25 JUL 2006

INDAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to United States Provisional Patent Application 60/351,597 filed January 25, 2002, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention is in the field of medicinal chemistry and relates to compounds that are protein kinase inhibitors, compositions containing such compounds and methods of use. More particularly, the compounds are inhibitors of AKT, PKA, PDK1, p70S6K, and ROCK kinases and are useful for treating diseases, such as cancer.

BACKGROUND OF THE INVENTION

[0001] The search for new therapeutic agents has been greatly aided in recent years by better understanding of the structure of enzymes and other biomolecules associated with target diseases. One important class of enzymes that has been the subject of extensive study is the protein kinases.

[0002] Protein kinases mediate intracellular signal transduction. They do this by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. There are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell. Examples of such stimuli include environmental and chemical stress signals (e.g. osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, H_2O_2), cytokines (e.g. interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α)), and growth factors (e.g. granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF). An extracellular stimulus may effect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis and regulation of cell cycle.

[0003] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include autoimmune diseases, inflammatory diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease or hormone-related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents. A challenge has been to find protein kinase inhibitors that act in a selective manner. Since there are numerable protein kinases that are involved in a variety of cellular responses, non-selective inhibitors may lead to unwanted side effects.

[0004] AKT (also known as PKB or Rac-PK beta), a serine/threonine protein kinase, has been shown to be overexpressed in several types of cancer and is a mediator of normal cell functions [(Khwaja, A., *Nature,* **401**, pp. 33-34, 1999); (Yuan, Z.Q., et al., *Oncogene*, **19, pp. 2324-2330,** 2000); (Namikawa, K., et al., *J Neurosci.*, **20, pp. 2875-2886,** 2000)]. AKT comprises an N-terminal pleckstrin homology (PH) domain, a kinase domain and a C-terminal "tail" region. Three isoforms of human AKT kinase (AKT-1, -2 and -3) have been reported so far [(Cheng, J.Q., *Proc. Natl. Acad. Sci. USA,* **89**, pp. 9267-9271, 1992); (Brodbeck, D. et al., *J. Biol. Chem.* **274**, pp. 9133-9136, 1999)]. The PH domain binds 3-phosphoinositides, which are synthesized by phosphatidyl inositol 3-kinase (PI3K) upon stimulation by growth factors such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor (IGF-1) [(Kulik et al., *Mol. Cell. Biol.*, **17**, pp. 1595-1606, 1997); (Hemmings, B.A., *Science*, **275**, pp. 628-630, 1997)]. Lipid binding to the PH domain promotes translocation of AKT to the plasma membrane and facilitates phosphorylation by another PH-domain-containing protein kinases, PDK1 at Thr308, Thr309, and Thr305 for the AKT isoforms 1, 2 and 3, respectively. A second, as of yet unknown, kinase is required for the phosphorylation of Ser473, Ser474 or Ser472 in the C-terminal tails of AKT-1, -2 and -3 respectively, in order to yield a fully activated AKT enzyme.

[0005] Once localized to the membrane, AKT mediates several functions within the cell including the metabolic effects of insulin (Calera, M.R. et al., *J. Biol. Chem.*, **273**, pp. 7201-7204, 1998), induction of differentiation and/or proliferation, protein synthesisans stress responses (Alessi, D.R. et al., *Curr. Opin. Genet. Dev.*, **8**, pp. 55-62, 1998).

[0006] Manifestations of altered AKT regulation appear in both injury and disease, the most important role being in cancer. The first account of AKT was in association with

human ovarian carcinomas where expression of AKT was found to be amplified in 15% of cases (Cheng, J.Q. et al., *Proc. Natl. Acad. Sci. U.S.A.*, **89**, pp. 9267-9271, 1992). It has also been found to be overexpressed in 12% of pancreatic cancers (Cheng, J. Q. et al., *Proc. Natl. Acad. Sci. U.S.A.* , **93**, pp. 3636-3641, 1996). It was demonstrated that AKT-2 was over-expressed in 12% of ovarian carcinomas and that amplification of AKT was especially frequent in 50% of undifferentiated tumours, suggesting that AKT may also be associated with tumour aggressiveness (Bellacosa, et al., *Int. J. Cancer*, **64**, pp. 280-285, 1995).

[0007] PKA (also known as cAMP-dependent protein kinase) has been shown to regulate many vital functions including energy metabolism, gene transcription, proliferation, differentiation, reproductive function, secretion, neuronal activity, memory, contractility and motility (Beebe, S.J., *Semin. Cancer Biol.*, **5**, pp. 285-294, 1994). PKA is a tetrameric holoenzyme, which contains two catalytic subunits bound to a homo-dimeric regulatory subunit (which acts to inhibit the catalytic sub-units). On binding of cAMP (enzyme activation), the catalytic subunits dissociate from the regulatory subunits to yield the active serine/threonine kinase (McKnight, G.S. et al., *Recent Prog. Horm. Res.*, **44**, pp. 307, 1988). Three isoforms of the catalytic subunit (C-α, C-β and C-γ have been reported to date (Beebe, S.J. et al., *J. Biol. Chem.* , **267**, pp. 25505-25512, 1992) with the C-α subunit being the most extensively studied, primarily because of its elevated expression in primary and metastatic melanomas (Becker, D. et al., *Oncogene*, **5**, pp. 1133, 1990). To date, strategies to modulate the activity of the C-α subunit involve the use of antibodies, molecules that block PKA activity by targeting regulatory dimers and antisense oligonucleotides expression.

