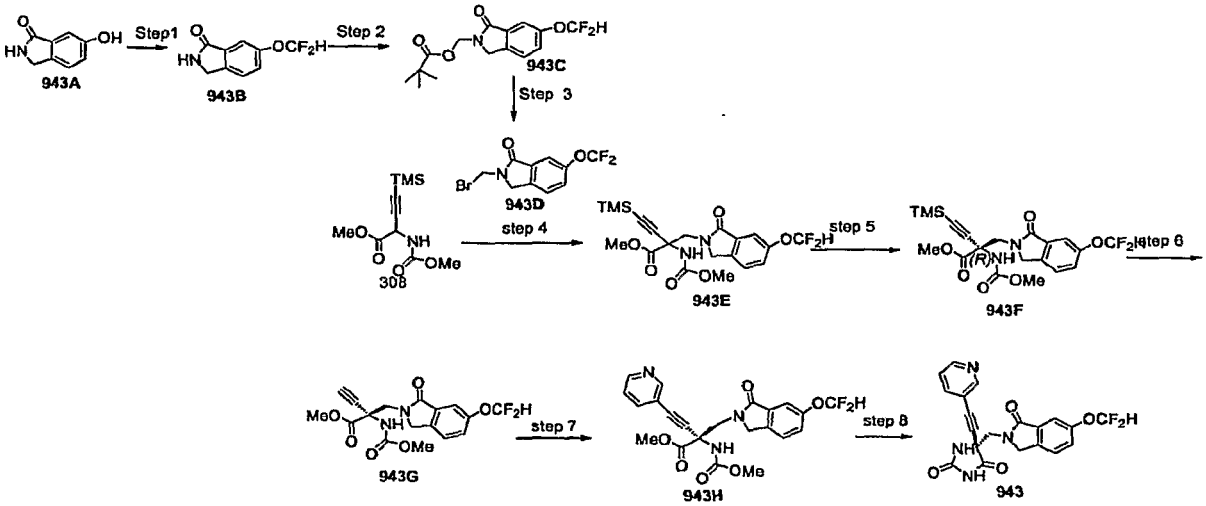
Example 2009



2009A 1522

Compound **2009A** (20 mg, 0.04 mmol) was dissolved in 2 mL of MeOH-CH_2Cl_2 (1:1 mixture) and reacted with trifluoroacetic acid (0.4 ml). The reaction mixture was stirred for 3 days at room temp and then at 40 °C for 20 hours. The solvent was removed by rotary evaporator and the residue was purified by preparative TLC to yield compound **1522** (2 mg, 12% yield).

Example 943



Step 1.

943A (0.35 g, 2.35 mmol) in 5 mL NMP was treated with Cs_2CO_3 (1.15 g, 3.5 mmol). The flask was equipped with a dry ice acetone trap and difluoro choro methane gas was bubbled for 2 h. another portion of Cs_2CO_3 (2.68 g, 8.2 mmol) was added excess of difluoro choro methane gas was bubbled in

before the bubbling was stopped and the reaction was stirred overnight. Another portion of Cs_2CO_3 (2.68 g, 8.2 mmol) was added excess of difluoro choro methane gas was bubbled in and the reaction was stirred at rt for 3 h. The reaction was diluted with 15 mL CH_2Cl_2 and washed with water (2 X 15 mL) and brine (1x15 mL). The organics were dried and concentrated to yield a crude which was purified by silica-gel prep plate chromatography using 3:1 ethyl acetate: hexane to yield 230 mg of pure product **943B**.

Step 2.

Compound **943B** (600 mg, 3.01 mmol) was dissolved in THF (40 mL) and DMPU (6 mL) and potassium *t*-butoxide (406 mg, 3.61 mmol) was added and stirred at rt for 2 h. Chloro pivalate (0.656 mL, 4.52 mmol) was added dropwise and stirred at rt for 2 h. The reaction was quenched with NH_4Cl-H_2O and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried and concentrated to yield a crude which was purified by silica-gel prep plate chromatography using 1:3 ethyl acetate: hexane to yield 700 mg of pure product **943C**.

Step 3.

Compound **943C** (1.4 g, 4.47 mmol) was dissolved in CH_2Cl_2(20 mL) and cooled to 0 °C. TMS bromide (1.13 mL, 8.58 mmol) was added dropwise. The reaction was stirred at 0 °C for 2 h and it was slowly warmed up to rt. Solvent was removed and it was dried under vacuum to give compound **943D** (1.2g, 92%).

Step 4.

Compound **308** (1.05 g, 4.3 mmol) and compound **943D** (1.1 g, 3.76 mmol) were dissolved in THF (40 mL) and cooled to -30°C. NaH (518 mg, 12.95 mmol) was added portionwise and the reaction mixture was stirred for 2 hours at -12°C. Acetic acid 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, 30% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) afforded the desired product **943E** (1.3 g, 76%).

Step 5

The two isomers 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 90% hexanes/2-propanol. The first isomer was the desired compound **943F** (400 mg, 80%).

Step 6:

Compound **943F** (450 mg, 1 mmol) was dissolved in THF (10 mL) and cooled to 0°C. Tetrabutylammonium fluoride (1 M in THF, 1.5 mL, 1.5 mmol) was added dropwise and the reaction was stirred for 20 min at 0°C. 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 **943G** (380 g, 99%). The product was used without purification.

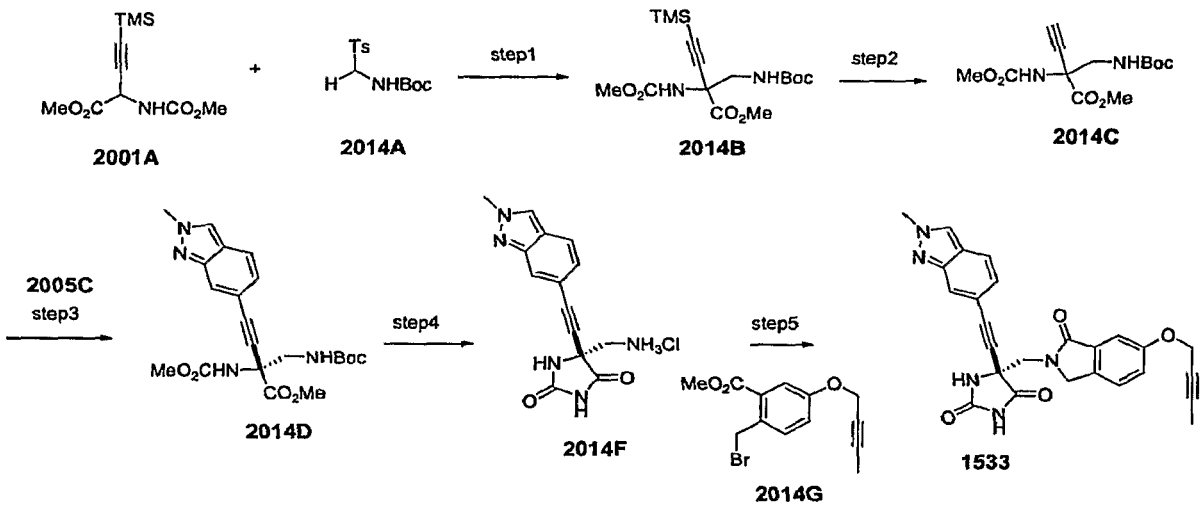
Step 7

Compound **943G** (50 mg, 0.13 mmol) was combined with 3-iodopyridine (40 mg, 2.0 mmol), $Pd(PPh_3)_2Cl_2$ (1 mg, cat.), CuI (2.5 mg, cat.), diisopropylamine (0.04 mL, 0.29 mmol) in DMF (5 mL) and stirred at 70°C for 1 h. 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, 66% EtOAc/Hexanes) afforded the desired product **943H** (46 mg, 77%).

Step 8.

Compound **943H** (46 mg, 0.1 mmol) was dissolved in 7 M ammonia solution (2 mL) and stirred in a sealed pressure tube at 90 °C overnight. The reaction mixture was cooled to room temperature and concentrated. The crude material was treated with EtOEt and the solid was collected by suction filtration to provide compound **943** (28 mg, 68%).

Example 2014



Step1

A solution of **2001A** (515 mg, 2.12 mmol) and **2014A** (730 mg, 2.54 mmol) in THF (15 mL) was cooled to -5 °C and treated with NaH (60% dispersion, 370 mg, 9.25 mmol) portionwisely. The mixture was stirred for 8 h at the temperature and was poured to a mixture of cold aqueous NH_4Cl solution and EtOAc. After stirring for 0.5 h, 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. The residue was purified by SiO_2 column chromatography (1 to 7% MeOH in CH_2Cl_2) to afford **2014B** (600 mg, 72% yield).

Step 2

A solution of **2014B** (600 mg, 1.51 mmol) in THF (10 mL) was treated with TBAF (1 M solution in THF, 1.8 mL, 1.8 mmol) at 0 °C. The mixture was stirred for 3 h at the temperature and poured to a mixture of ice-water and EtOAc. 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. The residue was purified by SiO_2 column chromatography (30% EtOAc in hexane) to afford **2014C** (329 mg, 73% yield).

Step 3

A mixture of **2014C** (168 mg, 0.56 mmol), **2005C** (124 mg, 0.58 mmol), $Pd(PPh_3)_2Cl_2$ (4.0 mg, 6 μmol), CuI (21 mg, 110 μmol), and diisopropylethylamine (0.39 mL, 0.24 mmol) in DMF (4 ml) was purged with N_2 and heated to 70 °C. After heating for 17 h, the mixture was cooled to 25 °C and the mixture was poured to an ice-water. The organic layers were extracted with EtOAc and 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 (1 to 5% MeOH in CH_2Cl_2) to afford racemic **2014D** (183 mg, 76% yield). The active enantiomer of **2014D** was separated by chiral HPLC on chiral OD column (IPA/hexane = 1:3) to afford active isomer **2014D** (50 mg).

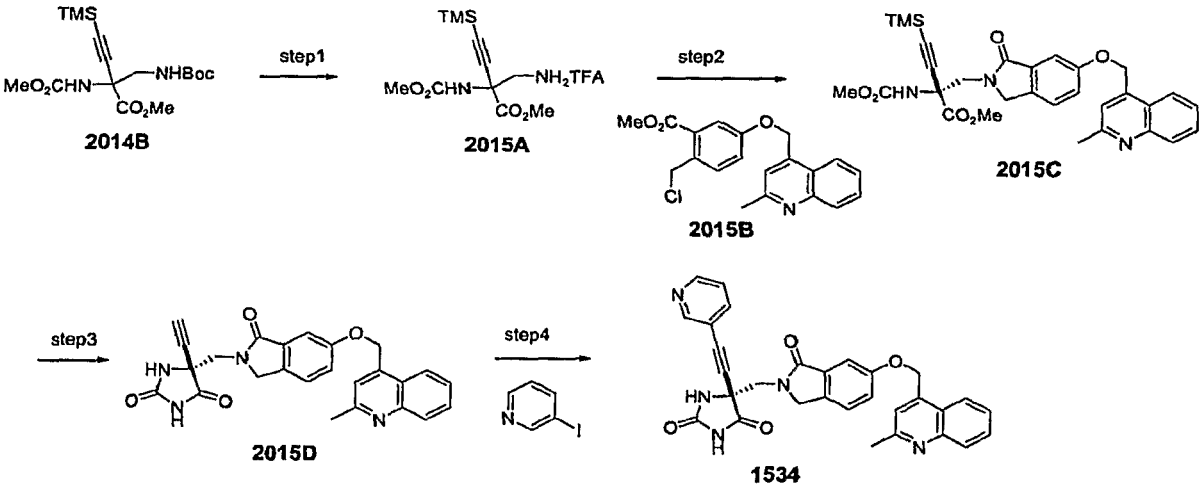
Step 4

2014D (49 mg, 0.11 mmol) was placed in a pressure vessel and dissolved in ammonia in MeOH (7 N solution, 7 mL). The solution was heated to 80 °C for 18 h and cooled to 25 °C followed by concentration. The residue was purified by preparative TLC (7% MeOH in CH_2Cl_2) to afford hydantoin **2014E** (not shown, 35 mg, 84% yield). **2014E** (34 mg, 0.089 mmol) was dissolved in 10% MeOH in CH_2Cl_2 (3 mL) and was treated with 4 N HCl in dioxane (0.3 mL). The mixture was stirred at 25 °C for 18 h and concentrated in vacuo to afford **2014F** (34 mg, quant.).

Step 5

A mixture of **2014F** (18 mg, 0.055 mmol), **2014G** (18 mg, 0.06 mmol), and diisopropylethylamine (48 μL, 0.28 mmol) in DMF (0.5 mL) was heated to 60 °C. The mixture was stirred for 16 h at the temperature and concentrated in vacuo. The residue was dissolved in EtOAc and washed with water, brine solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative TLC (10% MeOH in CH_2Cl_2) to afford **1533** (7 mg, 28% yield).

Example 2015



Step 1

A solution of **2014B** (193 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) was treated with trifluoroacetic acid (0.3 mL) at 25 °C. The mixture was stirred for 2 h at the temperature and concentrated in vacuo to afford **2015A** (280 mg, quant.).

Step 2

A mixture of **2015A** (580 mg, 1.2 mmol), **2015B** (435 mg, 1.22 mmol), and diisopropylethylamine (0.85 mL, 4.88 mmol) in DMF (7 mL) was heated to 80 °C. The mixture was stirred for 48 h at the temperature and concentrated in vacuo. The residue was dissolved in EtOAc and washed with water, brine solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (0 to 5% MeOH in CH_2Cl_2) to afford racemic **2015C** (180 mg, 28% yield). The active enantiomer of **2015C** was separated by chiral HPLC on chiral OD column (IPA/hexane = 1:3) to afford active isomer **2015C** (68 mg).

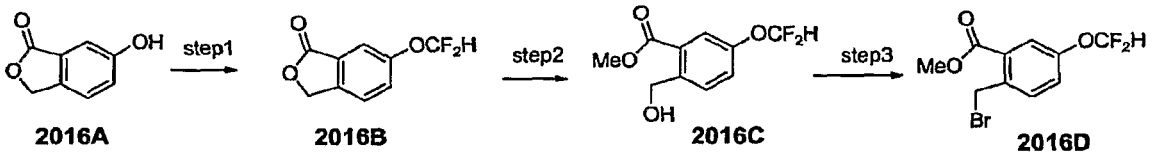
Step 3

A solution of **2015C** (68 mg, 0.12 mmol) in THF (2 mL) was treated with TBAF (1 M solution in THF, 0.16 mL, 0.16 mmol) at 0 °C. The mixture was stirred for 1.5 h at the temperature and poured to a mixture of ice-water and EtOAc. 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 provide desilylated compound after SiO_2 column separation (0 to 5% MeOH in CH_2Cl_2). The desilylated compound (48 mg, 0.098 mmol) was placed in a pressure vessel and dissolved in ammonia in MeOH (7 N solution, 10 mL). The solution was heated to 70 °C for 18 h and cooled to 25 °C followed by concentration to afford crude **2015D** (39 mg, 82% yield in 2steps).

Step 4

A mixture of **2015D** (39 mg, 0.089 mmol), 3-iodopyridine (37 mg, 0.18 mmol), $Pd(PPh_3)_2Cl_2$ (1.4 mg, 9 μmol), CuI (1.4 mg, 2 μmol), and diisopropylethylamine (0.027 mL, 0.20 mmol) in DMF (1 ml) was purged with N_2 and heated to 70 °C. After heating for 3 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 **1534** (27 mg, 59% yield).

Example 2016



2016A **2016B** **2016C** **2016D**

Step 1

To a suspension of **2016A** (1.46 g, 9.73 mmol) and K_2CO_3 (4.03 g, 29.2 mmol) in DMF (35 mL) in a 3-neck 100 mL flask equipped with dryice condenser was bubbled CF_2ClH gas and the mixture was heated to 70 °C. After 16 h stirring at the temperature, the mixture was cooled to 25 °C and diluted in EtOAc. The organic solution was washed with water, brine solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2) to afford **2016B** (900 mg, 46% yield).

Step 2

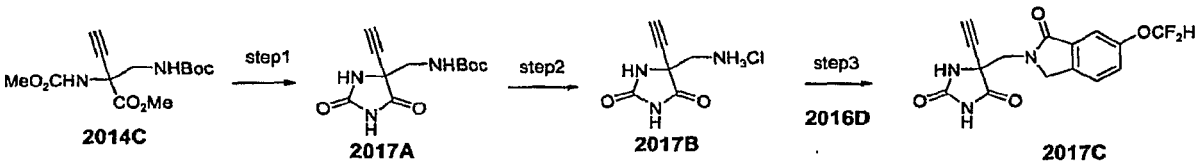
A suspension of **2016B** (428 mg, 2.14 mmol) in water (2.5 mL) was treated with 1N NaOH solution (2.14 mL, 2.14 mmol) and the mixture was stirred at 100 °C for 2 h. The mixture was cooled and concentrated in vacuo. The residual solid was dried by azeotropic distillation with tolune and dissolved in DMF (2.5 mL). The solution was treated with iodomethane (0.4 mL, 6.42 mmol) at 25 °C for 4 h followed by addition to ice-water. The organic layers were extracted with EtOAc and 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) to afford **2016C** (326 mg, 66% yield).

Step 3

A solution of **2016C** (50 mg, 0.22 mmol) in THF (1 mL) was treated with tribromophosphine (20 μL, 0.22 mmol) at 25 °C. The reaction mixture was stirred at the temperature for 20 h and added to aqueous $NaHCO_3$ solution.

The organic layers were extracted with $CH2Cl_2$ and 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 = 1:1) to afford **2016D** (16 mg, 25% yield).

Example 2017



Step 1

2014C (73 mg, 0.24 mmol) was placed in a pressure vessel and dissolved in ammonia in MeOH (7 N solution, 5 mL). The solution was heated to 80 °C for 18 h and cooled to 25 °C followed by concentration. The residue was purified by SiO_2 column chromatography (1 to 10% MeOH in CH_2Cl_2) to afford **2017A** (20 mg, 33% yield).

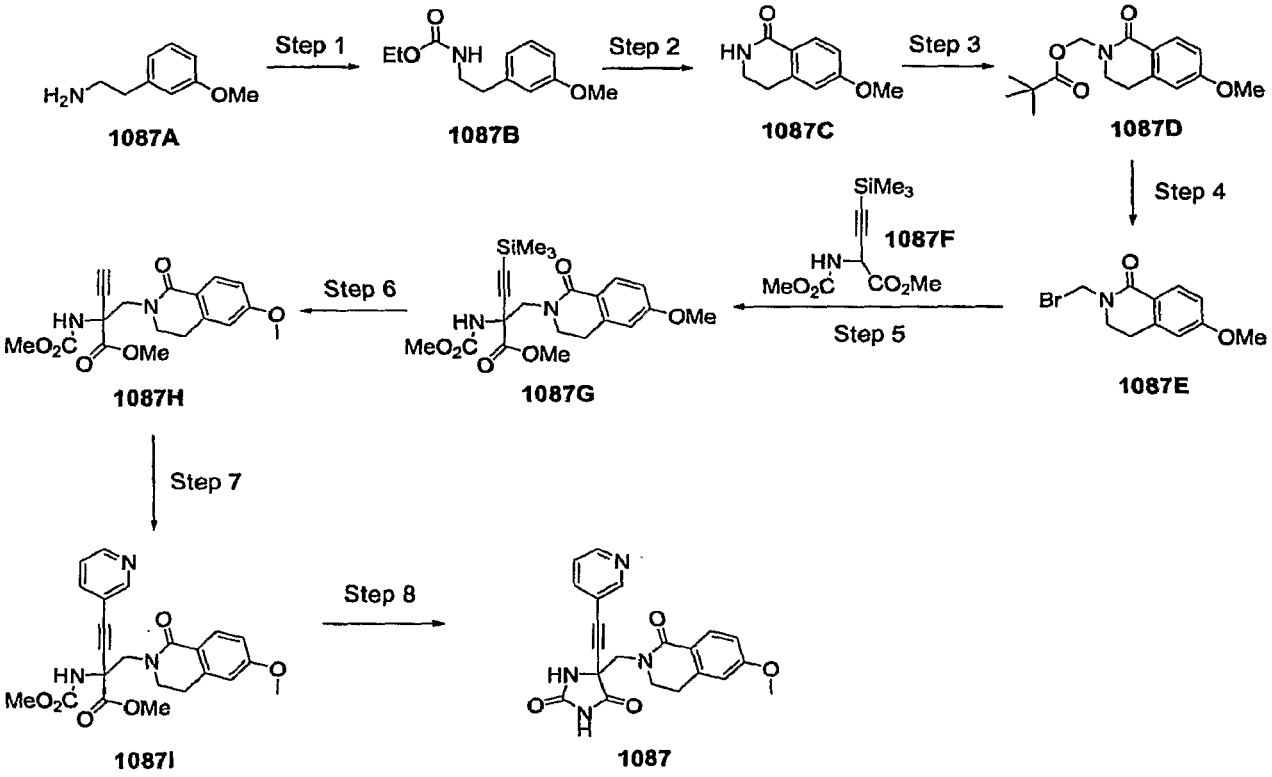
Step 2

2017A (20 mg, 0.08 mmol) in MeOH (2 mL) was treated with 4 N HCl in dioxane (1 mL) at 25 °C. The mixture was stirred at the temperature for 20 h and concentrated in vacuo to afford crude **2017B** (19.6 mg).

Step 3

A mixture of **2017B** (19.6 mg, 0.103 mmol), **2016B** (37 mg, 0.12 mmol), and diisopropylethylamine (0.11 mL, 0.6 mmol) in DMF (0.5 mL) was heated to 60 °C. The mixture was stirred for 48 h at the temperature and concentrated in vacuo. The residue was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford **2017C** (11 mg, 32% yield).

Example 1087



Step 1

Neat ethyl chloroformate (12.5 mL, 14.3 g, 132 mmol) was added dropwise over ~10 min to a stirred, ice-cold solution of Compound **1087A** (18.9 g, 125 mmol) and triethylamine (18.2 mL, 13.3 g, 132 mmol) in CH_2Cl_2 (400 mL). The solution was stirred at 0 °C for 1.5 h, after which solvents were removed by evaporation. The resulting liquid was dissolved in EtOAc (~400 mL) and the resulting solution was washed sequentially with water (2 x 100 mL) and brine (~100 mL). The organic layer was dried over anhydrous MgSO4, filtered, and concentrated to give Compound **1087B** as a pale yellow liquid (26.9 g, 96%).

Step 2

The transformation of Compound **1087B** to Compound **1087C** was carried out following the procedure of Sall and Grunewald, in Sall, D.J.; Grunewald, G.L. *J. Med. Chem.* **1987**, *30*, 2208–2216.