[0008] Rho-associated coiled-coil forming kinase (ROCK) (Ishizaki, T. et al., *EMBO J.*, **15**, pp. 1885-1893, 1996) is a 160 kDa serine/threonine kinase that activates the small G-protein RhoA. ROCK has been implicated in numerous diseases including hypertension [(Chitaley, et al., *Curr. Hypertens. Rep. 2001 Apr.*, **3(2)**, pp.139-144); (Uehata, M. et al., *Nature*, **389**, pp. 990-994, 1997)], erectile dysfunction (Chitaley, K. et al., *Nature Medicine*, **7**, pp. 119-122, 2001), angiogenesis (Uchida, S. et al., *Biochem. Biophys. Res. Commun.*, **269 (2)** , pp. 633-40, 2000), neuroregeneration (Bito, H. et al., *Neuron*, **26**, pp. 431-441, 2000), metastasis [(Takamura, M. et al., *Hepatology*, **33**, pp. 577-581, 2001); (Genda, T. et al., *Hepatology*, **30**, pp. 1027-1036, 1999)], glaucoma

(Rao, et al., *Invest. Ophthalmol. Vis. Sci.* , **42**, pp. 1029-37, 2001), inflammation (Ishizuka, T. et al., *J. Immunol.* , **167**, pp. 2298-2304, 2001), arteriosclerosis (Smimokawa, et al., *Arterioscler. Thromb. Vasc. Biol.* , **11**, pp. 2351-2358, 2000), immunosuppresion (Lou, Z. et al., *J. Immunol.* , **167**, pp. 5749-5757, 2001), restenosis (Seaholtz, et al., *Circ. Res.* , **84**, pp. 1186-1193, 1999), asthma (Yoshii, et al., *Am. J. Respir. Cell Mol. Biol.*, **20**, pp. 1190-1200, 1999), cardiac hypertrophy (Kuwahara, K. et al., *FEBS Lett.* , **452**, pp. 314-318, 1999).

[0009] The ribosomal protein kinases p70S6K-1 and -2 are members of the AGC sub-family of protein kinases that consists of, amongst others, PKB and MSK. The p70S6 kinases catalyze the phosphorylation and subsequent activation of the ribosomal protein S6, which has been implicated in the translational up-regulation of mRNAs coding for the components of protein synthetic apparatus.

[0010] These mRNAs contain an oligopyrimidine tract at their 5' transcriptional start site, termed a 5'TOP, which has been shown to be essential for their regulation at the translational level (Volarevic, S. et al., *Prog. Nucleic Acid Res. Mol. Biol.* **65**, pp 101-186, 2001). p70 S6K dependent S6 phosphorylation is stimulated in response to a variety of hormones and growth factors primarily via the PI3K pathway (Coffer, P.J. et al., *Biochem. Biophys. Res. Commun*, **198**, 7pp 780-786, 1994), which maybe under the regulation of mTOR, since rapamycin acts to inhibit p70S6K activity and blocks protein synthesis, specifically as a result of a down-regulation of translation of these mRNA's encoding ribosomal proteins (Kuo, C.J. et al., *Nature*, **358**, pp 70-73, 1992).

[0011] In vitro PDK1 catalyses the phosphorylation of Thr252 in the activation loop of the p70 catalytic domain, which is indispensable for p70 activity (Alessi, D.R., *Curr. Biol.*, **8**, pp 69-81, 1998). The use of rapamycin and gene deletion studies of dp70S6K from Drosophila and p70S6K1 from mouse have established the central role p70 plays in both cell growth and proliferation signaling.

[0012] The 3-phosphoinositide-dependent protein kinase-1 (PDK1) plays a key role in regulating the activity of a number of kinases belonging to the AGC subfamily of protein kinases (Alessi, D. et al., *Biochem. Soc. Trans,* **29**, pp. 1, 2001). These include isoforms of protein kinase B (PKB, also known as AKT), p70 ribosomal S6 kinase (S6K) (Avruch, J. et al., *prog. Mol. Subcell. Biol.,* 2001, **26**, pp. 115, 2001), and p90 ribosomal S6 kinase (Frödin, M. et al., *EMBO J.*, **19**, pp. 2924-2934, 2000). PDK1 mediated signaling is activated in response to insulin and growth factors and as a consequence of attachment of

the cell to the extracellular matrix (integrin signaling). Once activated these enzymes mediate many diverse cellular events by phosphorylating key regulatory proteins that play important roles controlling processes such as cell survival, growth, proliferation and glucose regulation [(Lawlor, M.A. et al., *J. Cell Sci.* , **114**, pp. 2903-2910, 2001), (Lawlor, M.A. et al., *EMBO J.* , **21**, pp. 3728-3738, 2002)]. PDK1 is a 556 amino acid protein, with an N-terminal catalytic domain and a C-terminal pleckstrin homology (PH) domain, which activates its substrates by phosphorylating these kinases at their activation loop (Belham, C. et al., *Curr. Biol.* , **9**, pp. R93-R96, 1999). Many human cancers including prostate and NSCL have elevated PDK1 signaling pathway function resulting from a number of distinct genetic events such as PTEN mutations or over-expression of certain key regulatory proteins [(Graff, J.R., *Expert Opin. Ther. Targets*, **6**, pp. 103-113, 2002), (Brognard, J., et al., *Cancer Res.* , **61**, pp. 3986-3997, 2001)]. Inhibition of PDK1 as a potential mechanism to treat cancer was demonstrated by transfection of a PTEN negative human cancer cell line (U87MG) with antisense oligonucleotides directed against PDK1. The resulting decrease in PDK1 protein levels led to a reduction in cellular proliferation and survival (Flynn, P., et al., *Curr. Biol.* , **10**, pp. 1439-1442, 2000). Consequently the design of ATP binding site inhibitors of PDK1 offers, amongst other treatments, an attractive target for cancer chemotherapy.

[0013] The diverse range of cancer cell genotypes has been attributed to the manifestation of the following six essential alterations in cell physiology: self-sufficiency in growth signaling, evasion of apoptosis, insensitivity to growth-inhibitory signaling, limitless replicative potential, sustained angiogenesis, and tissue invasion leading to metastasis (Hanahan, D. et al., *Cell*, **100**, pp. 57-70, 2000). PDK1 is a critical mediator of the PI3K signalling pathway, which regulates a multitude of cellular function including growth, proliferation and survival. Consequently inhibition of this pathway could affect four or more of the six defining requirements for cancer progression, as such it is anticipated that a PDK1 inhibitor will have an effect on the growth of a very wide range of human cancers.

[0014] Specifically, increased levels of PI3K pathway activity has been directly associated with the development of a number of human caners, progression to an aggressive refractory state (acquired resistance to chemotherapies) and poor prognosis. This increased activity has been attributed to a series of key events including decreased activity of negative pathway regulators such as the phosphatase PTEN, activating

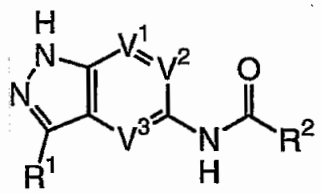
mutations of positive pathway regulators such as Ras, and overexpression of components of the pathway itself such as PKB, examples include: brain (gliomas), breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, thyroid [(Teng, D.H. et al., *Cancer Res.* , **57**, pp. 5221-5225, 1997), (Brognard, J. et al., *Cancer Res.* , **61**, pp. 3986-3997, 2001), (Cheng, J.Q. et al., *Proc. Natl. Acad. Sci.* , **93**, pp. 3636-3641, 1996), *Int. J. Cancer*, **64**, pp. 280, 1995), (Graff, J.R., *Expert Opin. Ther. Targets*, **6**, pp. 103-113, 2002), *Am. J. Pathol.* , **159**, pp. 431, 2001)].

[0015] Additionally, decreased pathway function through gene knockout, gene knockdown, dominant negative studies and small molecule inhibitors of the pathway have been demonstrated to reverse many of the cancer phenotypes *in vitro* (some studies have also demonstrated a similar effect *in vivo*) such as block proliferation, reduce viability and sensitize cancer cells to known chemotherapies in a series of cell lines, representing the following cancers: pancreatic [(Cheng, J.Q. et al., *Proc. Natl. Acad. Sci.* , **93**, pp. 3636-3641, 1996), *Neoplasia*, **3**, pp. 278, 2001)], lung [(Brognard, J. et al., *Cancer Res.* , **61**, pp. 3986-3997, 2001), *Neoplasia*, **3**, pp. 278, 2001)], ovarian [(Hayakawa, J. et al., *Cancer Res.* , **60**, pp. 5988-5994, 2000), *Neoplasia*, **3**, pp. 278, 2001)], breast (*Mol. Cancer Ther.*, **1**, pp. 707, 2002), colon [(*Neoplasia*, **3**, pp. 278, 2001), (Arico, S. et al., *J. Biol. Chem.*, **277**, pp. 27613-27621, 2002)], cervical (*Neoplasia*, **3**, pp. 278, 2001), prostate [(*Endocrinology*, **142**, pp. 4795, 2001), (Thakkar, H. et al. *J. Biol. Chem.*, **276**, pp. 38361-38369, 2001), (Chen, X. et al., *Oncogene*, **20**, pp. 6073-6083, 2001)] and brain (glioblastomas) [(Flynn, P. et al., *Curr. Biol.*, **10**, pp. 1439-1442, 2000)].

[0016] Accordingly, there is a great need to develop inhibitors of AKT, PKA, PDK1, p70S6K, and ROCK protein kinases that are useful in treating various diseases or conditions associated with AKT, PKA, PDK1, p70S6K, and ROCK activation, particularly given the inadequate treatments currently available for the majority of these disorders.

SUMMARY OF THE INVENTION

[0017] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of AKT, PKA, PDK1, p70S6K, and ROCK protein kinases. These compounds have the formula **I**:



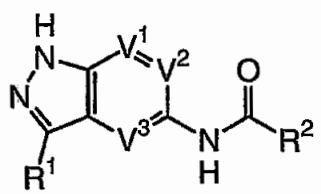
I

or a pharmaceutically acceptable salt thereof, wherein V^1, V^2, V^3, R^1, and R^2 are as defined below.

[0018] These compounds, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of disorders, including allergic disorders such as asthma, inflammatory disease, proliferative disorders, and neurological disorders.

DESCRIPTION OF THE INVENTION

[0019] The present invention relates to a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, T-R, or T-Ar;

each T is independently selected from a valence bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

each R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from Q-Ar, $Q\text{-}N(R^5)_2$, or $Q\text{-}C(R)(Q\text{-}Ar)R^3$, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4} alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-$OC(O)R^5$, Q-$CONHR^5$, Q-$OC(O)NHR^5$, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$;

R' is an optionally substituted C_{1-6} aliphatic group;

each R^4 is independently selected from R, COR^5, CO_2R^5, $CON(R^5)_2$, SO_2R^5, $SO_2N(R^5)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, N(R)COR, $N(R)CON(R^4)_2$, N(R)C(O)OR, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, OC(O)R, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

when V^1, V^2, and V^3 are each CH, T is a valence bond, and R^2 is Q-$C(R)(Q\text{-}Ar)R^3$, wherein Ar is an optionally substituted phenyl ring, then R^3 is other than Q-OR^5 or $C(O)NH_2$; and

when V^1, V^2, and V^3 are each CH and R^1 is hydrogen then R^2 is Q-$C(R)(Q\text{-}Ar)R^3$, wherein R^3 is other than R', Q-$OC(O)R^5$, or OCH_2phenyl.