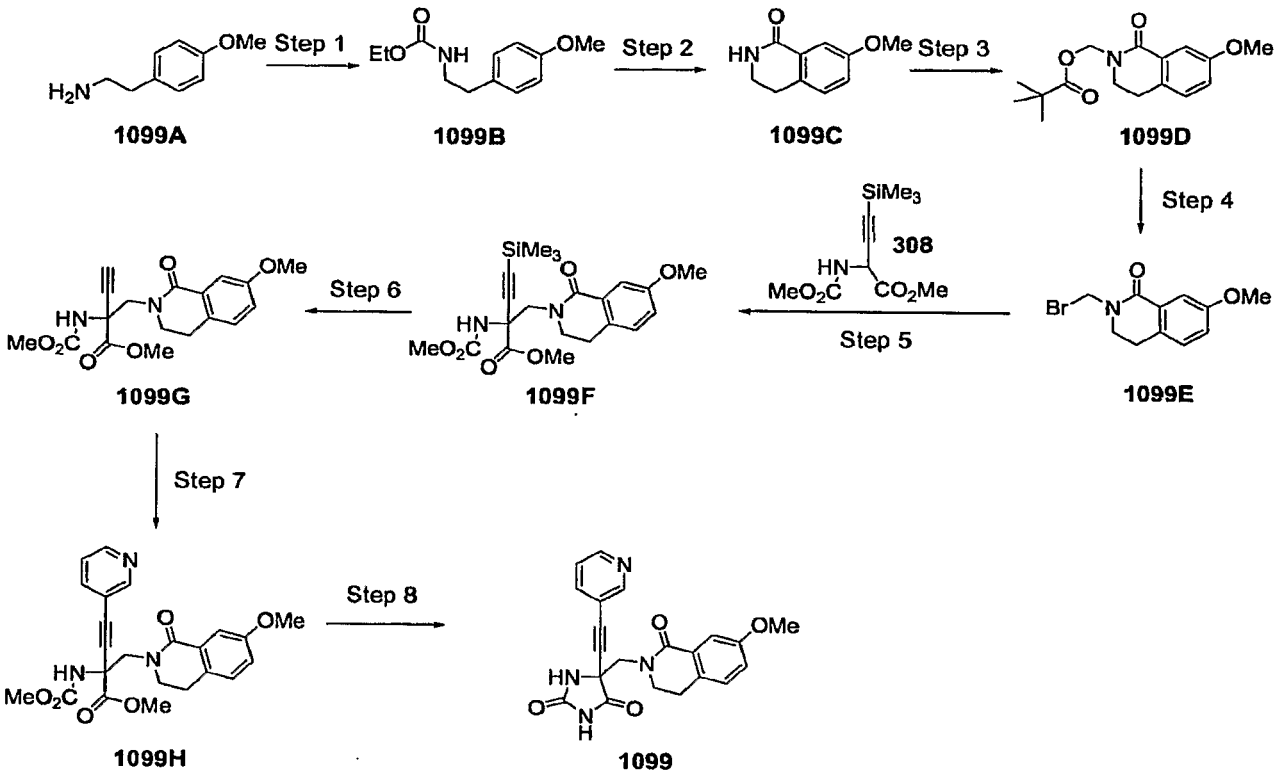
Step 3
The conversion of Compound **1087C** to Compound **1087D** was carried out following the procedure given in Example 300A, Step D.

Step 4
The conversion of Compound **1087D** to Compound **1087E** was carried out following the procedure given in Example 300A, Step E.

Step 5
Compounds **1087F** (2.45 g, 10.1 mmol) and **1087E** (2.86 g, 10.6 mmol) were admixed. Dry THF (80 mL) was added and the resulting suspension was cooled to –78 °C and stirred for 30 min. LHMDS solution (20 mL, 1 M in THF, 20 mmol) was added dropwise over 15 min. The reaction mixture was stirred at –78 °C for 2 h. Saturated aq. ammonium chloride solution (100 mL), followed by EtOAc (250 mL), were added to the stirred reaction mixture and the temperature was allowed to rise to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by sgc (10-100% EtOAc–hexane gradient) to afford Compound **1087G** (2.70 g, 62%) as a beige solid.

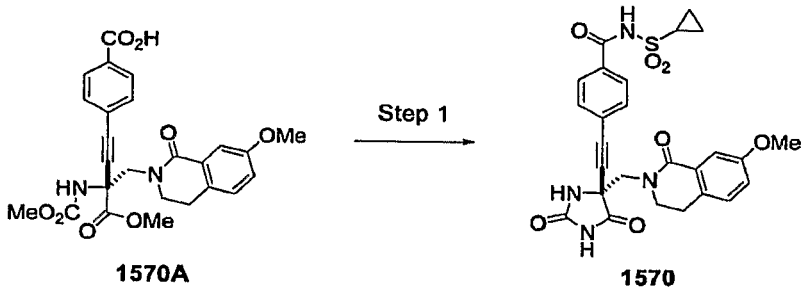
Steps 6, 7, 8
Compound **1087G** was converted to Compound **1087** in a three-step sequence following the procedure given in Example 300B, Steps D through F.

Example 1099



Compound **1099** was prepared by following the procedure given in Example **1087**, but starting with commercially available 4-methoxyphenethylamine (Compound **1099A**) instead of 3-methoxyphenethylamine (Compound **1087A**).

Example 1570



Compound **1570A** was prepared from Compound **400** and 4-iodobenzoic acid by sequential application of the procedures given in Parts H and I in Example **400**. Solid carbonyl diimidazole (19 mg, 0.12 mmol) was added in one

portion to a stirred solution of Compound **1570A** in THF (200 μL). The solution was stirred at 70 °C for 1.5 h, and was subsequently allowed to cool to rt. Solid cyclopropanesulfonamide (17 mg, 0.14 mmol) and DBU (43 μL, 43 mg, 0.29 mmol) were added sequentially and the reaction mixture was stirred at rt for 18 h. The solvent was evaporated and the residue was dissolved in DCM (50 mL). The solution was washed sequentially with 0.1 N aq hydrochloric acid (~25 mL), water (~25 mL) and brine (~25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford an off-white solid. The crude product was purified by PTLC (3:1 EtOAc–hexanes + 1% HCO_2H) to afford the desired Compound **1570** (24 mg, 48% yield) as a beige solid.

Proton NMR spectral data for certain of the Compounds are set forth below:

Compound 400B. ^{1}H NMR (400 Hz, DMSO-d_6) δ 11.2 (s, 1H), 8.8 (s, 1H), 8.6 (m, 2H), 8.0 (d, 1H), 7.6 (m, 2H), 7.2 (m, 2H), 4.6 (m, 2H), 4.05 (m, 2H), 3.8 (s, 3H).

Compound 417C. ^{1}H NMR (400 Hz, DMSO-d_6) δ 12.05 (s, 1H), 11.14 (s, 1H), 8.84 (d, J = 1.6 Hz, 1H), 6.63 (m, 1H), 7.27 (m, 2H), 7.18 (m, 2H), 6.19 (m, 1H), 4.59 (dd, J = 6.4 Hz, 16.8 Hz, 2H), 4.02 (m, 2H), 3.80 (s, 3H)

Compound 424. ^{1}H NMR (400 Hz, DMSO-d_6) δ 11.22 (s, 1H), 8.90 (d, 1H, J = 1.0 Hz), 8.38 (s, 1H), 7,72 (m, 2H), 7.55 (d, 1H, J = 8.4 Hz), 7.19 (m, 2H), 6.97 (m, 1H), 4.60 (m, 2H), 4.18 (s, 3H), 4.12 (m, 2H), 3.83 (s, 3H).

Compound 447. ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.85 (br s, 1H), 7.02 (br s, 1H), 7.91-7.88 (m, 2H), 7.77 – 7.74 (m, 1H), 7.61 (t, *J* = 8.20 Hz, 1H), 7.55 (d, *J* = 8.53 Hz, 1H), 7.23 – 7.17 (m, 2H), 4.64 – 4.5 (m, 2H), 4.15 – 4.01 (m, 2H), 3.82 (s, 3H).

Compound 494. ^{1}H NMR (400 Hz, DMSO-d_6) δ 11.2 (s, 1H), 8.9 (s, 1H), 8.7 (bs, 1H), 7.8 (s, 1H), 7.5 (d, 1H), 7.4-7.3 (m, 2H), 7.2-7.1 (m, 2H), 4.5 (dd, 2H, J = 17 Hz, 33 Hz), 4.05 (dd, 2H, J = 14 Hz, 20 Hz), 3.8 (s, 3 H).

Compound 507. ^{1}H NMR (400 Hz, DMSO-d_6) δ 11.2 (s, 1H), 8.9 (s, 1H), 7.8 (d, 1H), 7.5 (m, 1H), 7.4 (s, 1H), 7.2-7.1 (m, 3H), 4.6 (dd, 2H, J= 17 Hz, 26 Hz), 4.05 (dd, 2H, J = 14 Hz, 30 Hz), 3.8 (s, 3H), 3.0 (s, 3H).

Compound 554. ^{1}H NMR (400 Hz, DMSO-d_6) δ 11.27 (s, 1H), 8.93 (d, 1H, J = 1.2 Hz), 7.96 (bs, 2H) 7.52 (d, 1H, J = 8.4Hz), 7.23 (m, 2H), 1.17 (m, 1H), 4.54 (m, 2H), 4.07 (m, 2H), 3.8 (s, 3H).

Compound 555. ^{1}H NMR (400 Hz, DMSO-d_6) δ 11.73 (s, 1H), 11.14 (s, 1H), 8.79 (s, 1H), 7.54 (m, 2H), 7.17 (m, 2H), 6.20 (s, 1H), 4.52 (dd, J = 25.6 Hz, 17.6 Hz, 2H), 4.03 (m, 2H), 3.79 (s, 3H), 2.03 (s, 3H).

Compound 516. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 7.49 (m, 3H), 7.30 (m, 1H), 7.20 (m, 3H), 4.55 (dd, J = 36.8 Hz, 17.2 Hz, 2H), 4.07 (s, 2H), 3.80 (s, 3H).

Compound 490. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.9 (bs, 1H), 8.95 (s, 1H), 7.6 (m, 1H), 7.5 (d, 1H), 7.4 (m, 1H), 7.2-7.1 (m, 3H), 4.5 (m, 2H), 4.05 (s, 2H), 3.8 (s, 3H).

Compound 442. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 9.74 (s, 1H), 9.08 (d, 1h, J = 1.7 Hz), 8.66 (d, 1H, J = 6.1 Hz), 8.45 (d, 1H, J = 8.5 Hz), 8.29 d, 1H, J = 6.3 Hz), 8.19 (dd, 1H, J = 0.9, 7.2 Hz), 7.89 (dd, 1H, J = 7.6, 8.2 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.25 – 7.10 (m, 2H), 4.63 (m, 2H), 4.29 (d, 1H, J = 14.0 Hz), 4.15 (d, 1H, J = 13.9 Hz), 3.82 (s, 3H)

Compound 930. ^{1}H NMR (500 Hz, MeOH-d_4) δ 7.95 (d, 1H, J =4 Hz), 7.67 (dd, 1H, J =10 Hz, 1.5 Hz), 7.48 (d, 1H, J =8.5Hz), 7.33 (d, 1H, J =2.5 Hz), 7.22 (dd, 1H, J =2.5Hz, 8.5 Hz), 6.67 (dd, 1H, J =8 Hz, 5 Hz), 4.67 (q, 2H, J =17 Hz), 4.36 (d, 1H, J =14 Hz), 4.15 (d, 1H, J =14.5 Hz), 3.88 (s, 3H).

Compound 943. ^{1}H NMR (500Hz, MeOH-d_4) δ 8.630 (s, 1H), 8.568 (dd, J=2.0Hz, 5.1Hz, 1H), 7.925 (dt, J=1.5Hz, 8.2Hz, 1H), 7.648 (d, J=8.8Hz, 1H), 7.57(s, 1H), 7.452 (m, 2H), 6.940 (t, J=73.1Hz, 1H), 4.731 (dd, J=16.4Hz, 56.7Hz, 2H), 4.267 (dd, J=23.1Hz, 14.2Hz, 2H).

Compound 960. ^{1}H NMR (500Hz, MeOH-d_4) δ 8.492 (s, 2H), 8.137 (d, J=2.2Hz, 1H), 7.490 (d, J=8.5Hz, 1H), 7.337 (d, J=2.8Hz, 1H), 7.217 (dd, J=8.5Hz, 2.5Hz, 1H), 4.673 (dd, J=55.2Hz, 17.3Hz, 2H), 4.280 (dd, J=37.8Hz, 14.2Hz, 2H), 3.877 (s, 3H).

Compound 972. ^{1}H NMR (500Hz, MeOH-d_4) δ 9.319 (s, 1H), 8.159 (s, 1H), 8.083(d, J=8.5Hz, 1H), 7.547 (dd, J=2.3Hz, 8.6Hz, 1H), 7.482 (d, J=8.8Hz, 1H), 7.334 (d, J=2.5Hz, 1H), 7.209 (dd, J=8.5Hz, 2.5Hz, 1H), 4.669 (dd, J=59.9Hz, 16.7Hz, 2H), 4.277 (dd, J=29.6Hz, 14.8Hz, 2H), 3.871 (s, 3H).

Compound 1003. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (s, 1H), 9.01 (s, 1H), 8.59 (d, 1H, J = 4.5 Hz), 8.07 (d, 1H, J = 7.5 Hz), 7.55 (d, 1H, J = 8 Hz), 7.50 (t, 1H, J = 5.5 Hz), 7.21 (m, 2H), 4.62 (d, 1H, J = 17 Hz), 4.56 (d, 1H, J = 17 Hz), 4.18 (d, 1H, J = 14 Hz), 4.09 (d, 1H, J = 14 Hz), 3.83 (s, 3H), 2.58 (s, 3H).

Compound 1256. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (s, 1H), 10.84 (s, 1H), 8.91 (s, 1H), 8.66 (s, 1H), 7.55 (H, J = 8 Hz), 7.50 (d, 1H, J = 9 Hz), 7.48 (d, 1H, J = 9 Hz), 7.23 (d, 1H, J = 2.5 Hz), 7.20 (dd, 1H, J = 8, 2.5 Hz), 4.62 (d, 1H, J = 17 Hz), 4.54 (d, 1H, J = 17 Hz), 4.11 (d, 1H, J = 15 Hz), 4.07 (d, 1H, J = 15 Hz), 3.83 (s, 3H), 1.65 (s, 3H).

Compound 1009. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.63 (bs, 1H), 11.24 (s, 1H), 8.90 (S, 1H), 8.57 (bs, 1H), 7.55 (d, 1H, J = 8 Hz), 7.40 (bs, 1H), 7.33 (bs, 1H), 7.27 (m, 2H), 7.20 (d, 1H, J = 8.5 Hz), 4.62 (d, 1H, J = 16.5 Hz), 4.56 (d, 1H, J = 16.5 Hz), 4.15 (d, 1H, J = 14.5 Hz), 4.06 (d, 1H, J = 14.5 Hz), 3.84 (s, 3H).

Compound 1012. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.94 (s, 1H), 7.89 (s, 1H), 7.79 (d, 1H, J = 8.5 Hz), 7.56 (d, 1H, J = 8.5 Hz), 7.50 (d, 1H, J = 8.5 Hz), 7.26 (d, 1H, J = 2.5 Hz), 7.20 (dd, 1H, J = 9, 2.5 Hz), 4.64 (d, 1H, J = 17.5 Hz), 4.58 (d, 1H, J = 17.5 Hz), 4.18 (d, 1H, J = 14.5 Hz), 4.09 (d, 1H, J = 14.5 Hz), 3.84 (s, 3H).

Compound 1253. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.95 (s, 1H), 8.72 (s, 1H), 7.67 (d, 1H, J = 8 Hz), 7.63 (s, 1H), 7.55 (d, 1H, J = 8 Hz), 7.53 (d, 1H, J = 8 Hz), 7.25 (d, 1H, J = 2.5 Hz), 7.20 (dd, 1H, J = 8, 2.5 Hz), 4.63 (d, 1H, J = 17.5 Hz), 4.56 (d, 1H, J = 17.5 Hz), 4.41 (s, 2H), 4.15 (d, 1H, J = 14 Hz), 4.09 (d, 1H, J = 14 Hz), 3.84 (s, 3H).

Compound 1015. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.84 (s, 1H), 8.21 (s, 1H), 7.88 (d, 1H, J = 8 Hz), 7.56 (d, 1H, J = 8 Hz), 7.48 (d, 1H, J = 7.5 Hz), 7.25 (d, 1H, J = 2 Hz), 7.20 (dd, 1H, J = 8, 2 Hz), 7.14 (d, 1H, J = 7.5 Hz), 4.65 (d, 1H, J = 17.5 Hz), 4.61 (d, 1H, J = 17.5 Hz), 4.30 (d, 1H, J = 14 Hz), 4.15 (d, 1H, J = 14 Hz), 3.83 (s, 3H).

Compound 1155. ^{1}H NMR (500 MHz, MeOH-d_6) δ 8.90 (bs, 1H), 8.51 (d of d, 1H, J = 8 Hz, J = 2 Hz), 7.94 (d, 1H, 8 Hz), 7.49 (d, 1H, 9 Hz), 7.31 (d, 1H, J = 2 Hz), 7.23 (d of d, 1H, J = 9 Hz, 2 Hz), 4.69 (d, 1H, J = 17 Hz), 4.60 (d, 1H, J = 17 Hz), 4.35 (d, 1H, J = 14 Hz), 4.22 (d, 1H, 14 Hz), 3.88 (s, 3H).

Compound 1152. ^{1}H NMR (500 MHz, MeOH-d_6) δ 7.46-7.51 (m, 3H), 7.31 (s, 1H), 7.20 (d, 1H, J = 9 Hz), 6.66 (bs, 1H), 4.68 (d, 1H, J = 17 Hz). 4.57 (d, 1H, J = 17 Hz), 4.30 (d, 1H, J = 14 Hz), 4.23 (d, 1H, J = 14 Hz), 3.87 (s, 3H).

Compound 1129. ^{1}H NMR (500 MHz, MeOH-d_6) δ 7.67 (s, 1H), 7.51-7.46 (m, 1H), 7.39-7.26 (m, 3H), 7.24-7.13 (m, 2H), 6.46 (s, 1H), 4.74 (d, 1H, J = 17 Hz), 4.61 (d, 1H, J = 17 Hz), 4.25 (s, 2H), 3.88 (s, 3H).

Compound 1133. ^{1}H NMR (500 MHz, MeOH-d_6) δ 7.90-7.84 (m, 1H), 7.57-7.46 (m, 3H), 7.35-7.32 (m, 1H), 7.25-7.20 (m, 1H), 4.70 (d, 1H, J = 17 Hz), 4.60 (d, 1H, J = 17 Hz), 4.28 (d, 1H, J = 15 Hz), 4.22 (d, 1H, J = 15 Hz), 3.88 (s, 3H).

Compound 1134. ^{1}H NMR (500 MHz, MeOH-d_6) δ 7.97 (s, 1H), 7.93-7.88 (m, 1H), 7.66-7.61 (m, 1H), 7.52-7.47 (m, 2H), 7.33 (s, 1H), 7.24-7.19 (m, 1H), 4.71 (d, 1H, J = 17 Hz), 4.60 (d, 1H, J = 17 Hz), 4.28 (d, 1H, J = 15 Hz), 4.23 (d, 1H, J = 15 Hz), 3.88 (s, 3H).

Compound 1136. ^{1}H NMR (500 MHz, MeOH-d_6) δ 7.88-7.83 (m, 2H), 7.55-7.45 (m, 3H), 7.34-7.29 (m, 1H), 7.23-7.15 (m, 3H), 4.69 (d, 1H, J = 17 Hz), 4.59 (d, 1H, J = 17 Hz), 4.28 (d, 1H, J = 14 Hz), 4.21 (d, 1H, J = 14 Hz), 3.87 (s, 3H).

Compound 1146. ^{1}H NMR (400 MHz, MeOH-d_6) δ 7.50-7.48 (m, 2H), 7.42 (d, 2H, J = 8 Hz), 7.37-7.33 (m, 1H), 7.30-7.24 (m, 2H), 7.18-7.14 (m, 1H), 5.48 (s, 1H), 4.69 (d, 1H, J = 17 Hz), 4.55 (d, 1H, J = 17Hz), 4.23 (d, 1H, J = 14 Hz), 4.20 (d, 1H, J = 14 Hz), 3.83 (s, 3H).

Compound 1132. ^{1}H NMR (500 MHz, MeOH-d_6) δ 7.47-7.41 (m, 2H), 7.34-7.28 (m, 2H), 7.22-7.13 (m, 2H), 7.10-7.04 (m, 1H), 6.55-6.52 (m, 1H), 4.73

(d, 1H, J = 17 Hz), 4.60 (d, 1H, J = 17 Hz), 4.30 (d, 1H, J = 15 Hz), 4.27 (d, 1H, J = 15 Hz), 3.86 (s, 3H).

Compound 1091. ^{1}H NMR (500 MHz, CD_3OD) δ 8.09 (s, 1H), 7.60 (d, 2H, J = 8 Hz), 7.44–7.51 (m, 3H), 7.33 (d, 1H, J = 2H), 7.22 (dd, 1H, J = 8 Hz, 2 Hz), 4.70 (d, 1H, J = 17 Hz), 4.59 (d, 1H, J = 17 Hz), 4.27 (d, 1H, J = 14.5 Hz), 4.21 (d, 1H, J = 14.5 Hz), 3.88 (s, 3H).

Compound 1063. ^{1}H NMR (500 MHz, CD_3OD) δ 7.48 (d, 1H, J = 8.5 Hz), 7.33 (d, 1H, J = 2.5 Hz), 7.28 (bs, 1H), 7.20–7.30 (m, 2H), 7.11–7.19 (m, 1H), 4.70 (d, 1H, J = 17 Hz), 4.58 (d, 1H, J = 17 Hz), 4.28 (d, 1H, J = 14.5 Hz), 4.21 (d, 1H, J = 14.5 Hz), 3.88 (s, 3H).

Compound 1070. ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (s, 1H), 7.48 (d, 1H, J = 8.5 Hz), 7.32 (d, 1H, J = 2 Hz), 7.22 (dd, 1H, J = 8.5 Hz, 2 Hz), 7.17 (s, 1H), 4.67 (d, 1H, J = 16.5 Hz), 4.57 (d, 1H, J = 16.5 Hz), 4.16–4.28 (m, 4H), 3.88 (s, 3H).

Compound 1090. ^{1}H NMR (500 MHz, CD_3OD) δ 7.48 (d, 1H, J = 8.5 Hz), 7.33 (d, 1H, J = 2.5 Hz), 7.18–7.23 (m, 3H), 4.69 (d, 1H, J = 17 Hz), 4.57 (d, 1H, J = 17 Hz), 2.24 (d, 1H, J = 14.5 Hz), 2.21 (d, 1H, J = 14.5 Hz), 3.88 (s, 3H).

Compound 1092. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.62 (bd, 1H, J =12 Hz), 7.89 (dt, 1H, J = 8.3 Hz, 2 Hz), 7.83 (d, 1H, J = 8.3 Hz), 7.43–7.47 (m, 1H), 6.91 (dd, 1H, J = 8 Hz, 2.5 Hz), 6.86 (d, 1H, J = 2.5 Hz), 4.14 (d, 1H, J = 13.5 Hz), 4.02 (d, 1H, J = 13.5 Hz), 3.81 (s, 3H), 3.68–3.74 (m, 1H), 3.60–3.67 (m, 1H), 2.88–3.01 (m, 2H).

Compound 1098. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.21 (bs, 1H), 7.55 (d, 1H, J = 6 Hz), 7.17–7.26 (m, 2H), 4.63 (d, 1H, J = 17 Hz), 4.57

(d, 1H, J = 17 Hz), 4.17 (d, 1H, J = 13.5 Hz), 4.08 (d, 1H, J = 13.5 Hz), 3.83 (s, 3H), 2.47 (s, 3H).