[0020] As used herein, the following definitions shall apply unless otherwise indicated. The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

[0021] The term "aliphatic" or "aliphatic group" as used herein means a straight-chain or branched C_1-C_{12} hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of

unsaturation, but which is not aromatic (also referred to herein as "carbocycle" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. For example, suitable aliphatic groups include, but are not limited to, linear or branched or alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0022] The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety includes both straight and branched chains containing one to twelve carbon atoms. The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to twelve carbon atoms.

[0023] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

[0024] The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated ring having 0-4 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl).

[0025] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring".

[0026] The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic or tricyclic ring systems having five to fourteen ring members in which one or more ring members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members.

[0027] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and

wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0028] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group are selected from halogen, oxo, N_3, -R°, -OR°, -SR°, 1,2-methylene-dioxy, 1,2-ethylenedioxy, protected OH (such as acyloxy), phenyl (Ph), Ph substituted with R°, -O(Ph), O-(Ph) substituted with R°, $-CH_2$(Ph), $-CH_2$(Ph) substituted with R°, $-CH_2CH_2$(Ph), $-CH_2CH_2$(Ph) substituted with R°, $-NO_2$, -CN, $-N(R°)_2$, -NR°C(O)R°, -NR°C(O)N(R°)$_2$, -NR°CO_2R°, -NR°NR°C(O)R°, -NR°NR°C(O)N(R°)$_2$, -NR°NR°CO_2R°, -C(O)C(O)R°, -C(O)CH_2C(O)R°, -CO_2R°, -C(O)R°, -C(O)N(R°)$_2$, -OC(O)N(R°)$_2$, -S(O)$_2$R°, -SO_2N(R°)$_2$, -S(O)R°, -NR°SO_2N(R°)$_2$, -NR°SO_2R°, -C(=S)N(R°)$_2$, -C(=NH)-N(R°)$_2$, or $-(CH_2)_yNHC(O)R°$, wherein y is 0-4, each R° is independently selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl (Ph), -O(Ph), or $-CH_2$(Ph)–CH_2(Ph). Substituents on the aliphatic group of R° are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O-(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), -O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic.

[0029] An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and the following: =O, =S, =NNHR*, =NN(R*)$_2$, =N-, =NNHC(O)R*, =NNHCO_2(alkyl), =NNHSO_2(alkyl), or =NR*, where each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Substituents on the aliphatic group of R* are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O-(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), -O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic.

[0030] Substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from $-R^+$, -N(R^+)$_2$, -C(O)R^+, -CO_2R^+, -C(O)C(O)R^+, -C(O)CH_2C(O)R^+, -SO_2R^+, -SO_2N(R^+)$_2$, -C(=S)N(R^+)$_2$, -C(=NH)-N(R^+)$_2$, or -NR$^+$$SO_2R^+$; wherein R^+ is hydrogen, an

optionally substituted C_{1-6} aliphatic, optionally substituted phenyl (Ph), optionally substituted -O(Ph), optionally substituted -CH_2(Ph), optionally substituted -CH_2CH_2(Ph), or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring. Substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2, NH(C_{1-4} aliphatic), N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, OH, O-(C_{1-4} aliphatic), NO_2, CN, CO_2H, CO_2(C_{1-4} aliphatic), -O(halo C_{1-4} aliphatic), or halo C_{1-4} aliphatic.

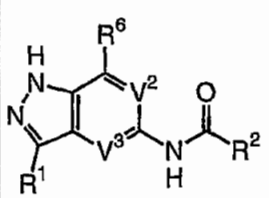
[0031] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of connection to the rest of the molecule.

[0032] The compounds of this invention are limited to those that are chemically feasible and stable. Therefore, a combination of substituents or variables in the compounds described above is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0033] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0034] Compounds of this invention may exist in alternative tautomeric forms. Unless otherwise indicated, the representation of either tautomer is meant to include the other.

[0035] One embodiment of the present invention relates to a compound of formula **Ia**:



Ia

or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are as defined above for compounds of formula **I**.

[0036] According to one preferred embodiment, the present invention relates to a compound of formula **I** wherein V^1 is N, V^2 is CH, and V^3 is CH.

[0037] Preferred compounds of formula **I** include those wherein V^1 is C-R^6, V^2 is CH, and V^3 is CH or N.

[0038] Another preferred embodiment of the present invention relates to a compound of formula **I** wherein V^1 is C-R^6, V^2 is CH, and V^3 is N.

[0039] Another preferred embodiment of the present invention relates to a compound of formula **I** wherein V^1 is C-R^6, V^2 is CH, and V^3 is CH.

[0040] According to another preferred embodiment, the present invention relates to a compound of formula **Ia** wherein V^2 is CH and V^3 is N.

[0041] According to another preferred embodiment, the present invention relates to a compound of formula **Ia** wherein V^2 and V^3 are each N.

[0042] Preferred R^1 groups of formula **I** or **Ia** include hydrogen, halogen, CN, $N(R^4)_2$, and optionally substituted C_{1-6} aliphatic. Examples of such R^1 groups include chloro, bromo, fluoro, NH_2, NHMe, NHEt, NH-(optionally substituted phenyl), NH-cyclohexyl, $NHCH_2$(optionally substituted phenyl), NHC(O)(optionally substituted phenyl), NHC(O)NH(optionally substituted phenyl), $NHC(O)CH_2$(optionally substituted phenyl), $NHC(O)CH_2CH_2$(optionally substituted phenyl), N(R)C(O)(optionally substituted phenyl), NHC(O)naphthyl, NHC(O)thienyl, NRC(O)thienyl, SC(O)thienyl, $CH_2C(O)$thienyl, NHC(O)pyridyl, NHC(O)furanyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, acetylenyl, and t-butyl.