Compound 1069. ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (d, 1H, J = 8.5 Hz), 7.32 (d, 1H, J = 2.5 Hz), 7.21 (dd, 1H, J = 8.5 Hz, 2.5 Hz), 7.15 (dd, 1H, J = 8 Hz, 1 Hz), 7.12 (d, 1H, J = 1 Hz), 7.01 (d, 1H, J = 8 Hz), 4.70 (d, 1H, J = 17 Hz), 4.59 (d, 1H, J = 17 Hz), 4.26 (d, 1H, J = 14 Hz), 4.20 (d, 1H, J = 14 Hz), 3.84 (s, 3H).

Compound 1099. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.2 (s, 1H), 8.83 (s, 1H), 8.71 (s, 1H), 8.66 (bd, 1H, J = 4 Hz), 7.99 (dt, 1H, J = 8 Hz, 2 Hz), 7.52–7.56 (m, 1H), 7.40 (d, 1H, J = 3 Hz), 7.24 (d, 1H, J = 8.5 Hz), 7.08 (dd, 1H, J = 8.5 Hz, 3 Hz), 4.17 (d, 1H, J = 14 Hz), 4.07 (d, 1H, J = 14 Hz), 3.78 (s, 3H), 3.69–3.75 (m, 1H), 3.61–3.67 (m, 1H), 2.84–2.96 (m, 2H).

Compound 1502. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.98 (s, 1H), 8.71 (s, 1H), 8.01 (m, 2H), 7.56 (d, 1H, J = 8.2 Hz), 7.24 (d, 1H, J = 2.6 Hz), 7.21 (dd, 1H, J = 8.2 Hz, 2.6 Hz), 4.63 (d, 1H, J = 17.1 Hz), 4.57 (d, 1H, J = 17.1 Hz), 4.16 (d, 1H, J = 13.9 Hz), 4.11 (d, 1H, J = 13.9 Hz), 3.84 (s, 3H), 3.30 (m, 2H), 1.19 (t, 3H, J = 7.2 Hz).

Compound 1505. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (s, 1H), 8.93 (s, 1H), 8.76 (s, 1H), 7.69 (s, 1H), 7.56 (d, 1H, J = 8.5 Hz), 7.45 (d, 1H, J = 9.4 Hz), 7.25 (d, 1H, J = 2.6 Hz), 7.21 (dd, 1H, J = 8.5 Hz, 2.6 Hz), 7.13 (dd, 1H, J = 9.4 Hz, 1.6 Hz), 4.63 (d, 1H, J = 17.1 Hz), 4.55 (d, 1H, J = 17.1 Hz), 4.13 (d, 1H, J = 14.2 Hz), 4.08 (d, 1H, J = 14.2 Hz), 3.83 (s, 3H), 2.33 (s, 3H).

Compound 1513. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.98 (s, 1H), 8.68 (s, 1H), 8.20 (s, 1H), 8.06 (dd, 1H, J = 8.2 Hz, 1.9 Hz), 8.04 (d, 1H, J = 8.2 Hz), 7.78 (brs, 1H), 7.56 (d, 1H, J = 8.5 Hz), 7.24 (d, 1H, J = 2.4 Hz),

7.21 (dd, 1H, J = 8.5 Hz, 2.4 Hz), 4.63 (d, 1H, J = 17.1 Hz), 4.57 (d, 1H, J = 17.1 Hz), 4.17 (d, 1H, J = 13.9 Hz), 4.11 (d, 1H, J = 13.9 Hz), 3.84 (s, 3H).

Compound 1519. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.85 (d, 1H, J = 1.2 Hz), 7.91 (d, 1H, J = 2.6 Hz), 7.55 (d, 1H, J = 8.3 Hz), 7.20 (m, 3H), 4.60 (d, 1H, J = 17.0 Hz), 4.51 (d, 1H, J = 17.0 Hz), 4.05 (s, 2H), 3.83 (s, 3H), 3.42 (s, 3H), 1.97 (s, 3H).

Compound 1520. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.97 (d, 1H, J = 1.2 Hz), 8.06 (m, 2H), 7.57 (d, 1H, J = 8.5 Hz), 7.41 (dd, 1H, J = 8.7 Hz, 1.6 Hz), 7.25 (d, 1H, J = 2.4 Hz), 7.21 (dd, 1H, J = 8.5 Hz, 2.4 Hz), 4.64 (d, 1H, J = 17.1 Hz), 4.57 (d, 1H, J = 17.1 Hz), 4.31 (s, 3H), 4.16 (d, 1H, J = 13.8 Hz), 4.12 (d, 1H, J = 13.8 Hz), 3.84 (s, 3H).

Compound 1523. ^{1}H NMR (500 MHz, CD_3OD) δ 8.08 (s, 1H), 7.92 (d, 1H, J = 1.0 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.48 (d, 1H, J = 8.4 Hz), 7.43 (dd, 1H, J = 8.6 Hz, 1.4 Hz), 7.34 (d, 1H, J = 2.6 Hz), 7.21 (dd, 1H, J = 8.2 Hz, 2.6 Hz), 4.71 (d, 1H, J = 17.1 Hz), 4.62 (d, 1H, J = 17.1 Hz), 4.30 (d, 1H, J = 14.2 Hz), 4.19 (d, 1H, J = 14.2 Hz), 3.88 (s, 3H).

Compound 1220B. ^{1}H NMR (500 Hz, dmso-d_6) δ 8.9 (bs, 1H,), 7.95 (d, 2H, J = 5Hz), 7.64 (d, 2H, J = 5Hz), 7.6 (d, 1H, J = 3 Hz), 7.28 (s, 1H), 7.2 (d, 1H, J = 3Hz), 4.6 (dd, 2H, J =16Hz, 9 Hz), 4.15 (dd, 2H, J =16 Hz, 9 Hz), 3.82 (s, 3H).

Compound 1206. ^{1}H NMR (500 Hz, dmso-d_6) δ 8.9 (bs, 1H,), 7.52 (d, 1H, J = 5Hz), 7.2 (m, 2H), 4.6 (dd, 2H, J = 8 Hz, 28 Hz), 4.2 (s, 2H), 3.81 (s, 3H), 212 (s, 3H).

Compound 1201. ^{1}H NMR (500 Hz, dmso-d_6) δ 8.92 (s, 1H,), 7.64 (d, 1H, J = 6Hz), 7.2-7.42 (m, 4H), 7.4 (d, 1H, J = 6 Hz), 6.72 (bs, 1H), 4.62 (d, 1H, J =8Hz), 4.58 (d, 2H, J = 8 Hz), 4.05 (m, 2H), 3.88 (s, 3H).

Compound 1200. ^{1}H NMR (500 Hz, dmso-d_6) δ 8.92 (s, 1H,), 8.65 (m, 2H), 7.4-7.75 (m, 5H), 4.66 (dd, 2H, J =16 Hz, 24 Hz),4.15 (m, 2H).

Compound 1220. ^{1}H NMR.(500Hz, dmso-d_6). 8.449(s.1H), 7.93(s,1H), 7.73 (t, 1H, J= 1.892 Hz), 6.55(d, 1H, J= 2.522 Hz), 6.69(d, 1H, J=8.512Hz), 6.41(dd, 1H, J= 2.52Hz, J =8.51Hz), 4.46-4.40(m, 1H), 3.87(dd, 2H, J=17.02Hz, J=54.85Hz) , 3.48(dd, 2H, J= 14.187Hz, J= 51.703Hz), 3.067(s, 3H), 0.92(d, 6H, J=6.62Hz).

Compound 1552. ^{1}H NMR (500 Hz, CD_3OD) δ 8.11 (s, 1H), 7.49 (d, 1H, *J* = 8.5 Hz), 7.33 (d, 1H, *J* = 2 Hz), 7.11–7.25 (m, 3H), 4.72 (d, 1H, *J* = 17 Hz), 4.60 (d, 1H, *J* = 17 Hz), 4.31 (d, 1H, *J* = 14.5 Hz), 4.23 (d, 1H, *J* = 14.5 Hz), 3.88 (s, 3H), 2.24 (s, 3H).

Compound 1562. ^{1}H NMR (500 MHz, MeOH-d_6) δ 7.63-7.61 (m, 2H) (bs, 1H), 7.57-7.55(m, 2H), 7.48 (d, 1H, 9 Hz), 7.32 (d, 1H, J = 3 Hz), 7.22 (d of d, 1H, J = 9 Hz, 3 Hz), 4.69 (d, 1H, J = 18 Hz), 4.58 (d, 1H, J = 18 Hz), 4.27 (d, 1H, J = 15 Hz), 4.21 (d, 1H, 15 Hz), 3.88 (s, 3H), 3.89-3.86 (m, 1H), 3.40-3.37 (m, 1H).

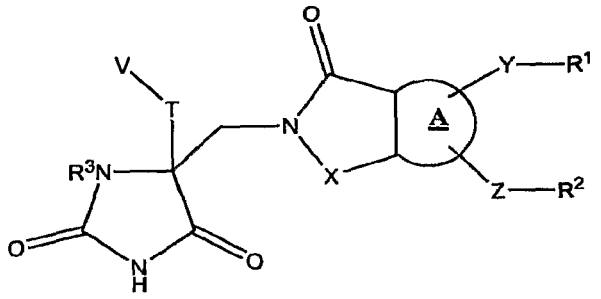
Compound 1576. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (s, 1H), 10.83 (s, 1H), 8.91 (s, 1H), 8.46 (s, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.35 (br. s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.24 (d, J = 2.5 Hz, 1H), 7.20 (m, 2H), 4.63 (d, J = 17 Hz, 1H), 4.54 (d, J = 17 Hz, 1H), 4.11 (d, J = 14 Hz, 1H), 4.07 (d, J = 14 Hz, 1H), 3.83 (s, 3H),.2.98 (m, 2H), 2.54 (m, 1H), 2.16 (m, 1H).

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, ester or isomer 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 alkynyl;

V is selected from the group consisting H, alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, and N-oxides of said heteroaryl and heterocyclyl, wherein when each of said cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, and N oxides of said heteroaryl and heterocyclyl contains two radicals on same or adjacent carbon atoms, said radicals may optionally be taken together with the carbon atom(s) to which they are attached to form a five- to eight-membered cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl ring, wherein each of the aforementioned cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl, optionally with said five- to eight-membered cycloalkyl, cycloalkenyl, 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, 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, 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;

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, -C(O)N(R^4)-S(O)$_2R^4$, -S(O)$_2$N(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)$_2$N(R^4)$_2$, -N(R^4)-C(O)OR^4, -OC(O)N(R^4)$_2$, -N(R^4)C(O)N(R^4)$_2$, -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)$_2$, -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, -C(O)N(R^4)-S(O)$_2R^4$, -S(O)$_2$N(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)$_2$N(R^4)$_2$, -N(R^4)-C(O)OR^4, -OC(O)N(R^4)$_2$, -N(R^4)C(O)N(R^4)$_2$, -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)$_2$, -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 $-N(alkyl)_2$;

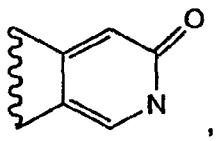
or when two R^{20} moieties when attached to the same or adjacent carbon atoms may optionally be taken together with the carbon atom(s) to which they are attached to form a cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl ring;;

R^{30} is selected from the group consisting of cyano, nitro, $-C(R^4)=N-OR^4$, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)R^4$, $-S(O)_2R^4$, $-N(R^4)S(O)_2R^4$, $-N(R^4)-C(O)-R^4$, $-C(O)N(R^4)-S(O)_2R^4$, $-S(O)_2N(R_4)-C(O)-R^4$, $-C(O)N(R^4)C(O)R^4$, $-C(O)N(R^4)C(O)NR^4$ $-S(O)_2N(R^4)_2$, $-N(R^4)-C(O)OR^4$, $-OC(O)N(R^4)_2$, $-N(R^4)C(O)N(R^4)_2$, $-S(O)_2N(R^4)_2$, $-S(O)_2N(R_4)-C(O)-R^4$, $-N(R^4)-C(=NR^4)-N(R^4)_2$, $-N(R^4)-C(=N-CN)-N(R^4)_2$, -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.

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

3. The compound of claim 1, 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.

4. The compound of claim 3, wherein said ring **A** is phenyl which is substituted with $-Y-R^1$ and $-Z-R^2$ as shown.

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

6. The compound of claim 5, wherein X is $-(C(R^3)_2)_m$, wherein m is 1 or 2.

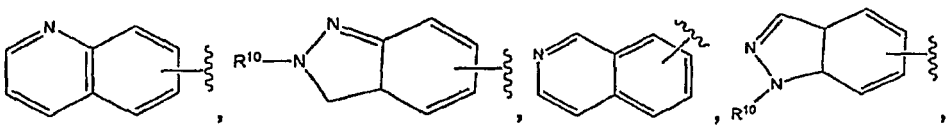
7. The compound of claim 6, wherein m is 1.

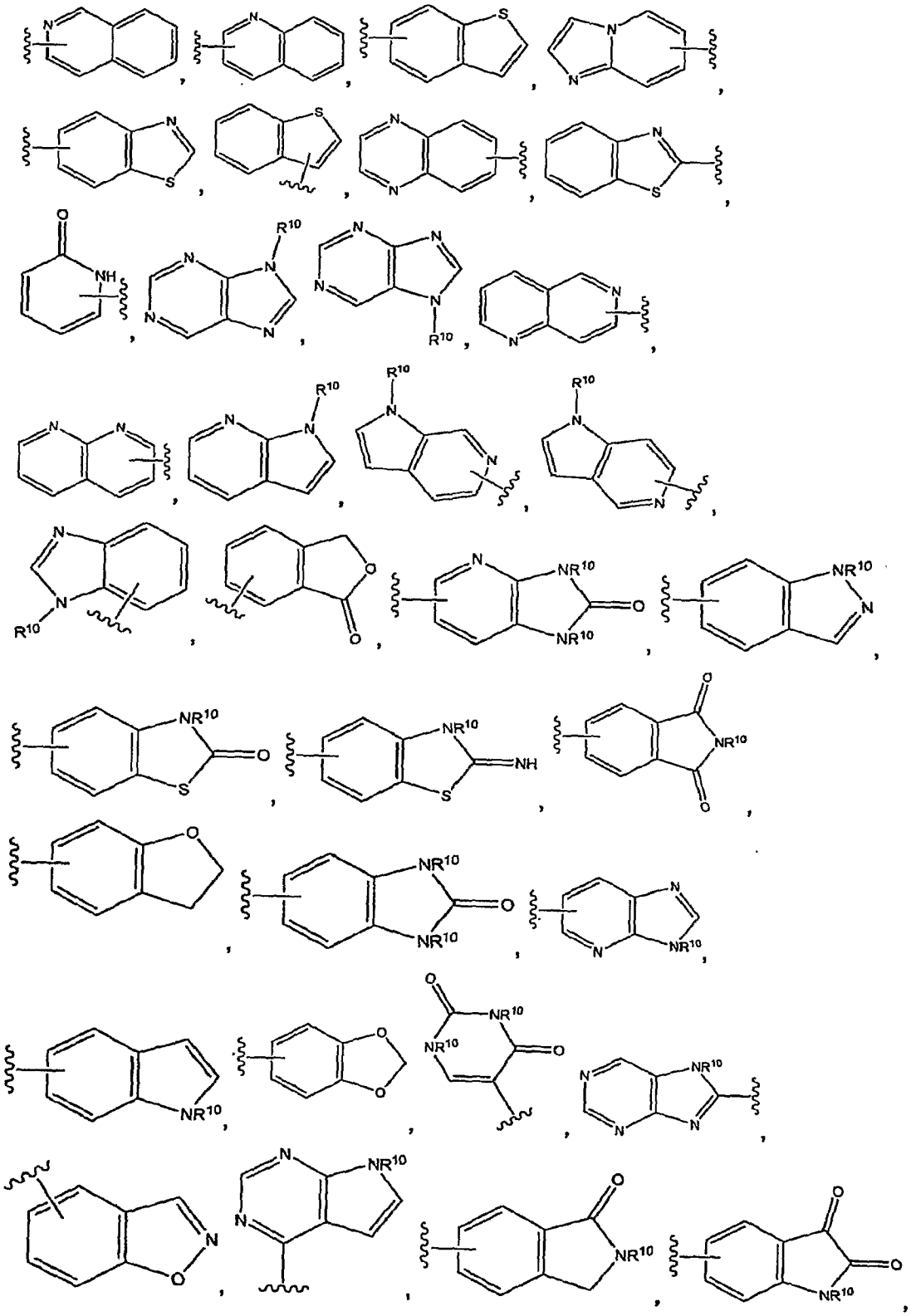
8. The compound of claim 1, 6, or 7, wherein R^3 is H.

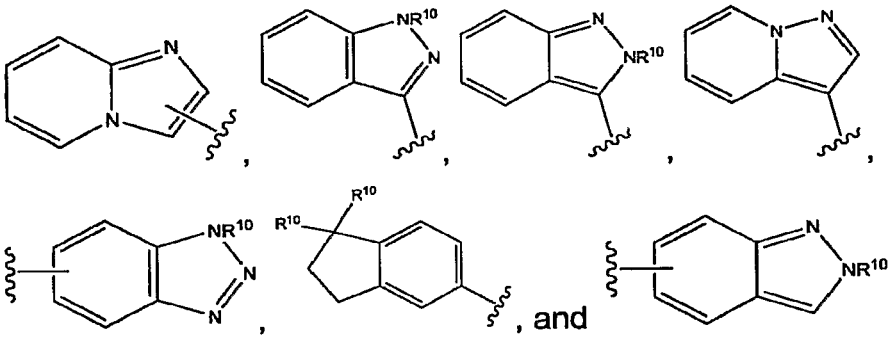
9. The compound of claim 1, wherein T is -C≡C-.

10. The compound of claim 1, wherein V is selected from the group consisting of H, aryl, heteroaryl, and N-oxide of said heteroaryl; wherein when each of the aforementioned aryl, and heteroaryl contains two radicals on same or adjacent carbon atoms, said radicals may optionally be taken together with the carbon atom(s) to which they are attached to form a five or six-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring; wherein said aryl and heteroaryl optionally with said five or six-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally substituted with one to four R^{10} moieties which can be the same or different.

11. The compound of claim 9, wherein V is selected from the group consisting of phenyl, naphthyl, pyrrolyl, furanyl, thiophenyl, pyrrazolyl, benzopyrazolyl, imidazoly, benzimidazolyl, furazanyl, pyridyl, pyridyl-N-oxide, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indazolyl, indolizinyl, quinolinyl, isopquinolinyl, quinazolinyl, pteridinyl, tetrazolyl, oxazolyl, isothiazolyl, thiazolyl,







optionally substituted with one or more R^{10} moieties such that the number of R^{10} moieties per V group does not exceed four.

12. The compound of claim 1, wherein R^{10} is selected from the group consisting of hydrogen, cyano, nitro, $-OR^4$, $-SR^4$, $-N(R^4)_2$, $-S(O)_2R^4$-, $-S(O)_2N(R^4)_2$, -haloalkoxy, $-C(O)OR^4$, $-C(O)R^4$, $-C(O)N(R^4)_2$, $-C(O)N(R^4)-S(O)_2R^4$, $-C(R^4)$=N-OR, halogen, alkyl, haloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of the alkyl, aryl, heteroaryl, and heterocyclyl 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 carbon atom are taken together with the carbon atom to which they are attached to form a heterocyclyl ring;

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; and

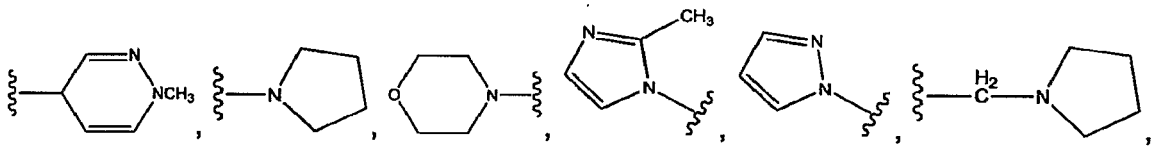
R^{30} is selected from the group consisting of halogen, alkyl, haloalkyl, hydroxy, alkoxy, heterocyclyl, $-C(R^4)$=N-OR, -O-alkyl-cycloalkyl, $-N(R^4)_2$, and $-C(O)N(R^4)_2$, wherein said R^{30} alkyl is substituted with a $-NH_2$.

13. The compound of claim 12, wherein R^{10} is selected from the group consisting of nitro, alkyl, halogen, haloalkyl, haloalkoxy, alkoxy, cyano, $-S(O)_2$-alkyl, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, cycloalkyl, aryl, heteroaryl, heterocyclyl, -alkyl-heterocyclyl, -cycloalkyl-NH_2, $-S(O)_2-NH_2$, $-S(O)_2$alkyl, $-C(O)NH_2$, hydroxy, -C(O)N(H)(cycloalkyl), -C(O)N(H)(alkyl), -N(H)(cycloalkyl), -C(O)O-alkyl, -C(O)OH, $-S(O)_2N(H)$(alkyl), $-S(O)_2OH$, -S-haloalkyl, $-S(O)_2$-

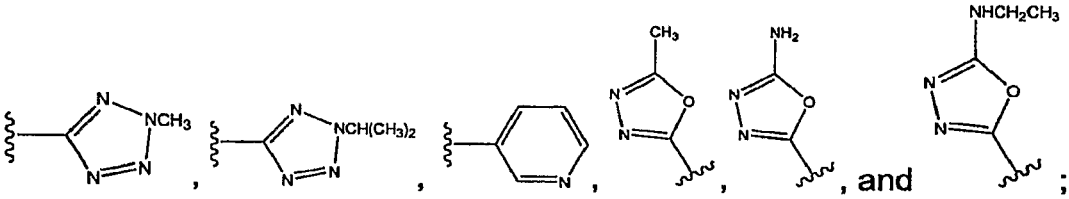
haloalkyl, hydroxyalkyl, alkoxyalkyl, -O-alkyl-cycloalkyl, -alkyl-O-alkyl-cycloalkyl, -C(O)alkyl, aminoalkyl, -alkyl-NH(alkyl), -alkyl-N(alkyl)$_2$, -CH=N-O-alkyl, -C(O)NH-alkyl-N(alkyl)$_2$, -C(O)-heterocyclyl, and -NH-C(O)-alkyl, wherein each of said R^{10} aryl and heteroaryl is optionally substituted with 1-2 moieties selected from the group consisting of alkyl, -NH_2, -NH(alkyl), and –N(alkyl)$_2$;

or wherein two R^{10} moieties attached to the same carbon atom are taken together with the carbon atom to which they are attached to form a heterocyclyl ring.