[0043] The optional substituents of the phenyl rings of R^1 of formula **I** or **Ia**, when present, are optionally substituted R°, halogen, nitro, CN, OR°, SR°, $N(R^\circ)_2$, SO_2R°, $C(O)R^\circ$, C(O)OR, and $C(O)N(R^\circ)_2$, wherein each R° is as defined *supra*. Examples of such groups include chloro, bromo, fluoro, CN, nitro, OMe, OPh, OCF_3, OCH_2Ph, OEt, $SCHF_2$, methyl, ethyl, isopropyl, propyl, vinyl, CF_3, acetylenyl, CH_2Ph, CH_2NH_2, $CH_2N(Et)_2$, CH_2morpholin-4-yl, CH_2piperdin-1-yl, CH_2imidazol-1-yl, CH_2piperazin-1-yl, $C(O)NH_2$, C(O)Me, SO_2Me, NHEt, and NHMe.

[0044] When R^1 of formula **I** or **Ia** is T-Ar, preferred Ar groups are selected from an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen,

or sulfur. Examples of such Ar rings include optionally substituted phenyl, thienyl, furan, and pyridyl rings. Preferred T moieties of the T-Ar group of R^1 are selected from a valence bond, -N(R)C(O)-, -NH-, -$NHCH_2$-, -$NHSO_2$-, -CH_2NH-, -SC(O)-, -$CH_2C(O)$-, -C≡C-, -CH_2- or -CH_2CH_2-. More preferred T moieties of the T-Ar group of R^1 are selected from -NHC(O)-, -NH-, -$NHCH_2$-, -CH_2-, -C≡C-, or -CH_2CH_2-. Most preferred T moieties of the T-Ar group of R^1 are selected from -N(R)C(O)-, -NH-, or -$NHCH_2$-. Preferred substituents on the Ar group, when present, include fluoro and CF_3, Me, Et, iPr, vinyl, acetylene, Ar, Cl, CF_3, nitro, CN, OMe, OPh, OCF_3, SO_2NH2, C(O)OEt, C(O)OH, CH_2CO_2H, $CH_2CH_2CO_2H$, CH_2NH_2 and $C(O)NH_2$, thienyl, oxazolyl, isoxazolyl, and tetrazolyl.

[0045] Preferred Q groups of formula **I** or **Ia** are selected from a valence bond, -CH_2-, or -CH_2CH_2-.

[0046] When R^2 of formula **I** or **Ia** is Q-Ar, preferred Ar groups are an optionally substituted ring selected from a 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such monocyclic rings include phenyl, pyridyl, pyrimidinyl, pyridonyl, furanyl, tetrazolyl, thienyl, cyclopentyl, cyclohexyl, and cycloheptyl. Examples of such bicyclic rings include benzo[1,3]dioxolyl, indan-1-onyl, naphthyl, benzothiophenyl, 2,3-dihydro-1*H*-isoindolyl, indanyl, benzofuranyl, and indolyl.

[0047] When present, preferred substituents on the Ar ring of R^2 include R^o, halogen, oxo, OR^o, phenyl, optionally substituted dialkylamino, haloalkyl, $C(O)R^o$, NHC(O)R, or SR^o. Examples of such preferred substituents include chloro, bromo, fluoro, OH, OMe, $NHC(O)CH_3$, OEt, C(O)phenyl, Ophenyl, $N(CH_2CH_2Cl)_2$, $N(Me)_2$, CF_3, and SCF_3. Other examples of preferred Ar groups of formula **I** or **Ia** also include those shown in Table 1 below.

[0048] When the R^2 group of formula **I** or **Ia** is Q-C(R)(Q-Ar)R^3, preferred R^3 groups include R', Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, and N(R)Q-$N(R^4)_2$. Examples of such R^3 groups include CH_2OH, OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NHCO_2$*t*-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl,

$NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)O$*t*-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

[0049] More preferably, the R^3 group of formula **I** or **Ia** is selected from OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NHCO_2$*t*-butyl, phenyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)O$*t*-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

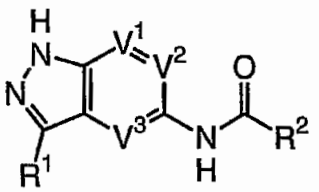
[0050] Most preferably, the R^3 group of formula **I** or **Ia** is selected from $CH_2CH_2NH_2$.

[0051] Preferred rings formed by the R and R^3 moieties of the Q-C(R)(Q-Ar)R^3 group of R^2 are selected from a 5-6 membered saturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such rings formed by R and R^3 include piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, and thiomorpholinyl.

[0052] When the R^2 group of formula **I** or **Ia** is Q-C(R)(Q-Ar)R^3, preferred Ar groups of the Q-C(R)(Q-Ar)R^3 moiety are selected from an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such monocyclic rings include phenyl, pyridyl, furanyl, pyridone, and thienyl. Examples of such bicyclic rings include benzo[1,3]dioxolyl, naphthyl, indanyl, and indolyl. When present, preferred substituents on the Ar ring of the Q-C(R)(Q-Ar)R^3 group of R^2 include R°, halogen, OR°, phenyl, $N(R^\circ)_2$, $NHC(O)R^\circ$, or SR°. Examples of such groups include fluoro, chloro, bromo, CF_3, OH, OMe, OPh, OCH_2Ph, SMe, NH_2, NHC(O)Me, methyl, ethyl, isopropyl, isobutyl, and cyclopropyl.