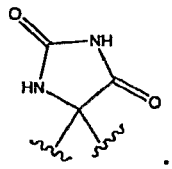
14. The compound of claim 13, wherein R^{10} is selected from the group consisting of hydrogen, nitro, methyl, fluoro, bromo, trifluoromethyl, chloro, difluoromethoxy, trifluoromethoxy, methoxy, hydroxyl, cyano, -$S(O)_2CH_3$, -NH_2, isopropyl, cyclopropyl, -cyclopropyl-NH_2,



-NH(cyclopropyl), -NH(CH_3), -$S(O)_2$-NH_2, -C(O)NH_2, -C(O)OCH_3, -C(O)OH, -$S(O)_2N(H)CH_3$, -C(O)NH(CH_3), -C(O)NH(cyclopropyl), -$S(O)_2OH$, -S-CF_3, -$S(O)_2$-CF_3, ethoxy, hydroxymethyl, methoxymethyl, isopropoxy, -OCH_2-cyclopropyl, -CH_2O-CH_2-cyclopropyl, -C(O)CH_3, -C(O)CH_3, -$CH(CH_3)OH$, -CH_2NH_2, -$CH(CH_3)NH_2$, -CH_2NH-CH_3, -$CH(CH_3)OH$, -CH_2NHCH_3, -CH=N-OCH_3, -$C(CH_3)$=N-OCH_3, -C(O)OCH_2CH_3, -C(O)$NHCH_2CH_2N(CH_3)_2$, -NH-C(O)CH_3,



; or wherein two R^{10} moieties, when attached to the same carbon atom are taken together with the carbon atom to which they are attached to form



15. The compound of claim 1, wherein Y is selected from the group consisting of a covalent bond and –O-.

16. The compound of claim 15, wherein Y is a covalent bond.

17. The compound of claim 15, wherein Y is –O-.

18. The compound of claim 1, wherein Z is selected from the group consisting of a covalent bond and –O-.

19. The compound of claim 18, wherein Z is –O-.

20. The compound of claim 1, wherein R^1 is selected from the group consisting of hydrogen, cyano, halogen, alkyl, aryl, heteroaryl, haloalkyl, and alkynyl; wherein said R^1 alkyl is unsubstituted or substituted with an aryl, heteroaryl, or heterocyclyl, wherein when said aryl, heteroaryl, or heterocyclyl 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 said aryl, heteroaryl or heterocyclyl substitutent of said R^1 alkyl optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties.

21. The compound of claim 1, wherein R^2 is selected from the group consisting of hydrogen, cyano, halogen, alkyl, aryl, heteroaryl, haloalkyl, and alkynyl; wherein said R^1 alkyl is unsubstituted or substituted with an aryl, heteroaryl, or heterocyclyl, wherein when said aryl, heteroaryl, or heterocyclyl 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 said aryl, heteroaryl or heterocyclyl substitutent of said R^1 alkyl optionally with said five- to eight-membered cycloalkyl, aryl, heterocyclyl or

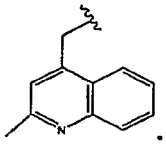
heteroaryl ring is unsubstituted or optionally independently substituted with one to four R^{20} moieties.

22. The compound of claim 16, wherein R^1 is halogen or cyano.

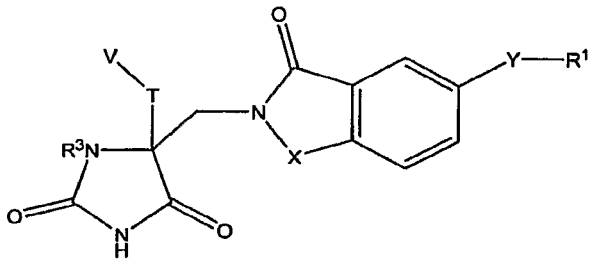
23. The compound of claim 22, wherein R^1 is fluoro, chloro, or cyano.

24. The compound of claim 17, wherein R^1 is selected from the group consisting of alkyl, haloalkyl, and alkynyl; wherein said R^1 alkyl is unsubstituted or substituted with a 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- or six-membered aryl; wherein said heteroaryl substituent of said R^1 alkyl, optionally with said five- or six-membered aryl is substituted with alkyl.

25. The compound of claim 24, wherein R^1 is selected from the group consisting of CH_3, $-CH_2-C\equiv C-CH_3$, difluoromethyl, and



26. The compound of claim 1, wherein, the compound of Formula (I) is represented by the compound of formula (III):

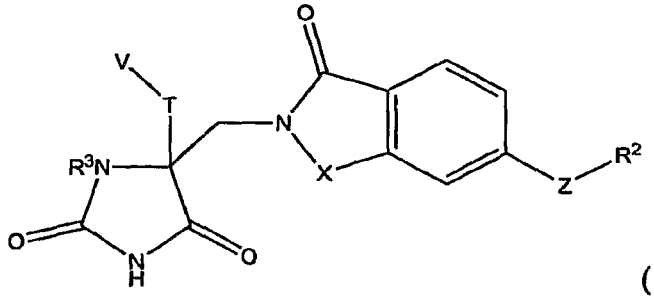


(III),

wherein in formula (III), X is $-(CH_2)_{1-2}-$, and T, V, Y, R^1, and R^3 are as set forth in Formula (I).

27. The compound of claim 26, wherein X is $-CH_2-$.

28. The compound of claim 1, wherein, the compound of Formula (I) is represented by the compound of formula (IV):

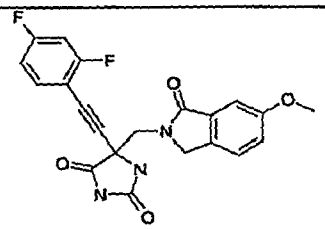
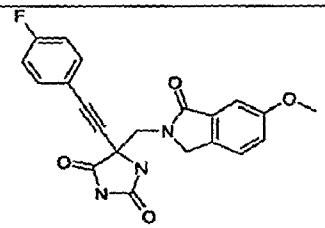
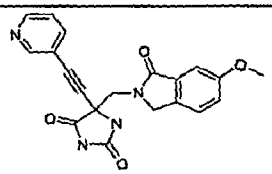
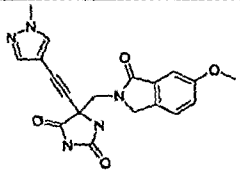
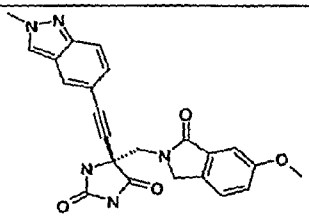
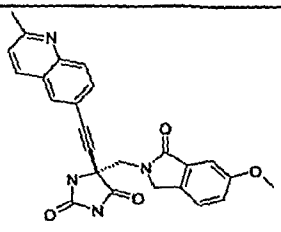


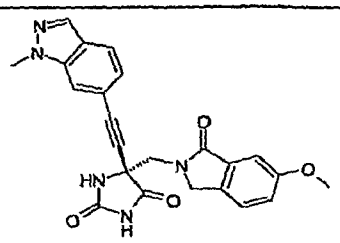
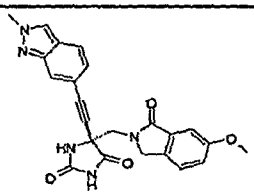
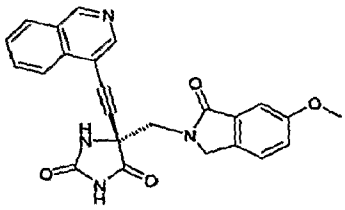
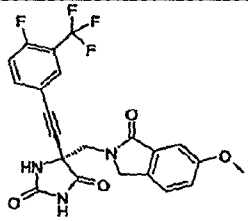
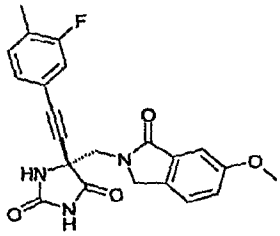
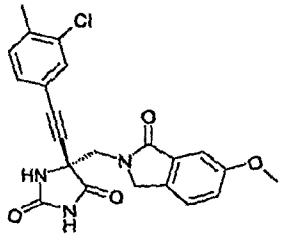
(IV),

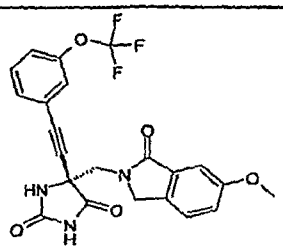
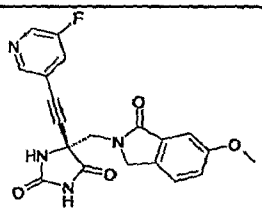
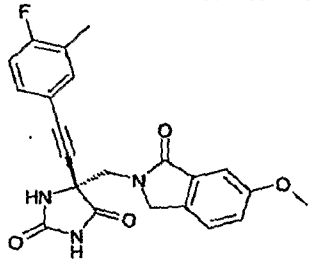
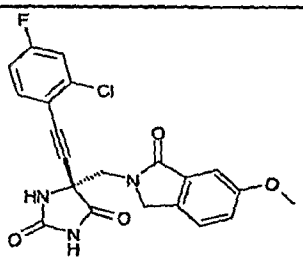
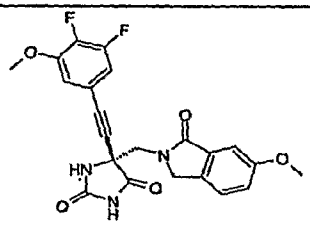
wherein in formula (IV), X is $-(CH_2)_{1-2}-$, T, V, Y, R^1, and R^3 are as set forth in Formula (I).

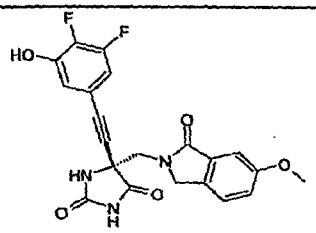
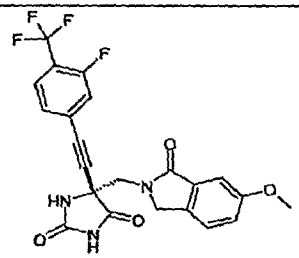
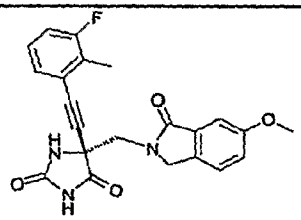
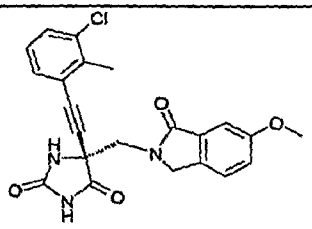
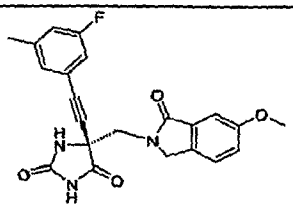
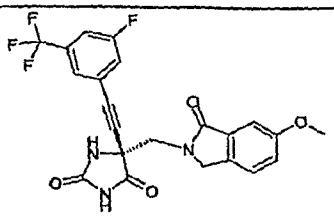
29. The compound of claim 28, wherein X is $-CH_2-$.

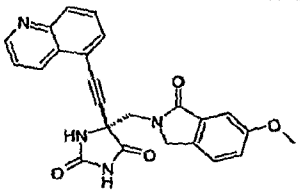
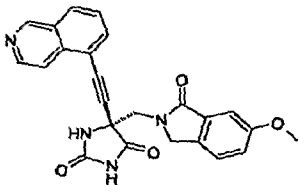
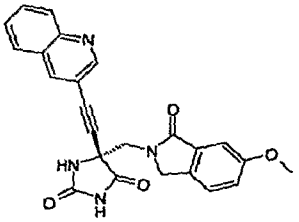
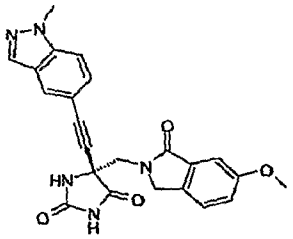
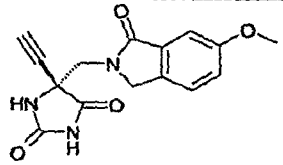
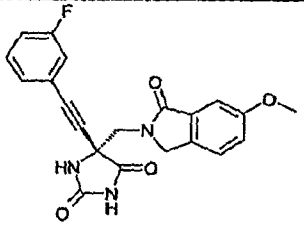
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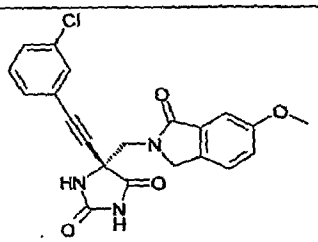
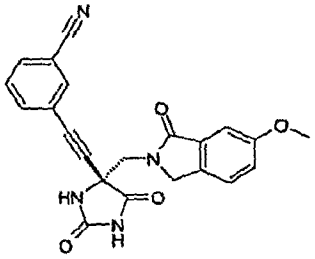
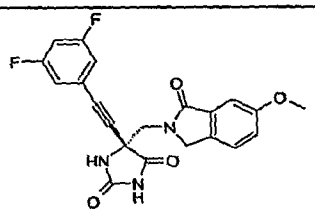
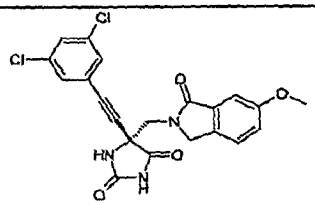
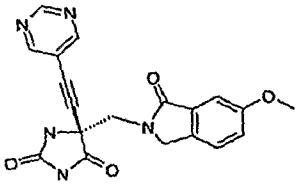
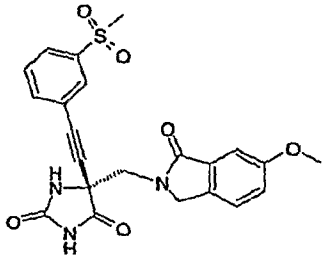
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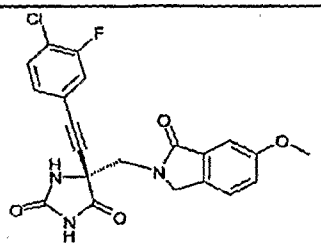
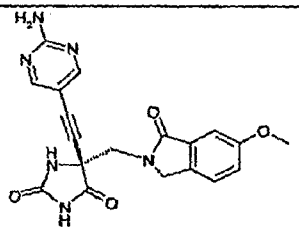
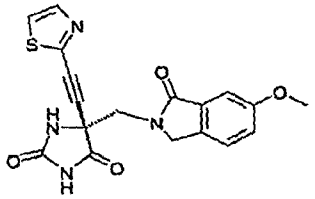
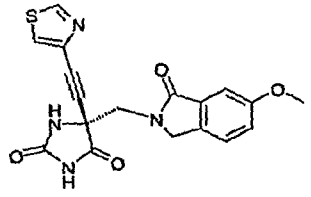
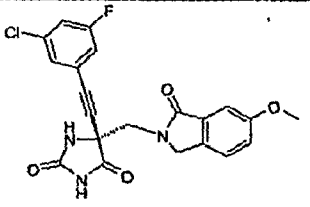
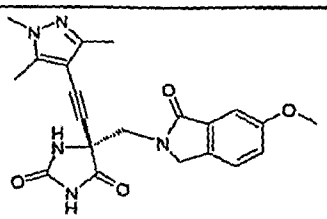
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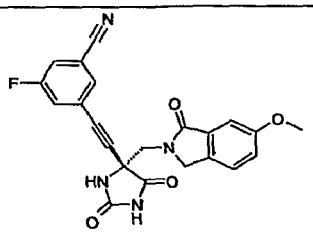
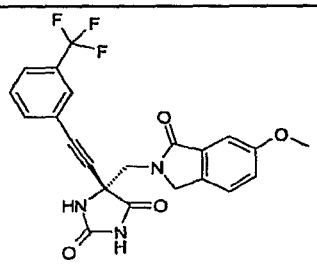
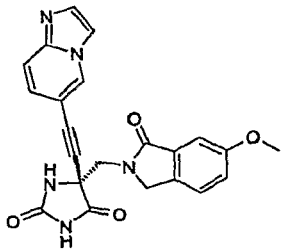
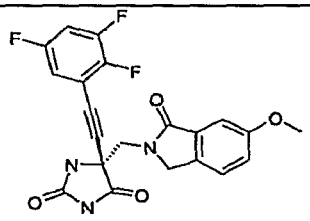
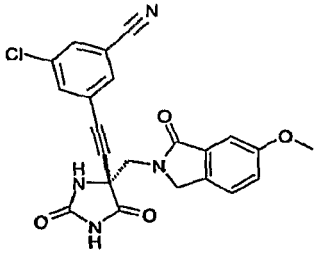
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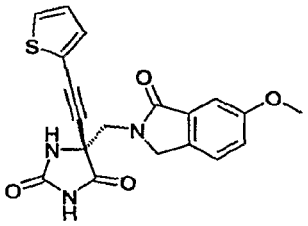
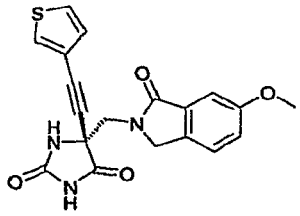
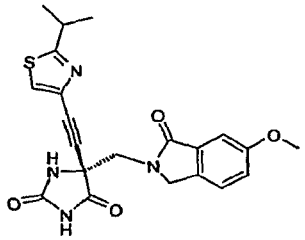
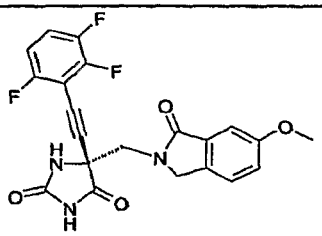
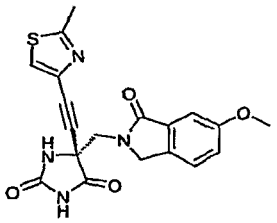
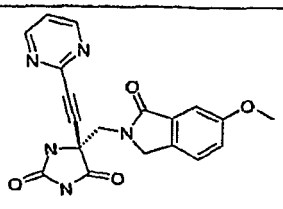
Compound ID	Structures
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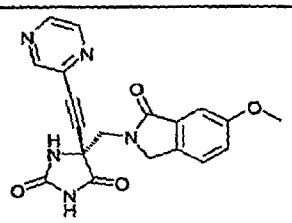
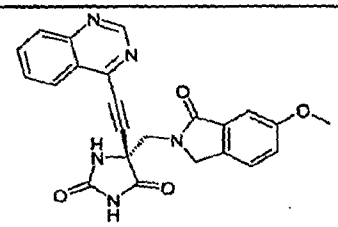
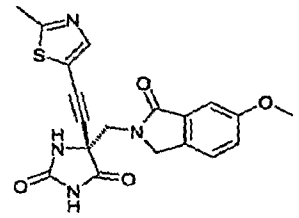
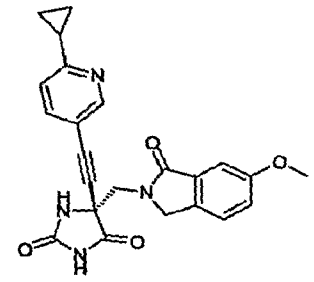
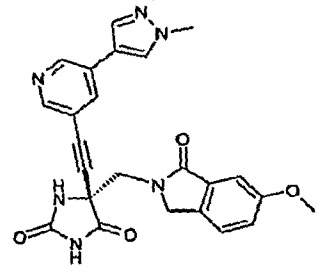
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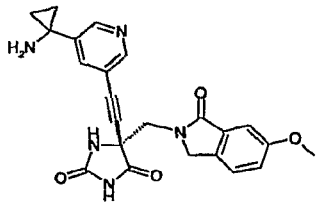
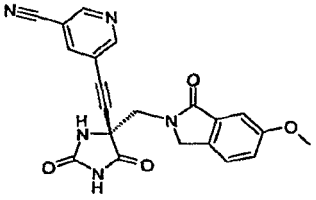
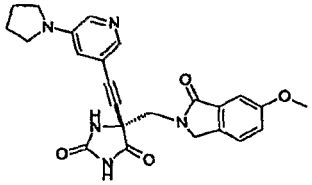
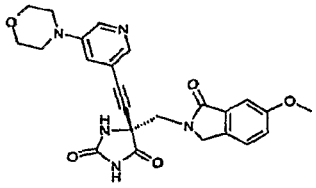
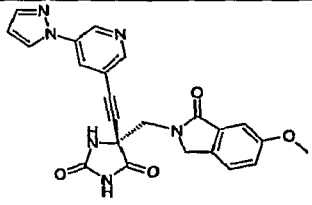
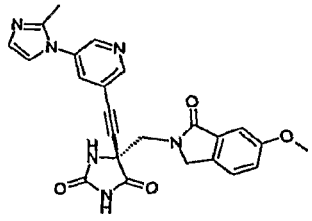
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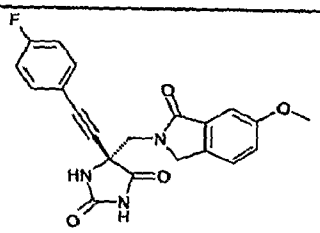
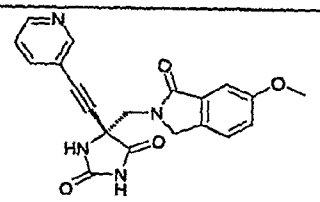
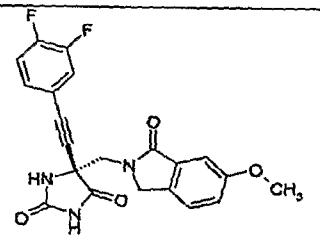
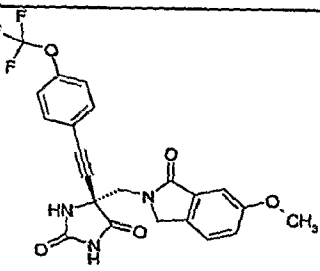
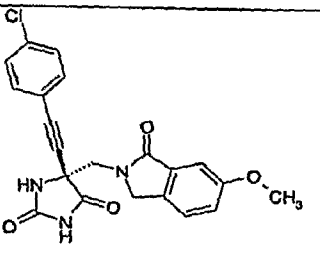
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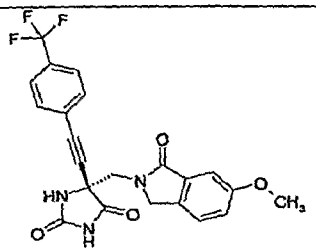
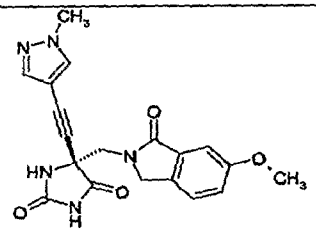
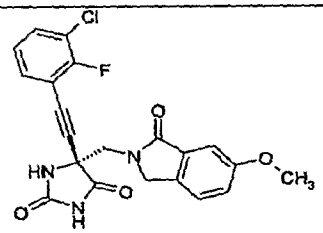
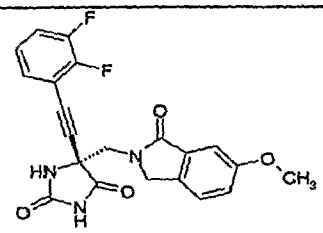
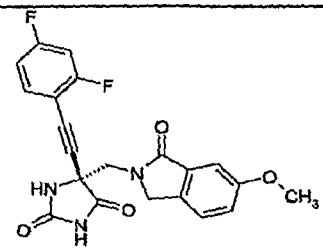
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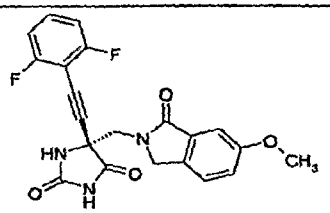
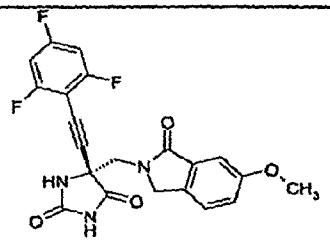
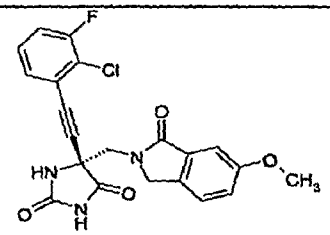
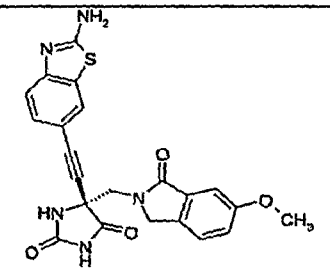
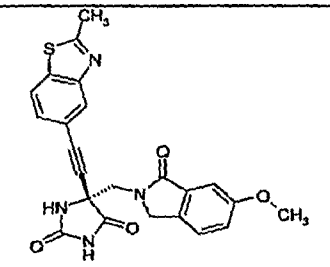
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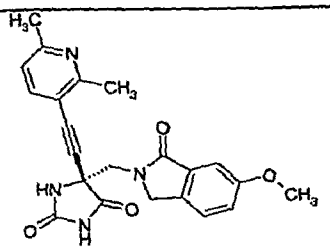
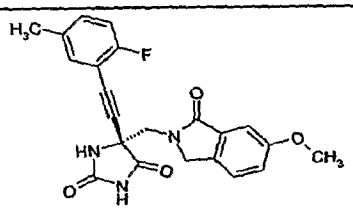
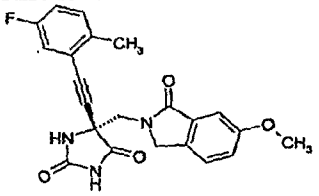
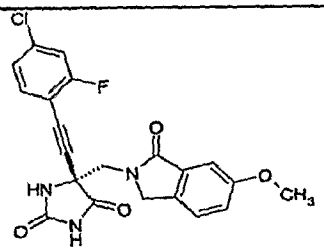
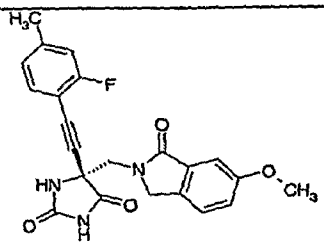
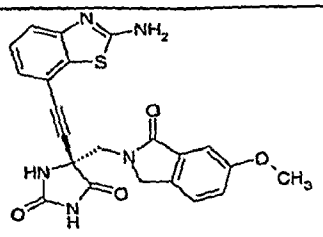
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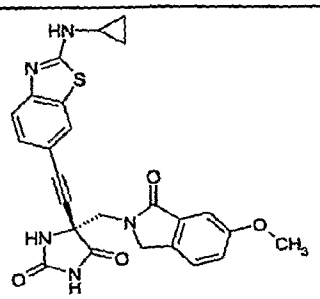
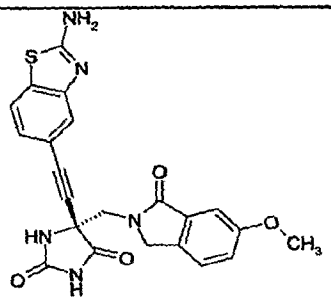
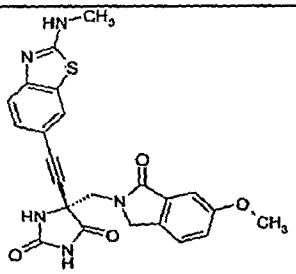
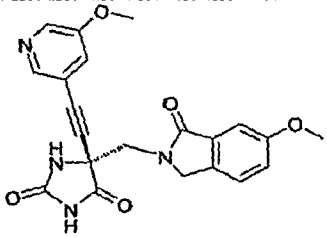
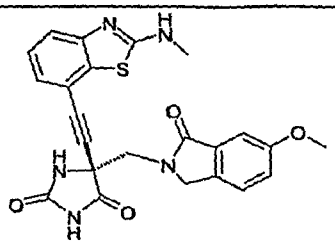
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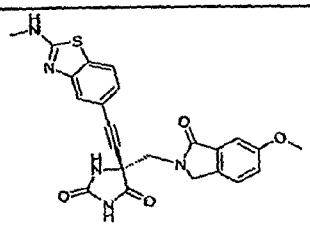
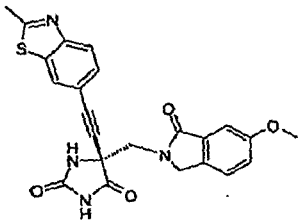
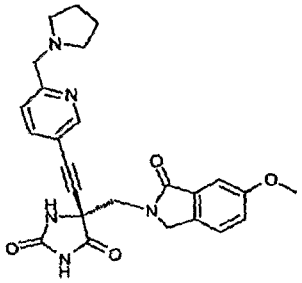
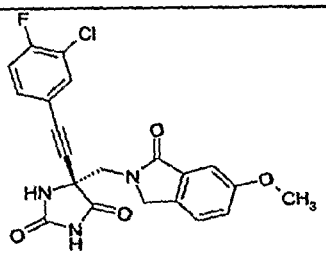
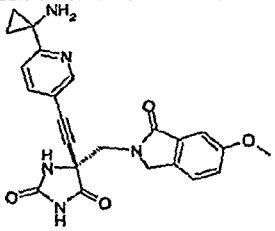
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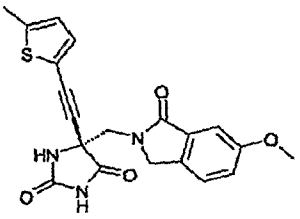
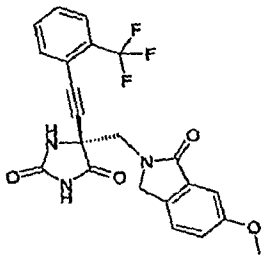
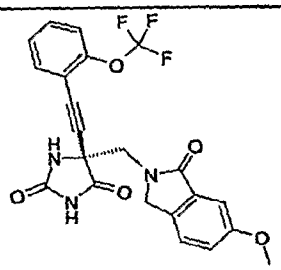
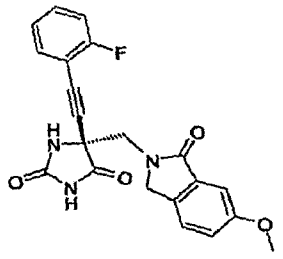
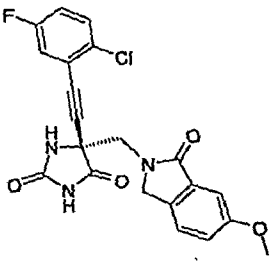
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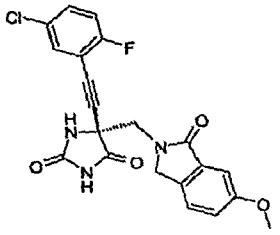
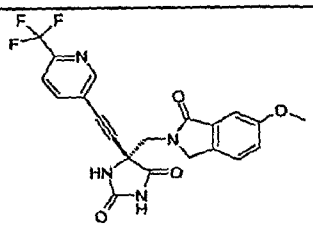
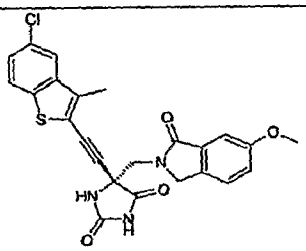
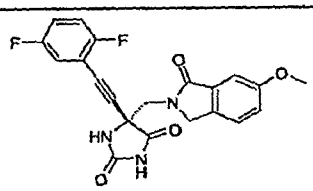
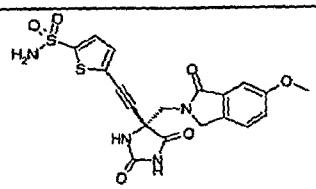
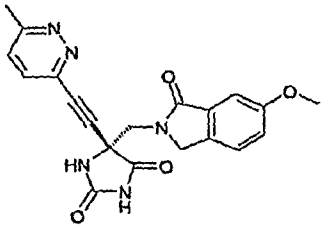
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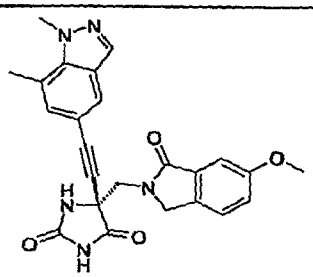
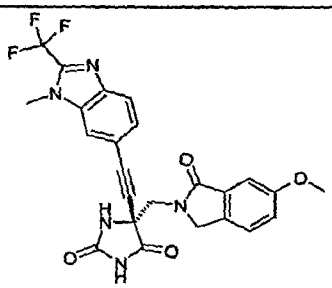
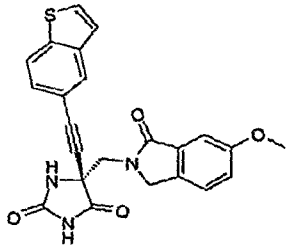
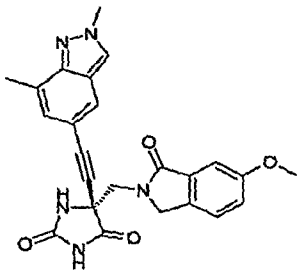
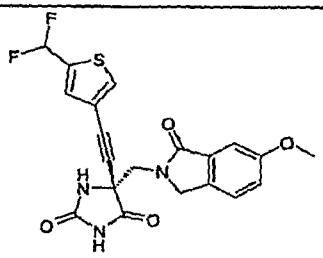
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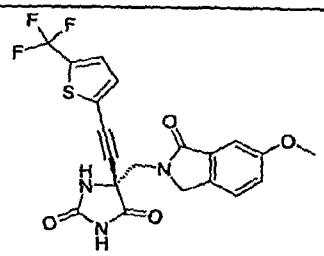
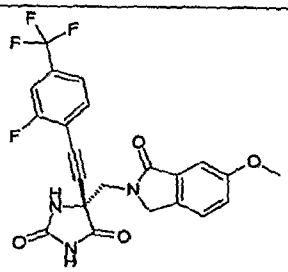
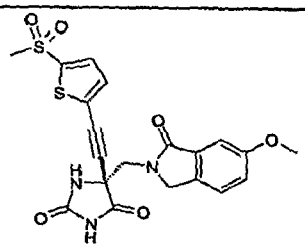
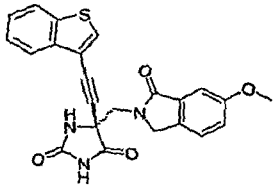
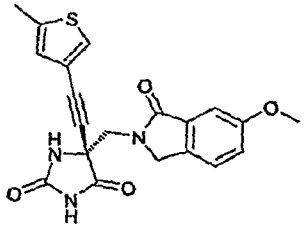
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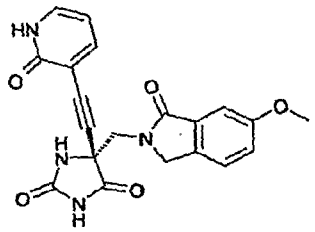
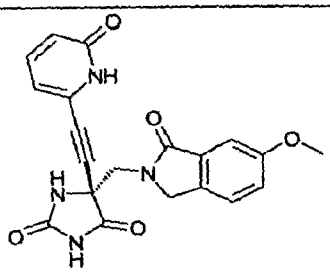
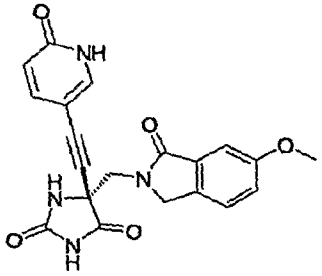
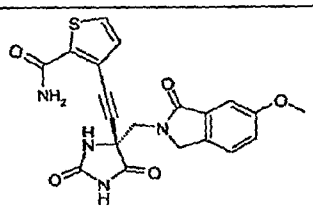
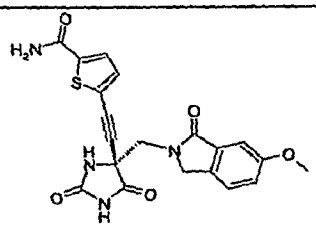
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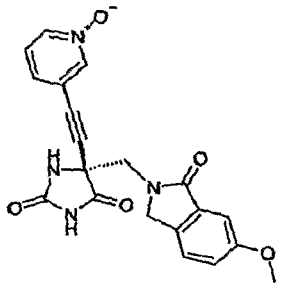
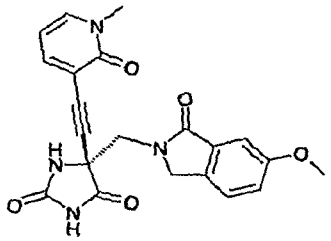
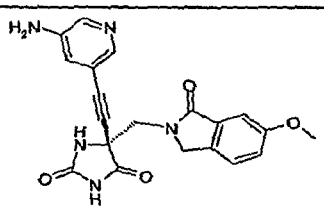
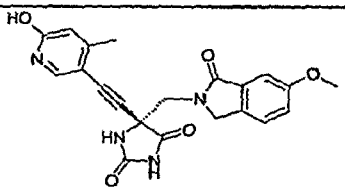
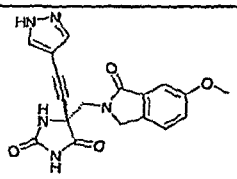
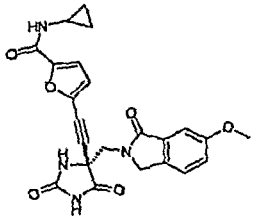
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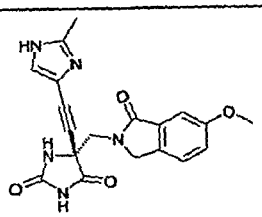
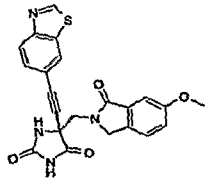
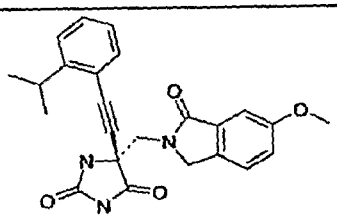
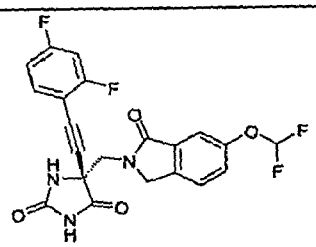
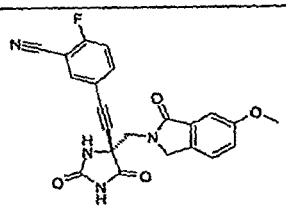
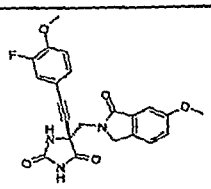
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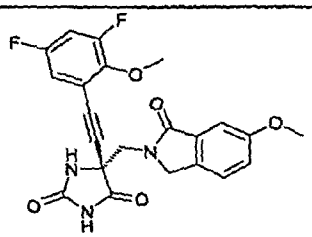
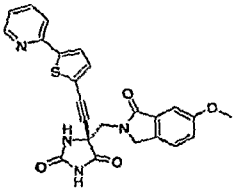
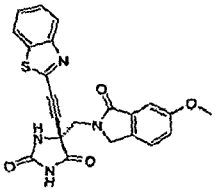
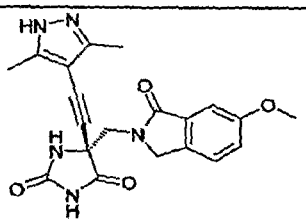
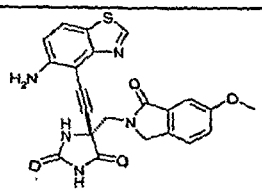
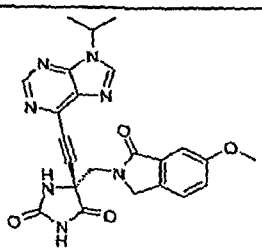
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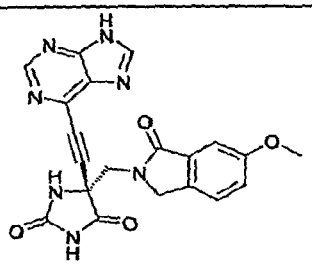
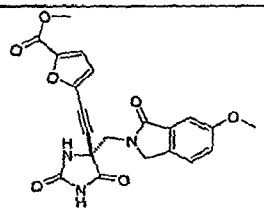
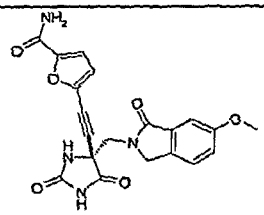
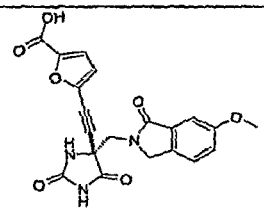
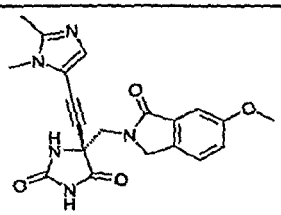
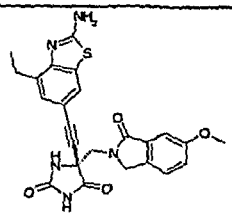
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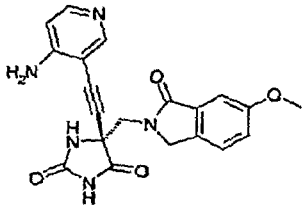
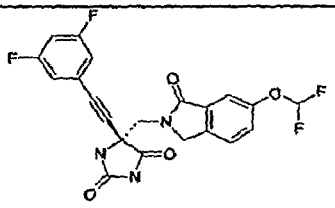
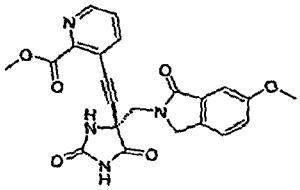
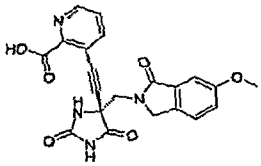
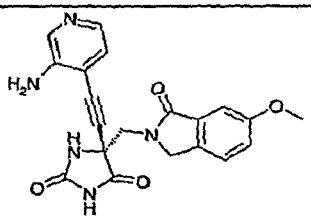
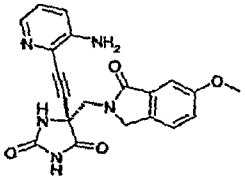
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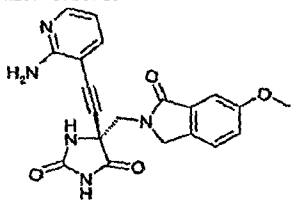
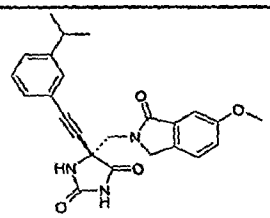
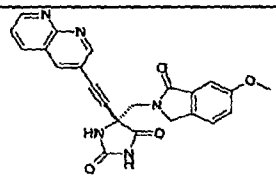
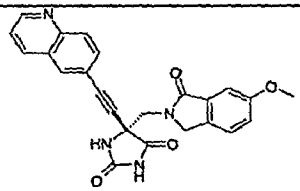
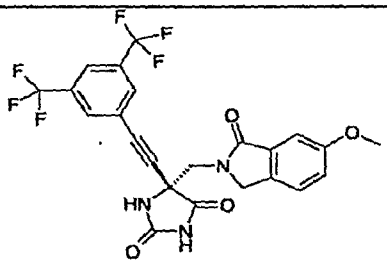
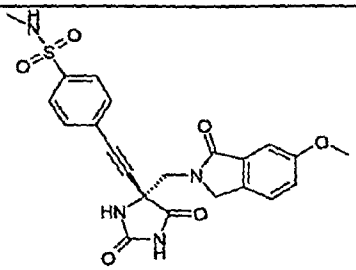
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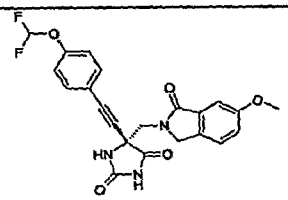
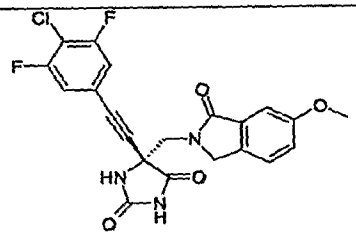
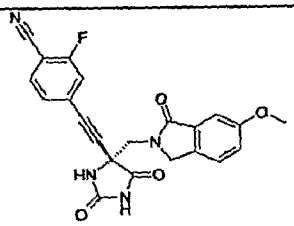
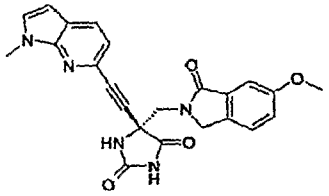
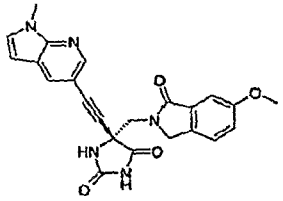
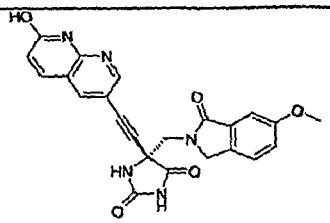
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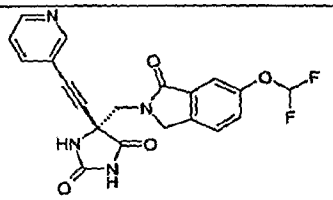
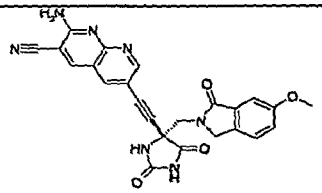
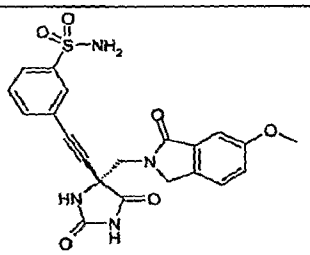
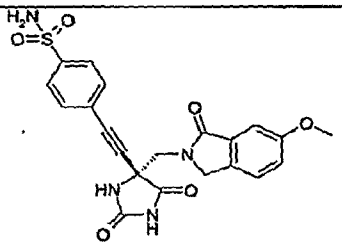
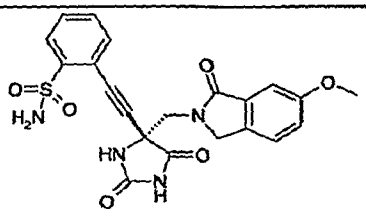
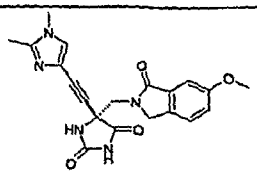
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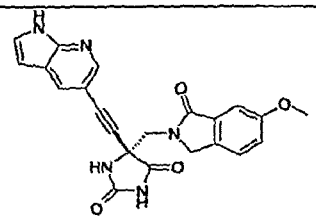
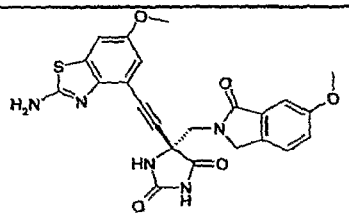
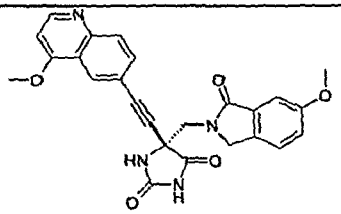
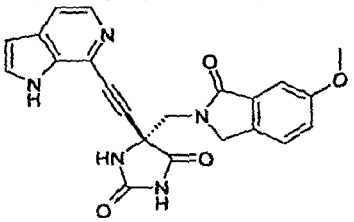
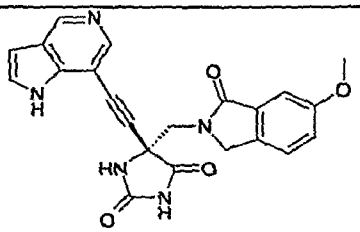
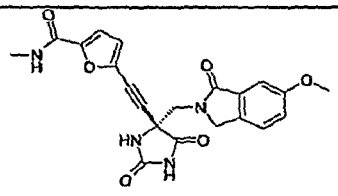
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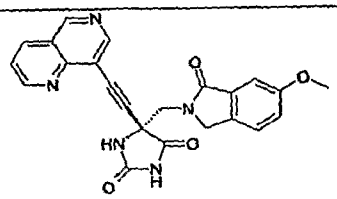
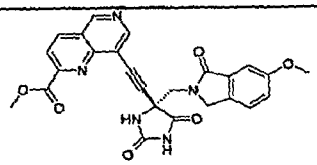
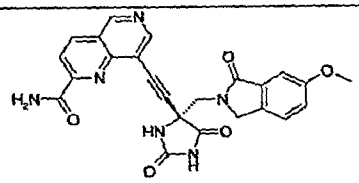
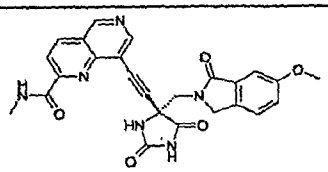
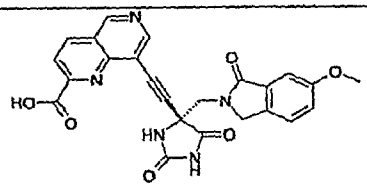
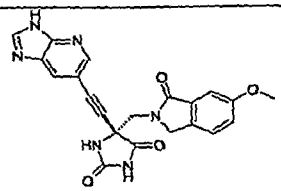
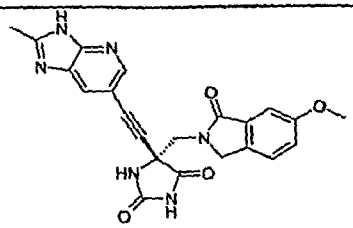
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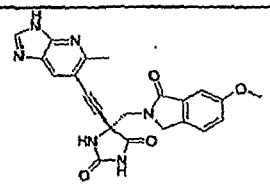
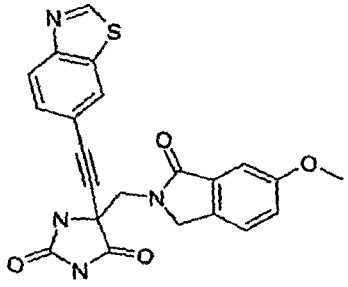
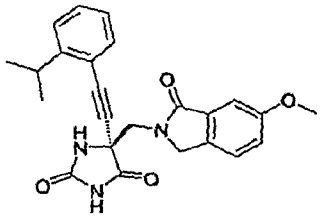
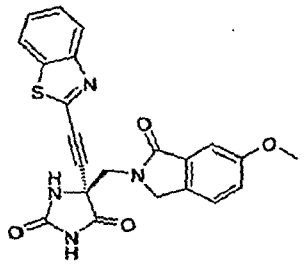
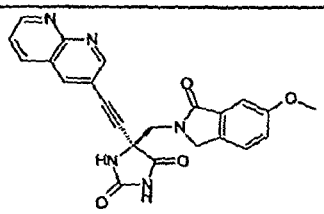
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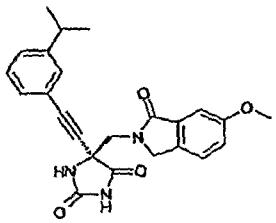
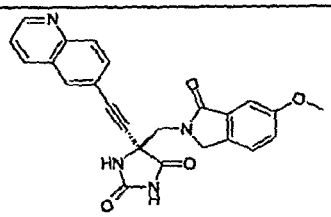
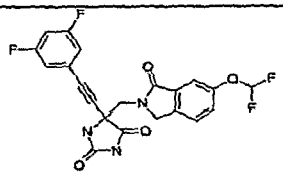
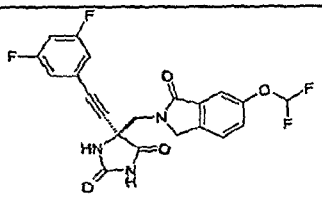
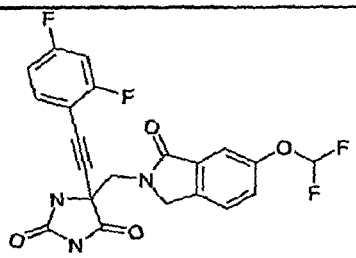
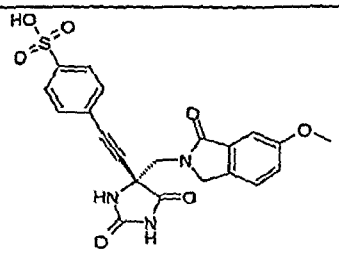
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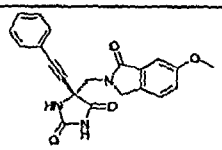
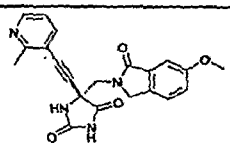
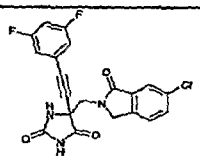
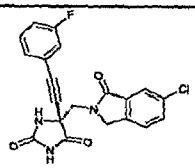
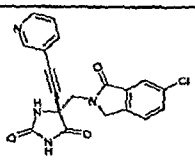
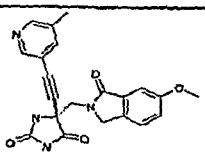
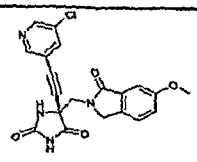
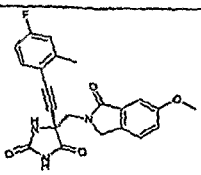
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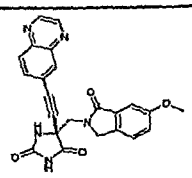
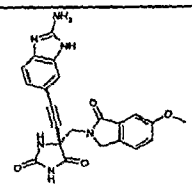
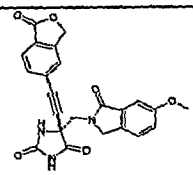
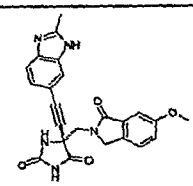
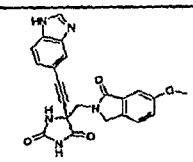
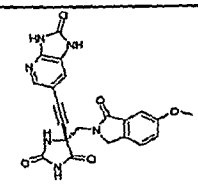
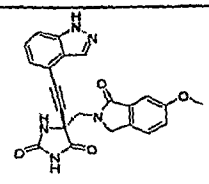
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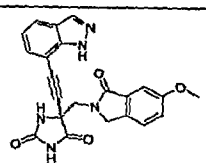
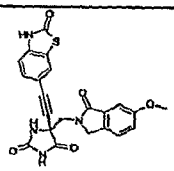
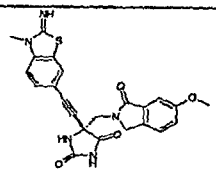
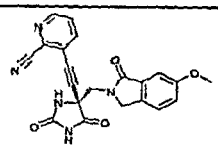
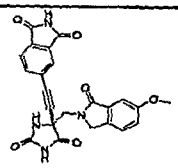
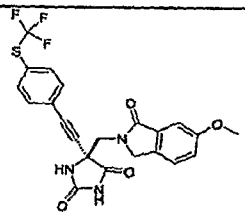
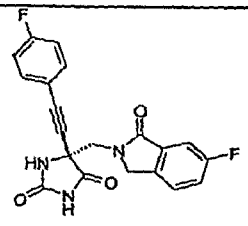
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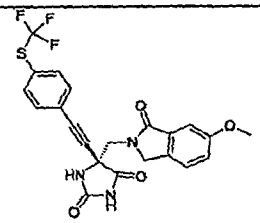
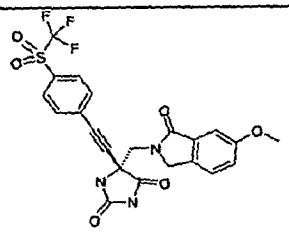
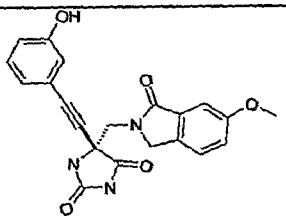
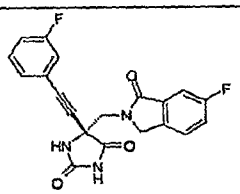
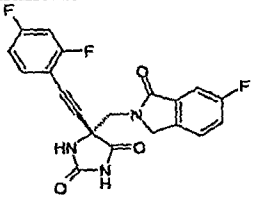
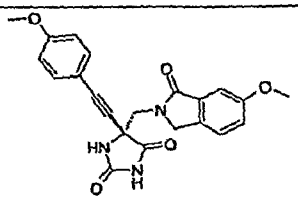
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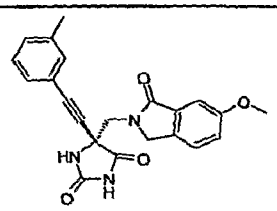
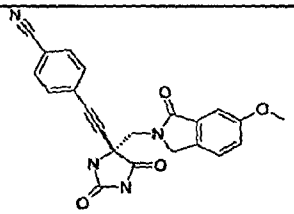
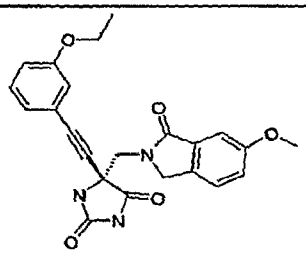
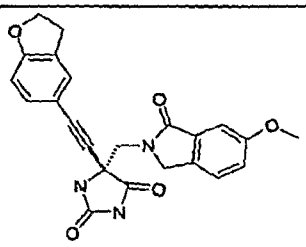
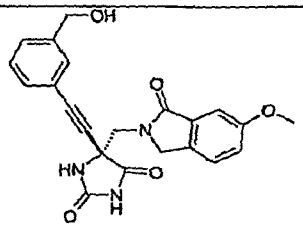
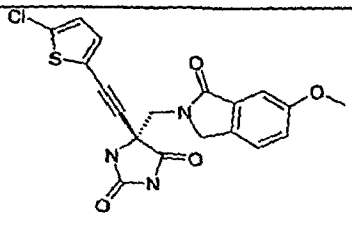
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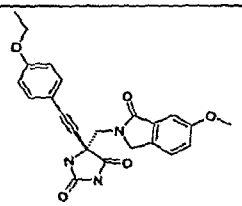
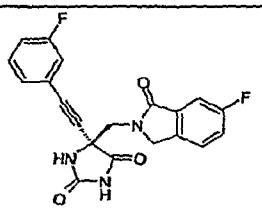
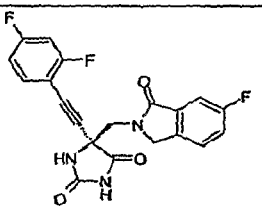
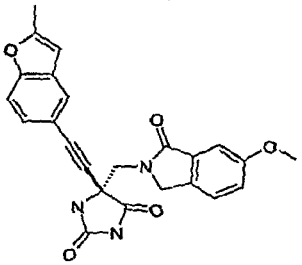
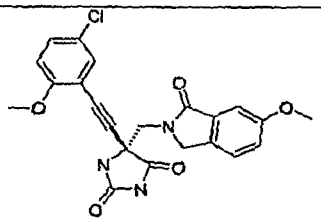
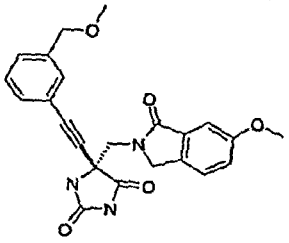
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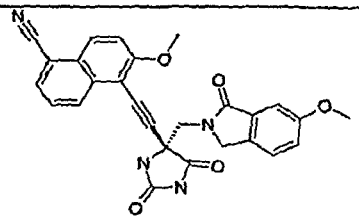
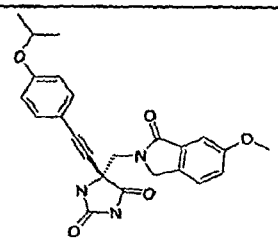
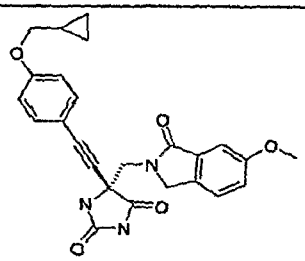
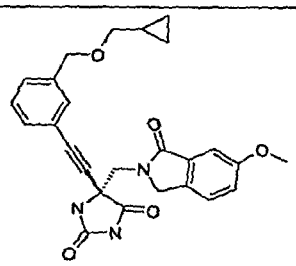
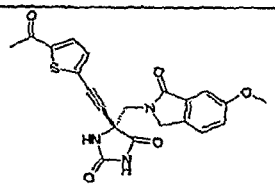
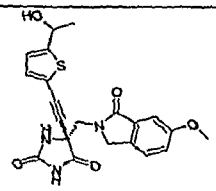
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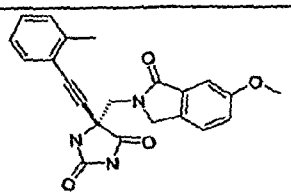
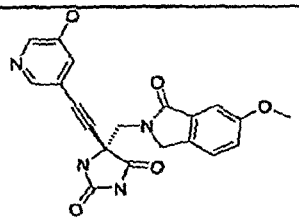
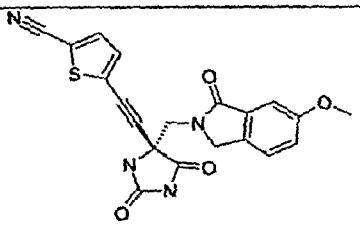
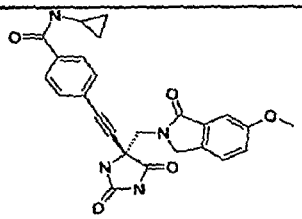
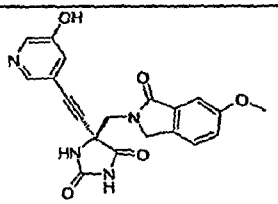
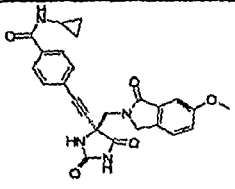
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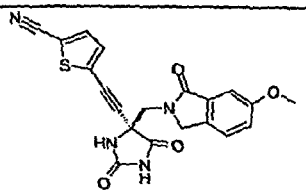
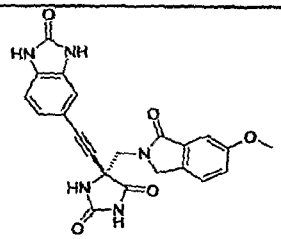
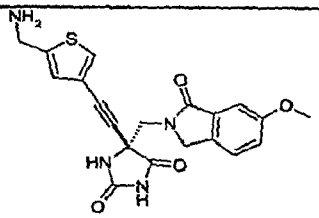
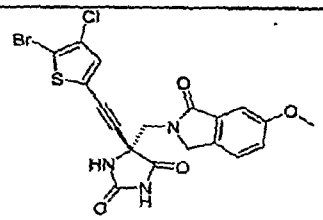
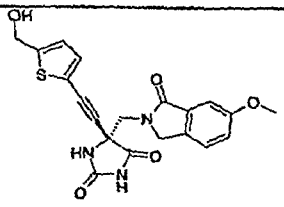
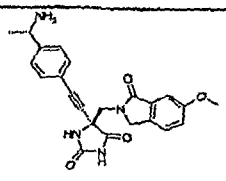
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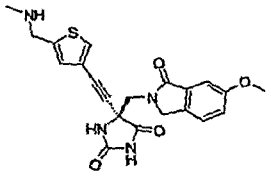
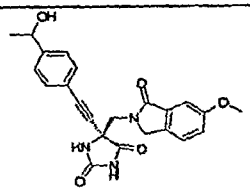
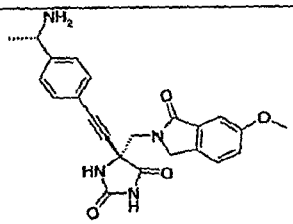
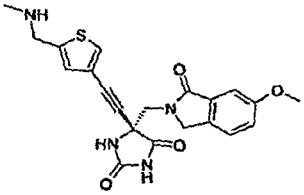
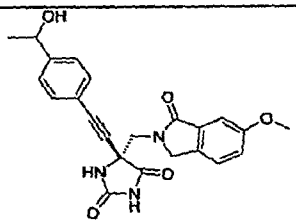
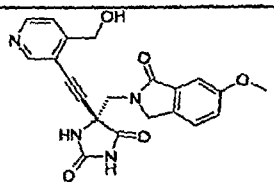
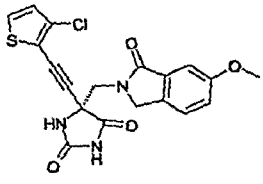
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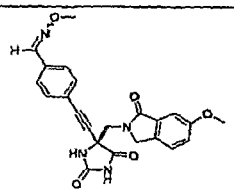
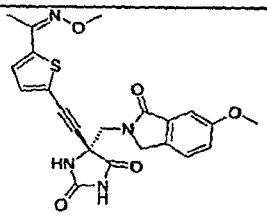
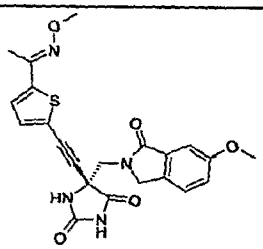
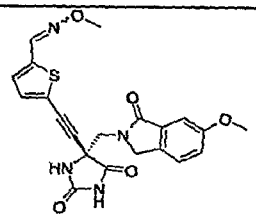
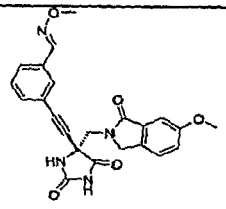
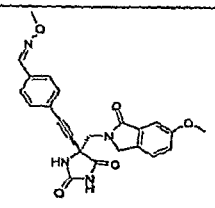
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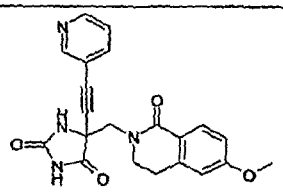
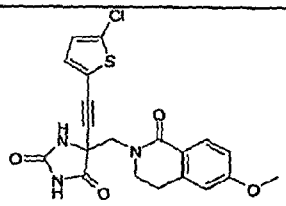
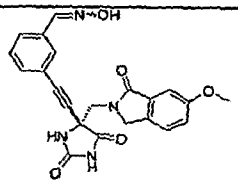
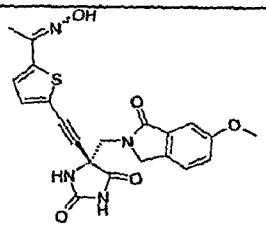
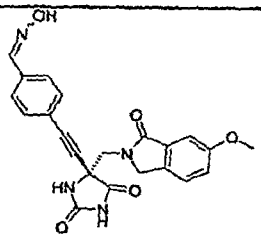
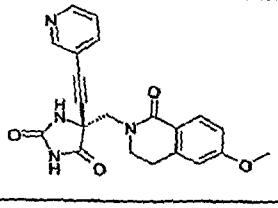
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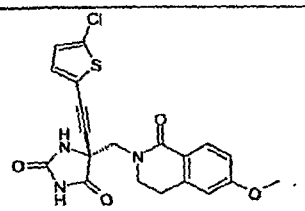
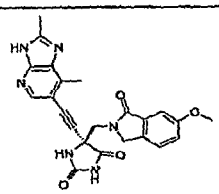
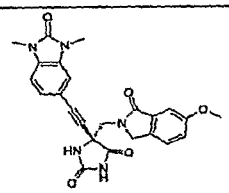
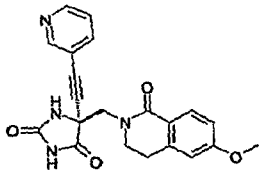
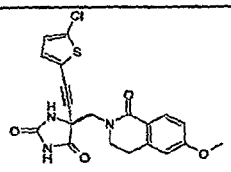
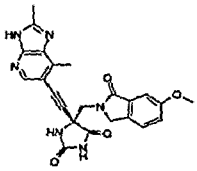
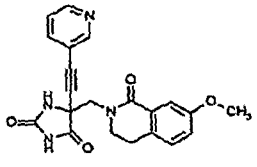
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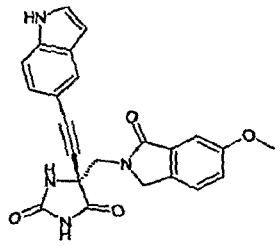
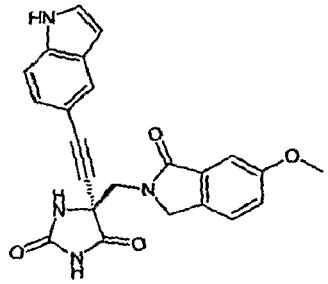
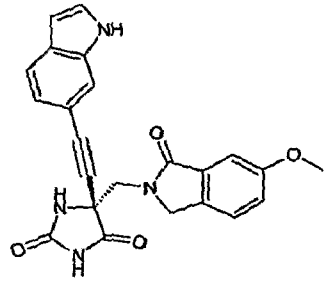
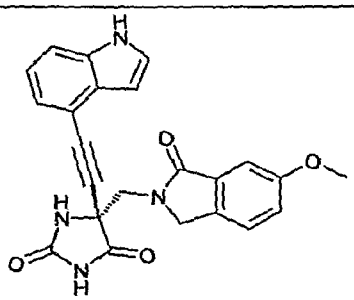
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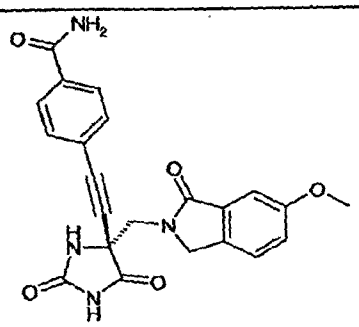
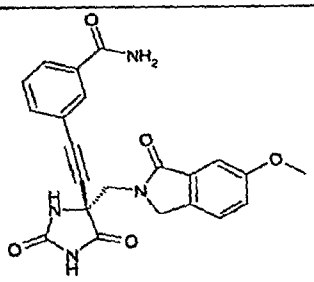
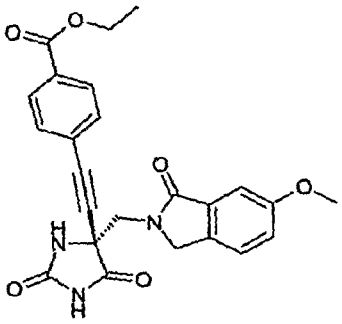
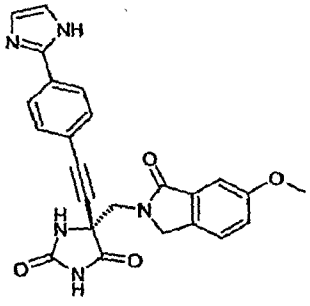
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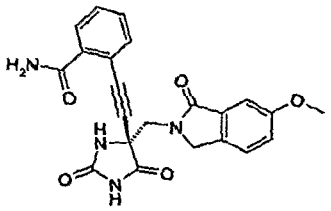
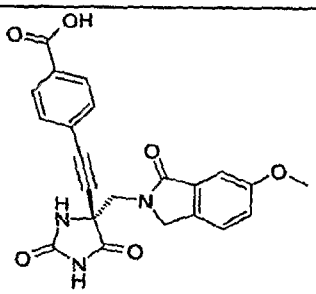
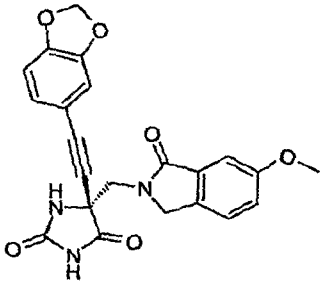
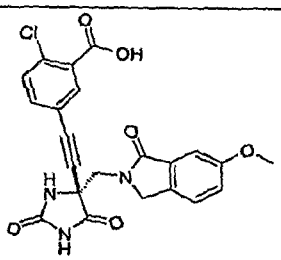
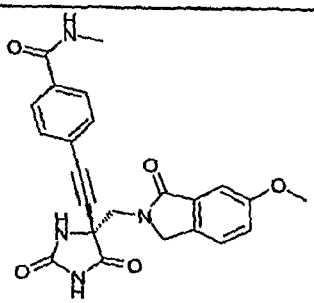
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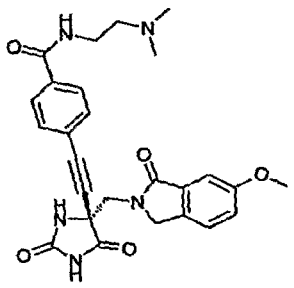
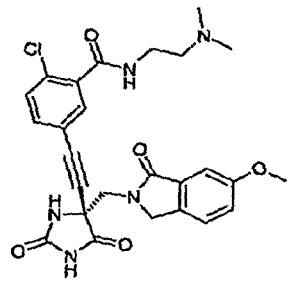
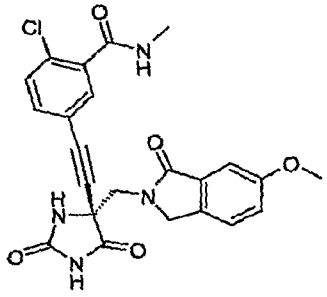
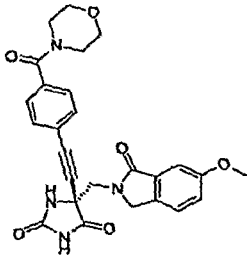
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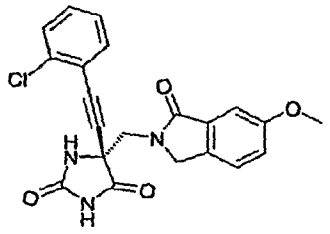
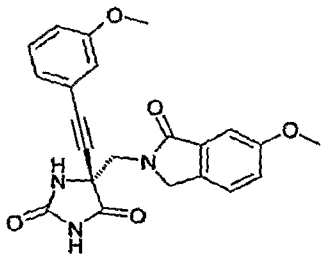
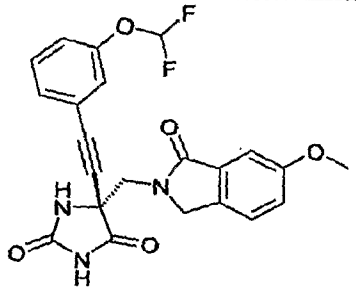
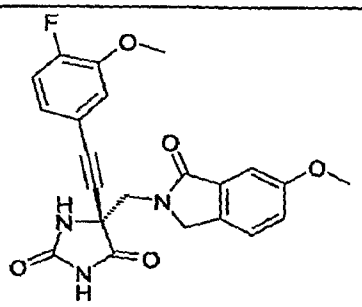
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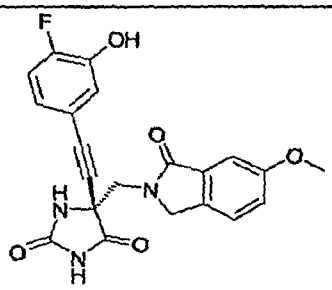
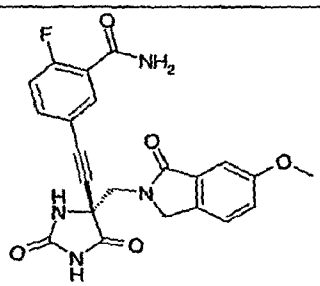
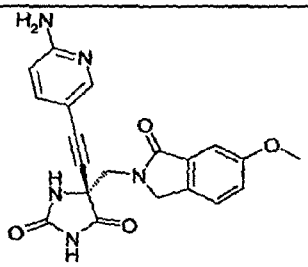
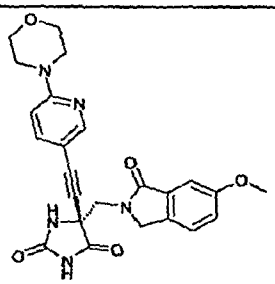
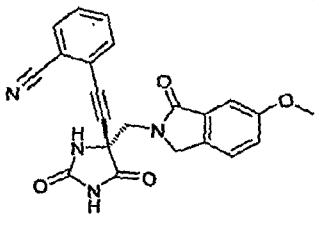
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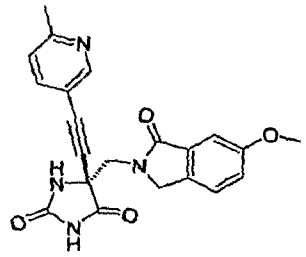
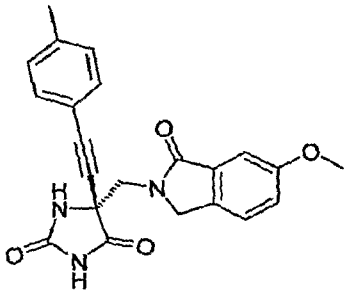
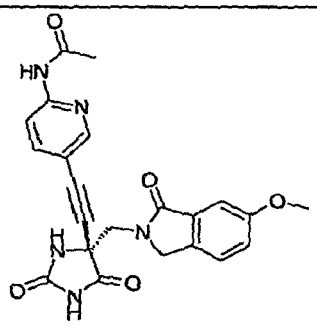
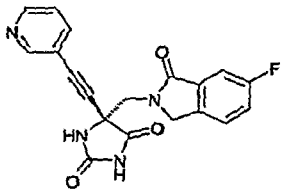
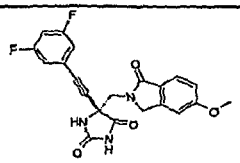
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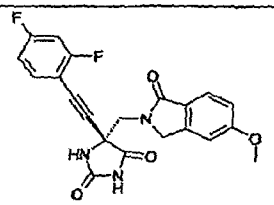
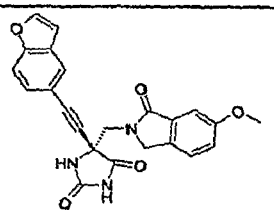
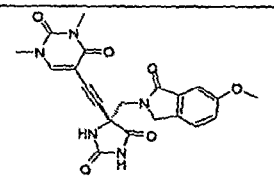
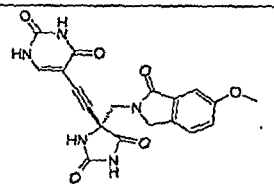
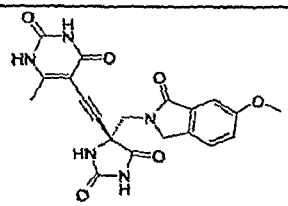
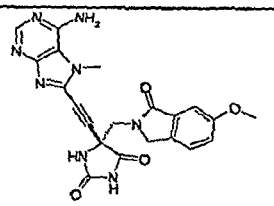
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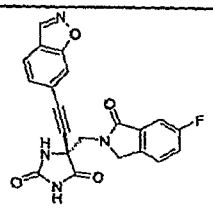
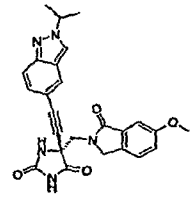
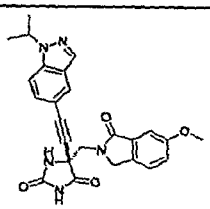
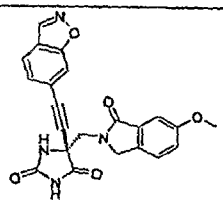
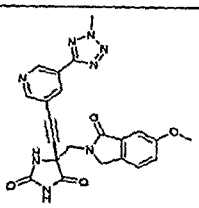
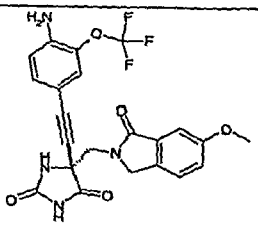
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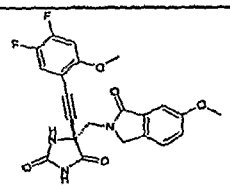
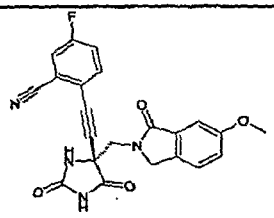
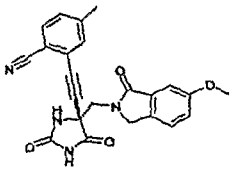
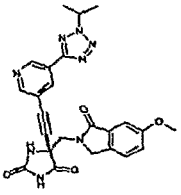
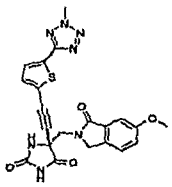
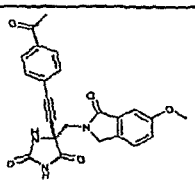
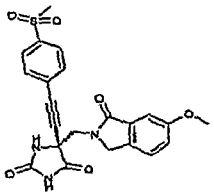
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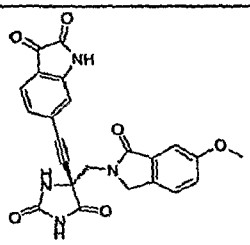
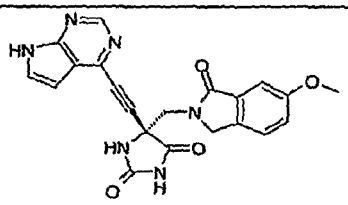
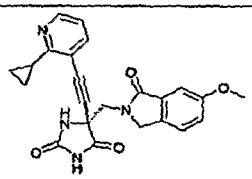
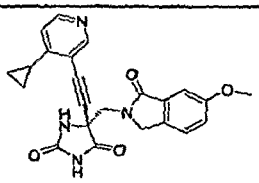
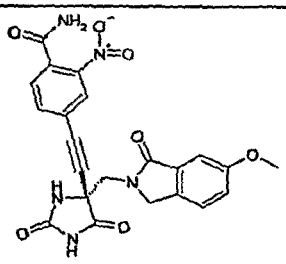
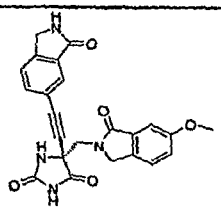
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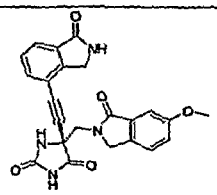
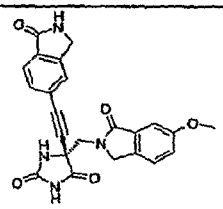
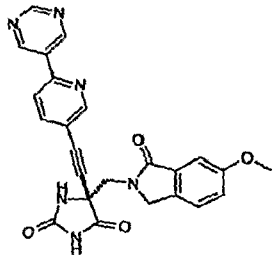
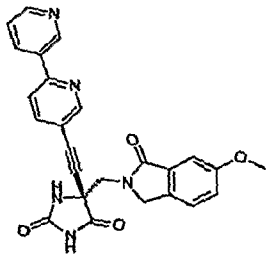
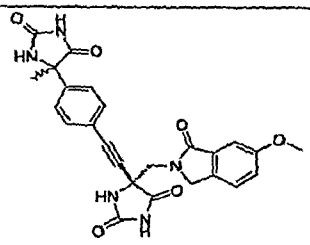
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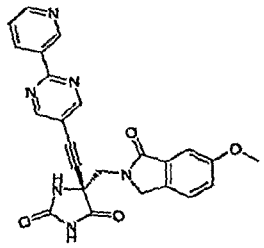
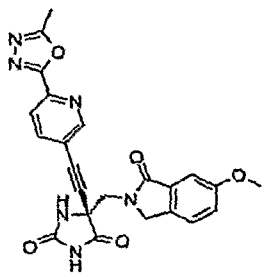
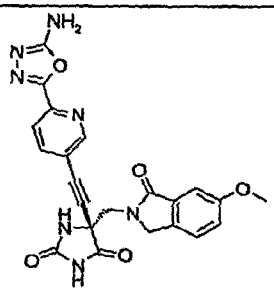
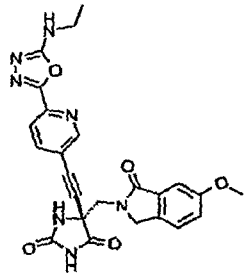
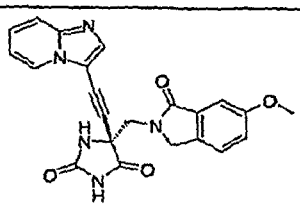
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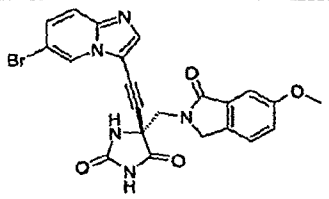
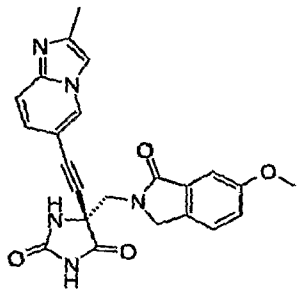
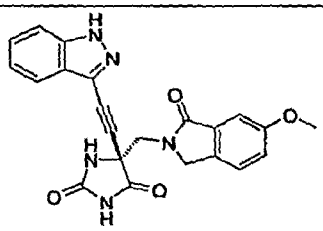
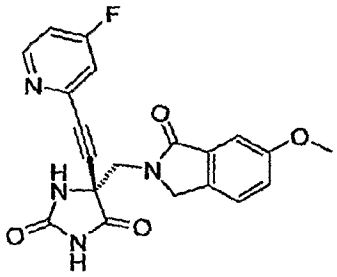
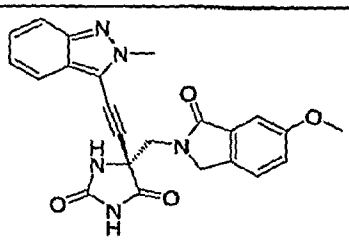
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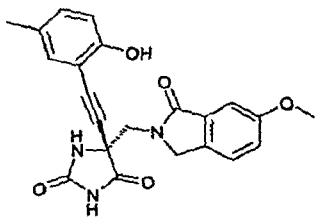
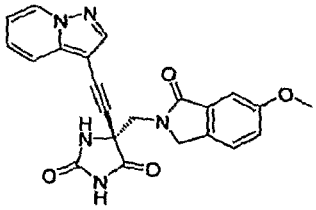
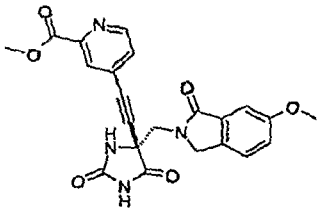
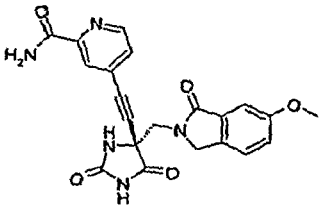
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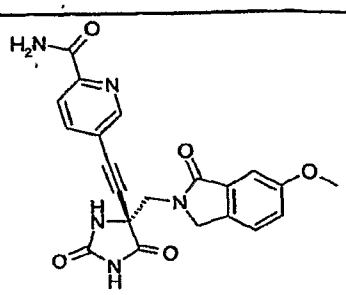
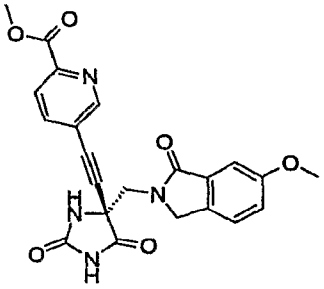
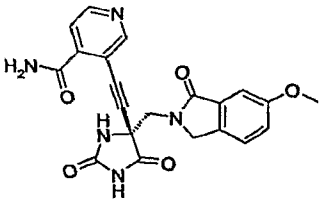
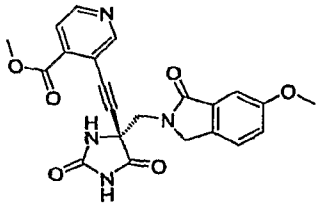
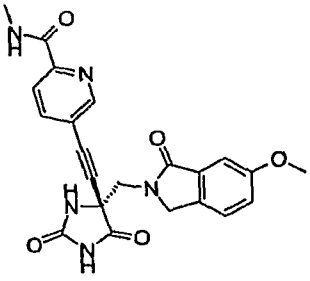
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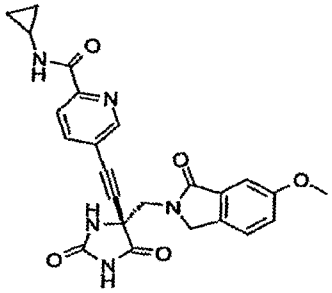
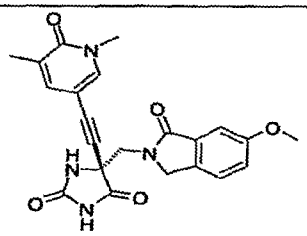
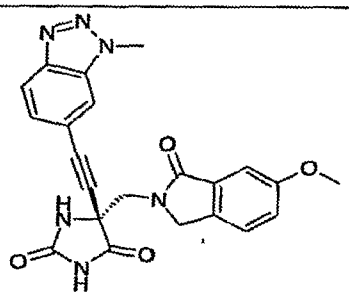
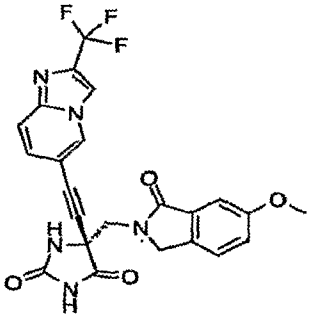
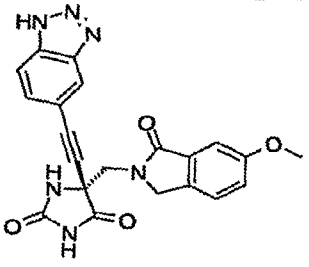
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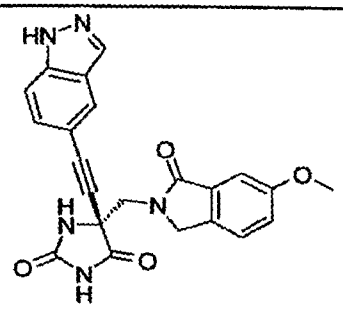
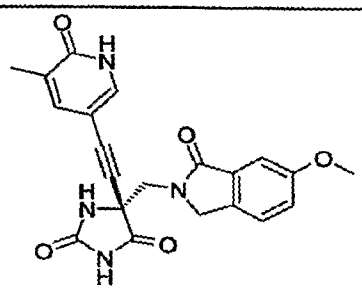
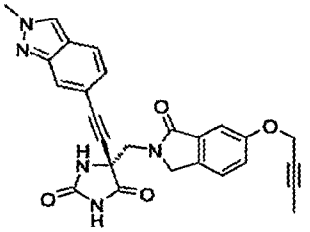
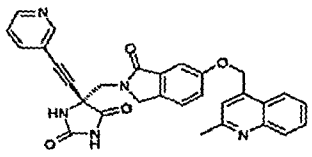
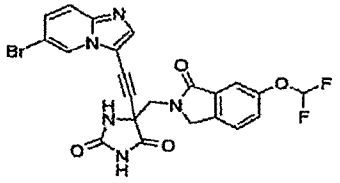
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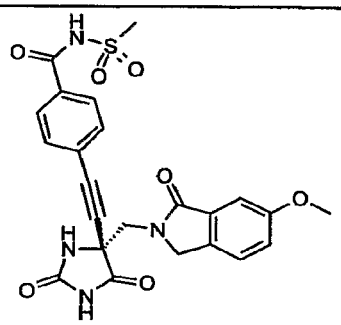
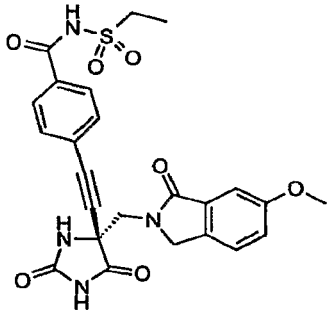
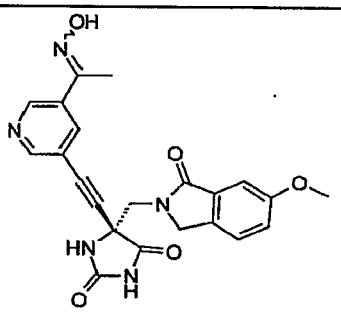
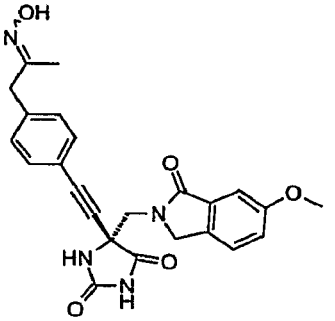
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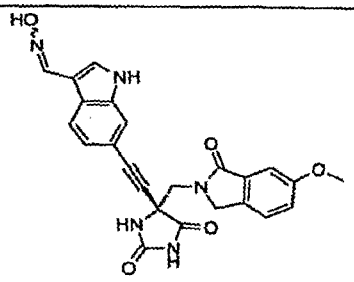
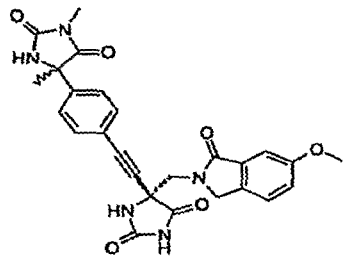
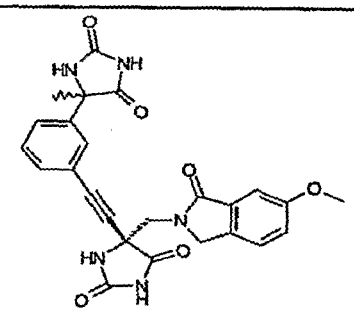
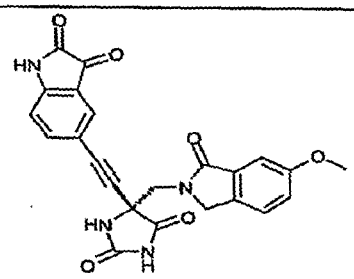
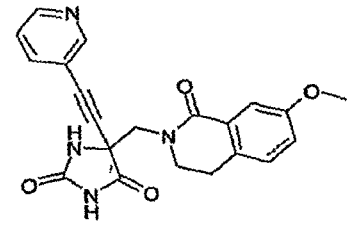
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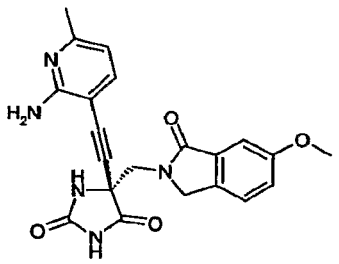
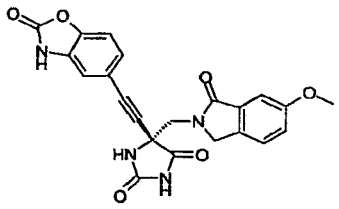
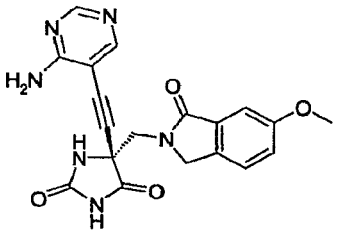
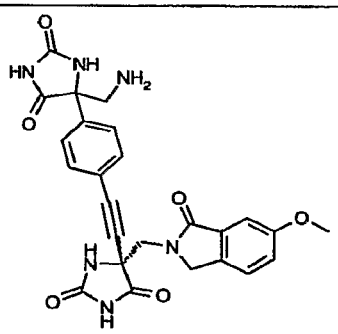
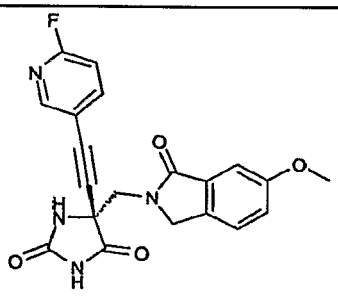
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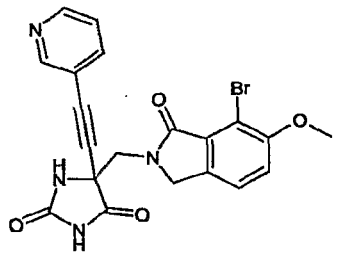
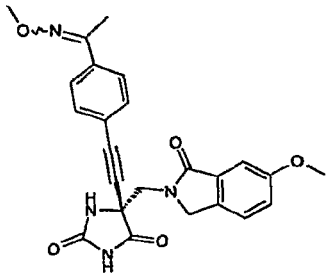
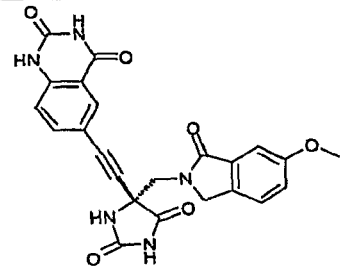
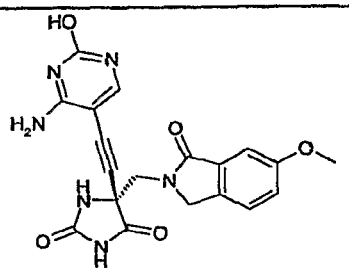
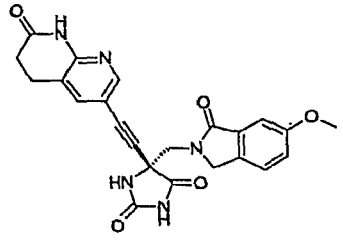
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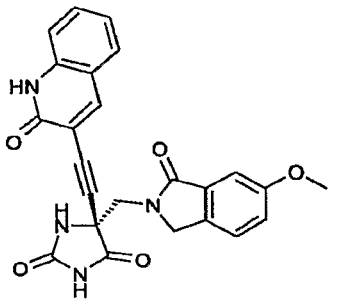
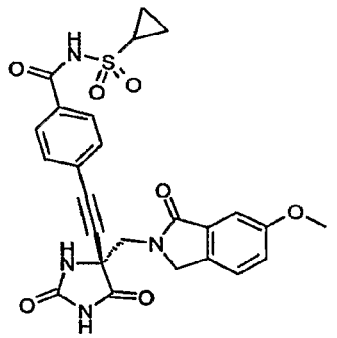
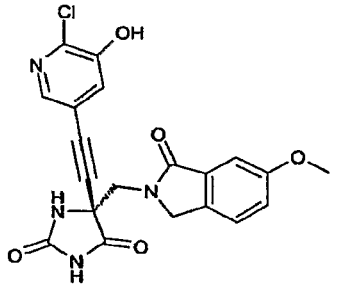
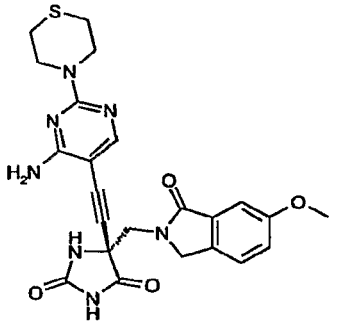
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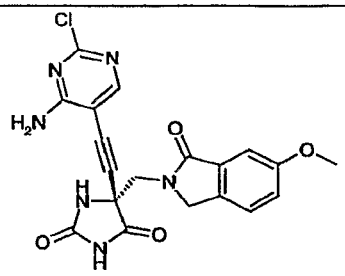
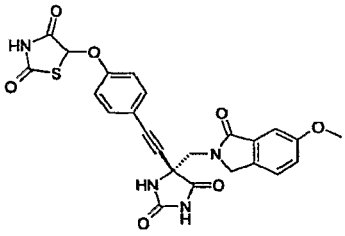
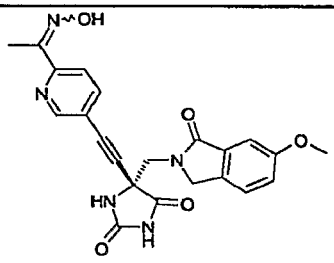
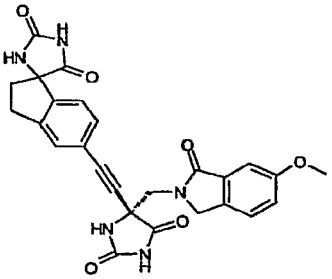
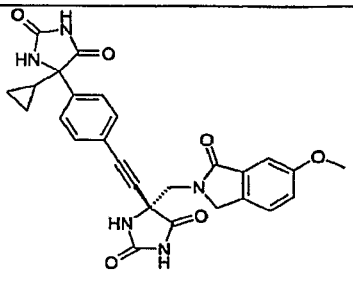
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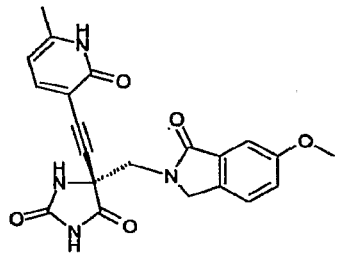
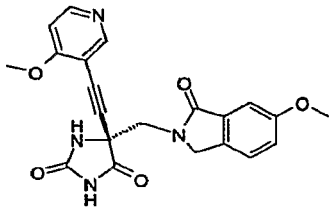
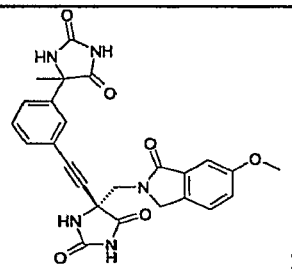
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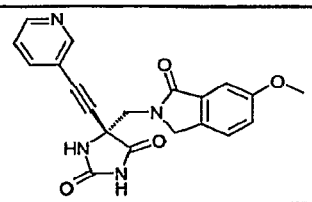
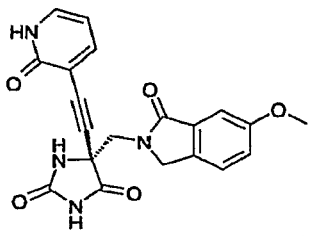
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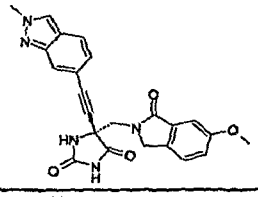
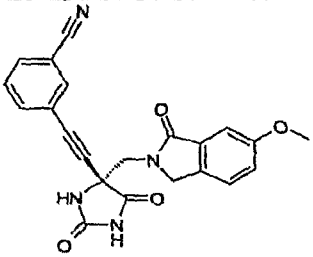
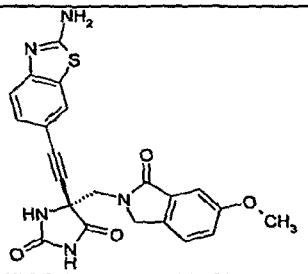
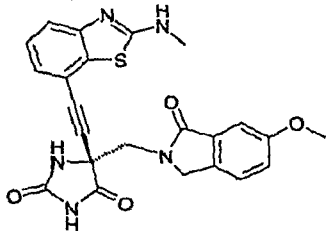
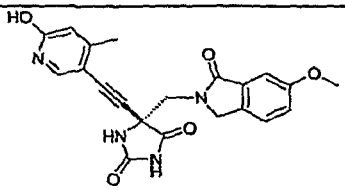
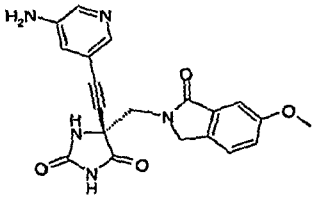
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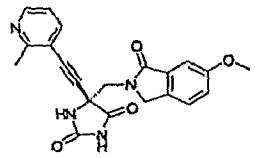
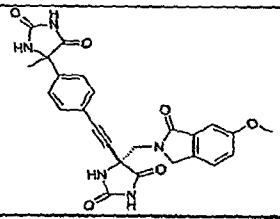
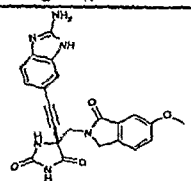
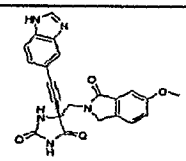
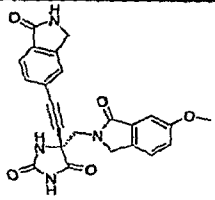
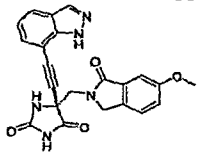
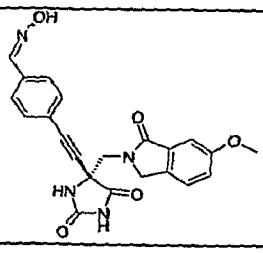
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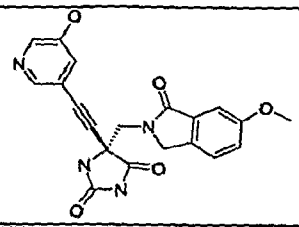
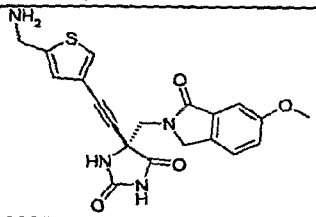
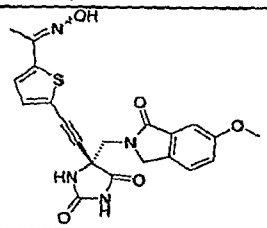
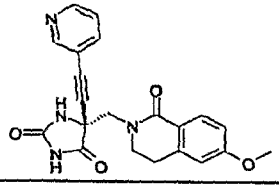
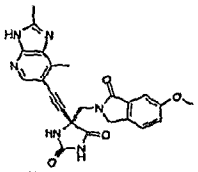
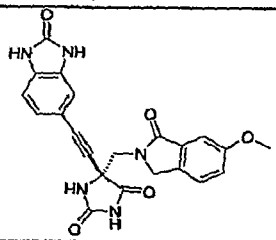
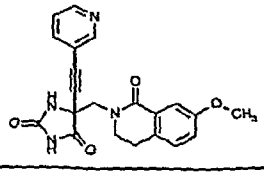
or a pharmaceutically acceptable salt, solvate, or ester thereof.