[0053] Preferred R^6 groups of formula **I** or **Ia**, when present, are selected from halogen, R, and Ar^1. More preferred R^6 groups of formula **I** or **Ia**, when present, are selected from halogen, optionally substituted C_{1-4} aliphatic, or an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such groups include chloro, bromo, methyl, ethyl, *t*-butyl, cyclopropyl, isopropyl, phenyl, and pyridyl.

[0054] According to another embodiment, the present invention relates to a compound of formula **I'**:



I'

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, T-R, or T'-Ar;

T is selected from a valence bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

T' is a C_{1-6} alkylidene chain, wherein up to two methylene units of T' are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

each R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from Q-Ar, $Q\text{-}N(R^5)_2$, or $Q\text{-}C(R)(Q\text{-}Ar)R^3$, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4} alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, $Q\text{-}OR^5$, $Q\text{-}OC(O)R^5$, $Q\text{-}CONHR^5$, $Q\text{-}OC(O)NHR^5$, $Q\text{-}SR^5$, $Q\text{-}N(R^4)_2$, $N(R)(Q\text{-}Ar)$, $N(R)C(O)Q\text{-}N(R^4)_2$, or $N(R)Q\text{-}N(R^4)_2$;

R' is an optionally substituted C_{1-6} aliphatic group;

each R^4 is independently selected from R, COR^5, CO_2R^5, $CON(R^5)_2$, SO_2R^5, $SO_2N(R^5)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, $N(R)COR$, $N(R)CON(R^4)_2$, $N(R)C(O)OR$, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, $OC(O)R$, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

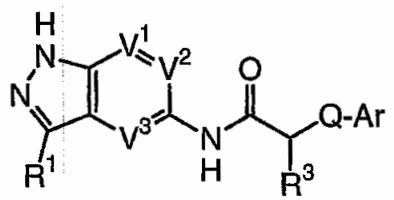
each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

when V^1, V^2, and V^3 are each CH and R^1 is hydrogen, then R^2 is $Q\text{-}C(R)(Q\text{-}Ar)R^3$, wherein R^3 is other than R', $Q\text{-}OC(O)R^5$, or OCH_2phenyl.

[0055] Preferred R^1 and R^2 groups of formula **I'** are those described above for compounds of formulae **I** and **Ia**. When R^1 is T'-Ar, preferred T' groups of formula **I'** are selected from -NHC(O)-, -NH-, $-NHCH_2$-, $-NHSO_2$-, $-CH_2NH$-, $-CH_2$-, -C≡C-, or $-CH_2CH_2$-. More preferred T' groups of formula **I'** are selected from -NHC(O)-, -NH-, $-NHCH_2$-, $-NHSO_2$-, or $-CH_2NH$-.

[0056] According to another embodiment, the present invention relates to a compound of formula **Ib**:



Ib

or a pharmaceutically acceptable salt thereof, wherein R^1, R^3, Q, and Ar are as defined above for compounds of formula **I**.

[0057] Preferred R^1 groups of formula **Ib** include those described above for compounds of formula **I** and **Ia**.

[0058] Preferred V^1, V^2, and V^3 groups of formula **Ib** are the preferred V^1, V^2, and V^3 groups set forth for compounds of formula **I**, *supra*.

[0059] Preferred Q groups of formula **Ib** include those described above for compounds of formula **I** and **Ia**.

[0060] Preferred Ar groups of formula **Ib** include an optionally substituted ring selected from a 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such monocyclic rings include phenyl, pyridyl, thienyl, furanyl, cyclopentyl, cyclohexyl, and cycloheptyl. Examples of such bicyclic rings include benzo[1,3]dioxolyl, indan-1-onyl, naphthyl, benzothiophenyl, 2,3-dihydro-1*H*-isoindolyl, indanyl, benzofuranyl, and indolyl. When present, preferred substituents on the Ar group of formula **Ib** include R°, halogen, OR°, phenyl, optionally substituted dialkylamino, haloalkyl, $C(O)R^{\circ}$, or SR°. Examples of such preferred substituents include tetrazolyl, oxazolyl, isoxazolyl, chloro, bromo, fluoro, OH, OMe, OEt, C(O)phenyl, Ophenyl, $N(CH_2CH_2Cl)_2$, $N(Me)_2$, CF_3, and SCF_3.

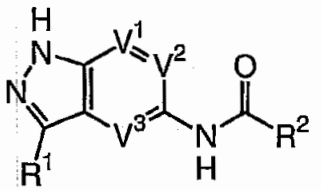
[0061] Preferred R^3 groups of formula **Ib** include R', Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, and N(R)Q-$N(R^4)_2$. Examples of such R^3 groups include CH_2OH, OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $CH_2CH_2N(Me)_2$, $CH_2CH_2NH_2$, $NHCO_2t$-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

[0062] More preferably, the R^3 group of formula **Ib** is selected from OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NHCO_2t$-butyl, phenyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

[0063] Most preferably, the R^3 group of formula **Ib** is selected from $CH_2CH_2NH_2$.

[0064] Preferred rings formed by the R and R^3 moieties of the Q-C(R)(Q-Ar)R^3 group of formula **Ib** are selected from a 5-6 membered saturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such rings formed by R and R^3 include piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, and thiomorpholinyl.

[0065] Another embodiment of the present invention relates to a compound of formula **IIa**:



IIa

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, or T-R;

T is selected from a valence bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

each R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4} alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-$OC(O)R^5$, Q-$CONHR^5$, Q-$OC(O)NHR^5$, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$;

R' is an optionally substituted C_{1-6} aliphatic group;

each R^4 is independently selected from R, COR, CO_2R, $CON(R)_2$, SO_2R, $SO_2N(R)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, $N(R)COR$, $N(R)CON(R^4)_2$, $N(R)C(O)OR$, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, $OC(O)R$, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that when R^1 is hydrogen then R^3 is other than R', Q-$OC(O)R^5$, or OCH_2phenyl.