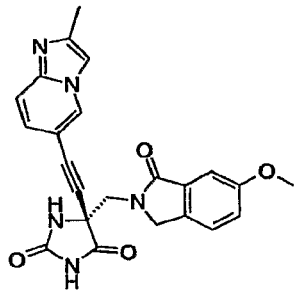
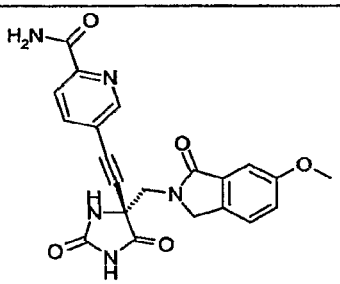
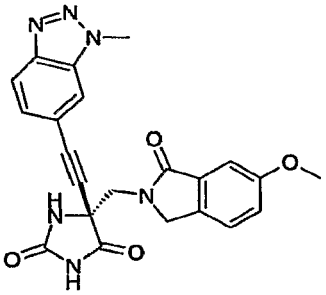
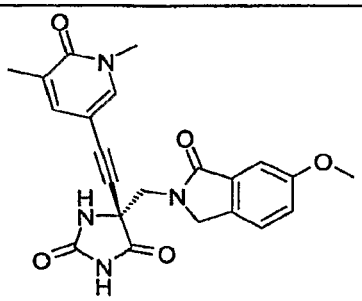
31. The compound of claim 30, selected from the group consisting of:

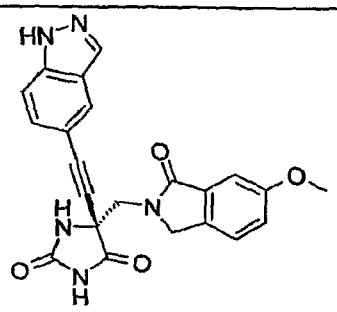
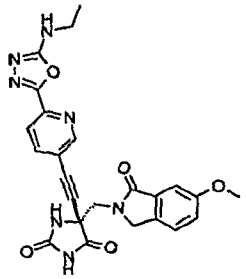
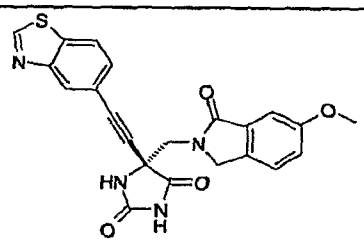
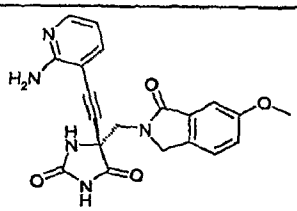
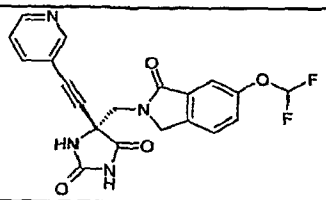
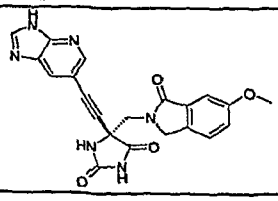
Compound ID	Structures
400B	
417C	