[0066] Preferred R^1 groups of formula **IIa** include halogen, $N(R^4)_2$, and optionally substituted C_{1-6} aliphatic. Examples of such groups include chloro, bromo, fluoro, NH_2, NHMe, NHEt, NH-cyclohexyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, acetylenyl, and t-butyl.

[0067] Preferred V^1, V^2, and V^3 groups of formula **IIa** are the preferred V^1, V^2, and V^3 groups set forth for compounds of formula **I**, *supra*.

[0068] Preferred Q groups of formula **IIa** are selected from a valence bond, $-CH_2-$, or $-CH_2CH_2-$.

[0069] Preferred R^3 groups of formula **IIa** include R', Q-OR^5, Q-$N(R^4)_2$, Ar^1, $N(R)C(O)Q\text{-}N(R^4)_2$, and $N(R)Q\text{-}N(R^4)_2$. Examples of such R^3 groups include CH_2OH, OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $CH_2CH_2N(Me)_2$, $CH_2CH_2NH_2$, $NHCO_2t$-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

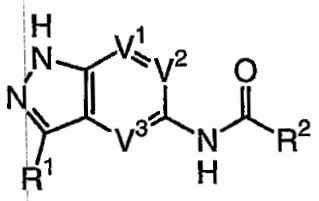
[0070] More preferably, the R^3 group of formula **IIa** is selected from OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NHCO_2t$-butyl, phenyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

[0071] Most preferably, the R^3 group of formula **IIa** is selected from $CH_2CH_2NH_2$.

[0072] Preferred rings formed by the R and R^3 moieties of R^2 of formula **IIa** are selected from a 5-6 membered saturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such rings formed by R and R^3 include piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, and thiomorpholinyl.

[0073] Preferred Ar groups of R^2 of formula **IIa** are selected from an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such monocyclic rings include phenyl, pyridyl, furanyl, and thienyl. Examples of such bicyclic rings include benzo[1,3]dioxolyl, naphthyl, indanyl, and indolyl. When present, preferred substituents on the Ar ring of the Q-C(R)(Q-Ar)R^3 group of R^2 of formula **IIa** include R°, halogen, OR°, phenyl, $N(R^\circ)_2$, $NHC(O)R^\circ$, or SR°. Examples of such groups include fluoro, chloro, bromo, CF_3, OH, OMe, OPh, OCH_2PH, SMe, NH_2, NHC(O)Me, methyl, ethyl, isopropyl, isobutyl, and cyclopropyl.

[0074] Another embodiment relates to a compound of formula **IIb**:



IIb

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is T-Ar;

each T is independently selected from a valence bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

each R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4} alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-$OC(O)R^5$, Q-$CONHR^5$, Q-$OC(O)NHR^5$, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$;

R' is an optionally substituted C_{1-6} aliphatic group;

each R^4 is independently selected from R, COR^5, CO_2R^5, $CON(R^5)_2$, SO_2R^5, $SO_2N(R^5)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, N(R)COR, $N(R)CON(R^4)_2$, N(R)C(O)OR, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, OC(O)R, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that when V^1, V^2, and V^3 are each CH,T is a valence bond, and R^2 is Q-C(R)(Q-Ar)R^3, wherein Ar is an optionally substituted phenyl ring, then R^3 is other than Q-OR^5 or $C(O)NH_2$.

[0075] Preferred V^1, V^2, and V^3 groups of formula **IIb** are those set forth for compounds of formula **I**, *supra*.

[0076] Preferred Ar groups of R^1 of formula **IIb** are selected from an optionally substituted 5-6 membered aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Preferred T moieties of the T-Ar group of R^1 of formula **IIb** are selected from a valence bond, -NHC(O)-, -NH-, $-NHCH_2-$, $-NHSO_2-$, $-CH_2NH-$, -C≡C-, $-CH_2-$ or $-CH_2CH_2-$. Most preferred T moieties of the T-Ar group of R^1 are selected from -NHC(O)-, -NH-, $-NHCH_2-$, $-CH_2-$ or $-CH_2CH_2-$. Examples of R^1 groups of formula **IIb** include $NHCH_2$(optionally substituted phenyl), NHC(O)(optionally substituted phenyl), NHC(O)NH(optionally substituted phenyl), $NHC(O)CH_2$(optionally substituted phenyl), $NHC(O)CH_2CH_2$(optionally substituted phenyl), NHC(O)(optionally

substituted phenyl), NHC(O)naphthyl, NHC(O)thienyl, NHC(O)pyridyl, NHC(O)furanyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, acetylenyl, and t-butyl.

[0077] Preferred substituents on the Ar group of R^1 of formula **IIb**, when present, include R°, halogen, nitro, CN, OR°, SR°, $N(R^\circ)_2$, SO_2R°, $C(O)R^\circ$, C(O)OR, and $C(O)N(R^\circ)_2$, wherein each R° is as defined *supra*. Examples of such groups include chloro, bromo, fluoro, CN, nitro, OMe, OPh, OCF_3, OCH_2Ph, OEt, $SCHF_2$, methyl, ethyl, isopropyl, propyl, vinyl, CF_3, acetylenyl, CH_2Ph, CH_2NH_2, $CH_2N(Et)_2$, CH_2morpholin-4-yl, CH_2piperdin-1-yl, CH_2imidazol-1-yl, CH_2piperazin-1-yl, $C(O)NH_2$, C(O)Me, SO_2Me, NHEt, and NHMe.

[0078] Preferred Q groups of formula **IIb** are those set forth above for compounds of formula **I** and **Ib**.