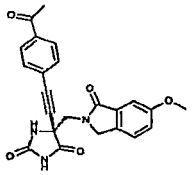
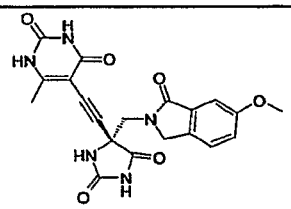
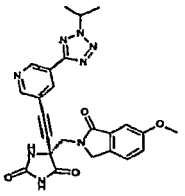
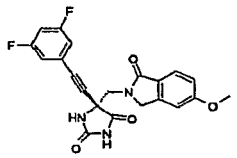
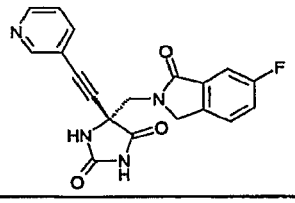
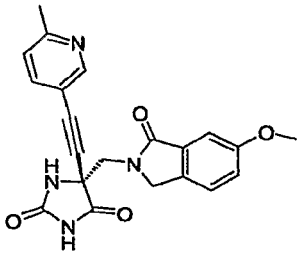
Compound ID	Structures
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447	
494	
507	
555	
554	

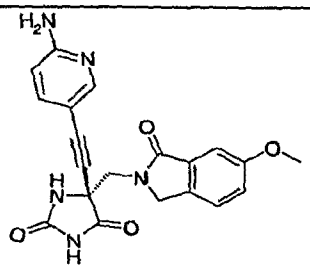
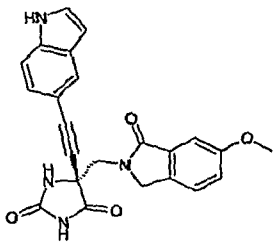
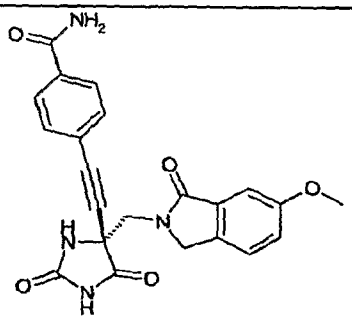
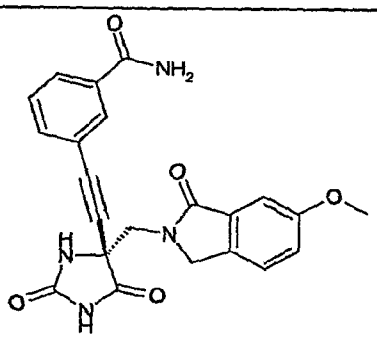
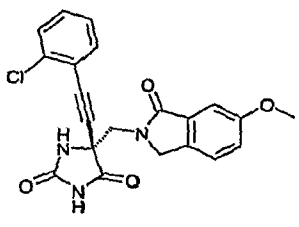
Compound ID	Structures
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1256	
1009	
1012	
1253	
1015	
1091	

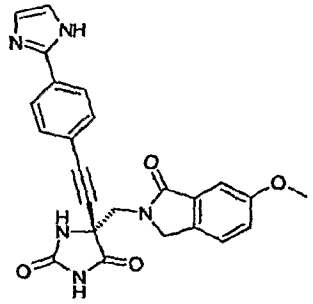
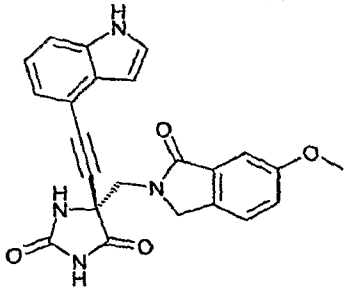
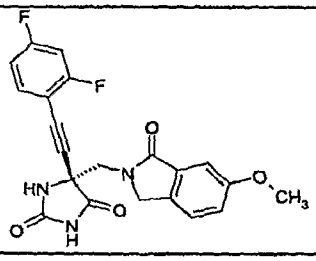
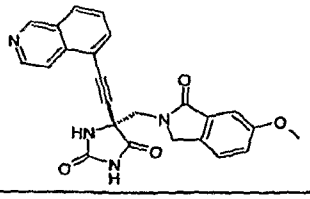
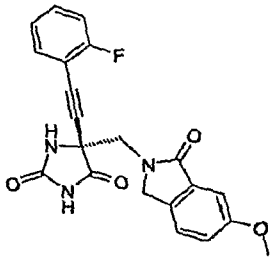
Compound ID	Structures
1063	
1070	
1090	
1092	
1098	
1069	
1099	

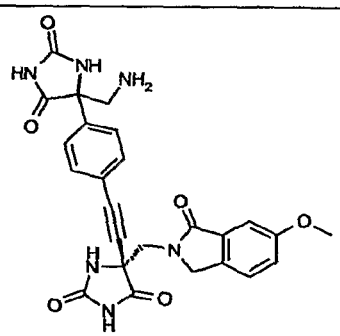
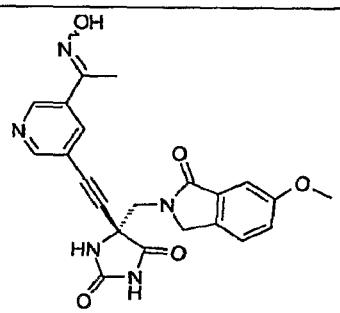
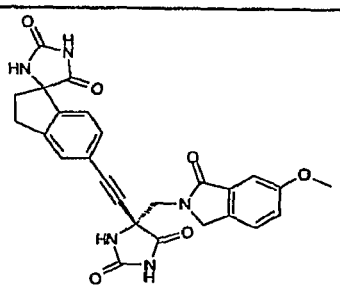
Compound ID	Structures
1505	
1513	
1520	
1519	

Compound ID	Structures
1523	
1502	
972	
930	
943	
960	

Compound ID	Structures
1220B	
1206	
1220	
1201	
1200	
1155	

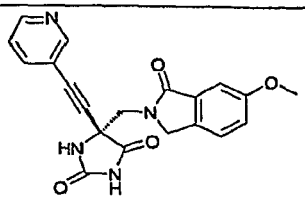
Compound ID	Structures
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1129	
1133	
1134	
1146	

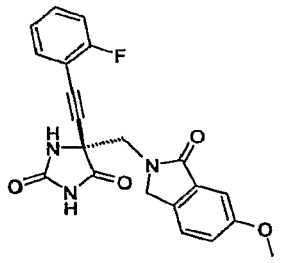
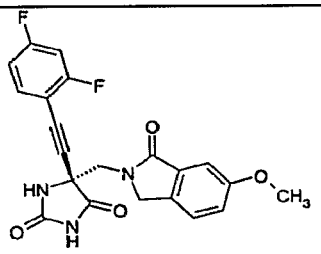
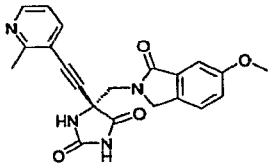
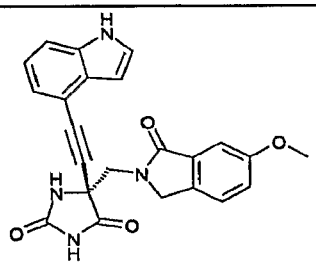
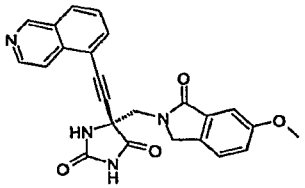
Compound ID	Structures
1136	
1132	
490	
442	
516	

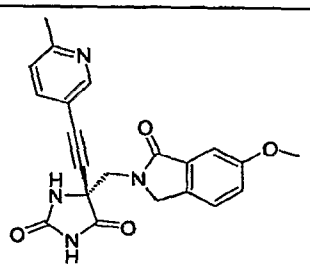
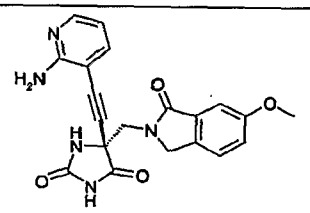
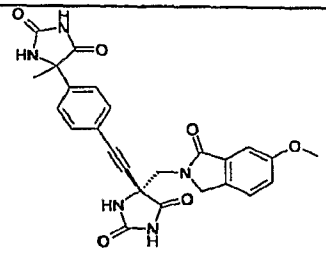
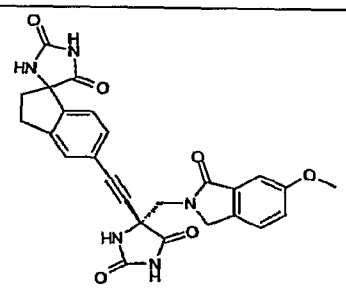
Compound ID	Structures
1562	
1552	
1576	

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

32. The compound of claim 31, selected from the group consisting of:

Compound ID	Structures
400B	

Compound ID	Structures
516	
490	
1003	
1132	
442	

Compound ID	Structures
1155	
930	
1256	 and
1576	 ;

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

33. A compound of claim 1 in purified form.

34. 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.

35. 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.

36. 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 33.

37. 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.

38. 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.

39. 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.

40. 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.

41. 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.

42. 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.

43. 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.

44. 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.

45. 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.

46. 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.

47. 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.

48. 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.

49. The method of claim 36, 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.

50. A method of claim 37, 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.

51. A method of claim 38, 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.