[0079] Preferred R^3 groups of formula **IIb** include R', $Q\text{-}OR^5$, $Q\text{-}N(R^4)_2$, Ar^1, $N(R)C(O)Q\text{-}N(R^4)_2$, and $N(R)Q\text{-}N(R^4)_2$. Examples of such R^3 groups include CH_2OH, OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $CH_2CH_2N(Me)_2$, $CH_2CH_2NH_2$, $NHCO_2t$-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

[0080] More preferably, the R^3 group of formula **IIb** is selected from CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NHCO_2t$-butyl, phenyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

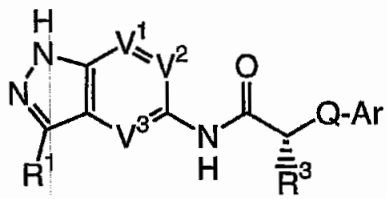
[0081] Most preferably, the R^3 group of formula **IIb** is selected from $CH_2CH_2NH_2$.

[0082] Preferred rings formed by the R and R^3 moieties of R^2 of formula **IIb** are selected from a 5-6 membered saturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Examples of such rings formed by R and R^3 include piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, and thiomorpholinyl.

[0083] Preferred Ar groups of R^2 of formula **IIb** are selected from an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from

nitrogen, oxygen, or sulfur. Examples of such monocyclic rings include phenyl, pyridyl, pyrimidinyl, pyridonyl, furanyl, tetrazolyl, thienyl, cyclopentyl, cyclohexyl, and cycloheptyl. Examples of such bicyclic rings include benzo[1,3]dioxolyl, indan-1-onyl, naphthyl, benzothiophenyl, 2,3-dihydro-1*H*-isoindolyl, indanyl, benzofuranyl, and indolyl. When present, preferred substituents on the Ar ring of the Q-C(R)(Q-Ar)R^3 group of R^2 of formula **IIb** include R^o, halogen, OR^o, phenyl, $N(R^o)_2$, $NHC(O)R^o$, or SR^o. Examples of such groups include fluoro, chloro, bromo, CF_3, OH, OMe, OPh, OCH_2PH, SMe, NH_2, NHC(O)Me, methyl, ethyl, isopropyl, isobutyl, and cyclopropyl.

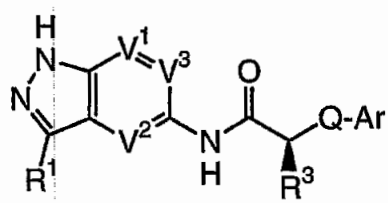
[0084] According to another embodiment, the present invention relates to a compound of formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein R^1, R^3, Q, and Ar are as defined above for compounds of formula **I**. Preferred V^1, V^2, V^3, R^1, R^3, Q, and Ar groups of formula **III** are those set forth above for compounds of formula **I** or **Ib**.

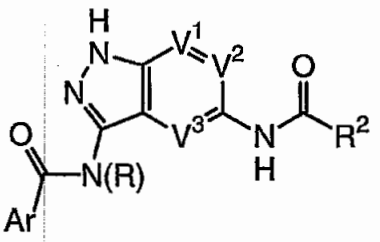
[0085] According to another embodiment, the present invention relates to a compound of formula **IV**:



IV

or a pharmaceutically acceptable salt thereof, wherein R^1, R^3, Q, and Ar are as defined above for compounds of formula **I**. Preferred V^1, V^2, V^3, R^1, R^3, Q, and Ar groups of formula **IV** are those set forth above for compounds of formula **I** or **Ib**.

[0086] According to another embodiment, the present invention relates to a compound of formula **V**:



V

or a pharmaceutically acceptable salt thereof, wherein:

each R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4} alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-OC(O)R^5, Q-CONHR^5, Q-OC(O)NHR^5, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$;

R' is an optionally substituted C_{1-6} aliphatic group;

each R^4 is independently selected from R, COR^5, CO_2R^5, $CON(R^5)_2$, SO_2R^5, $SO_2N(R^5)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, N(R)COR, N(R)CON$(R^4)_2$, N(R)C(O)OR, CON$(R^4)_2$, OC(O)N$(R^4)_2$, CO_2R, OC(O)R, N(R)SO_2R, N(R)SO_2N$(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

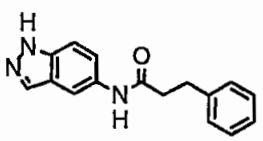
[0087] Preferred Ar groups of formula **V** are those set forth for compounds of formula **I** or **Ib**, *supra*.

[0088] Preferred V^1, V^2, and V^3 groups of formula **V** are those set forth for compounds of formula **I** or **Ib**, *supra*.

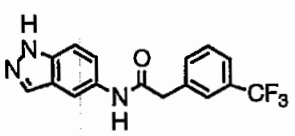
[0089] Preferred R^2 groups of formula **V** are those set forth for compounds of formula **I** or **Ib**, *supra*.

[0090] Representative compounds of formula **I** are set forth in Table 1 below.

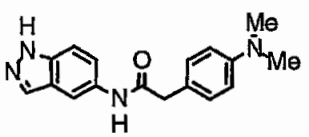
Table 1.



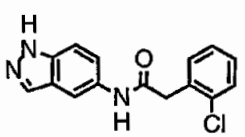
I-1



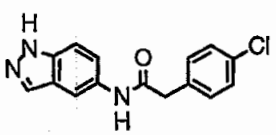
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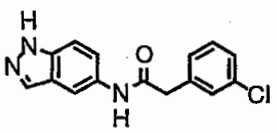
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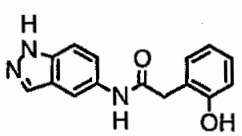
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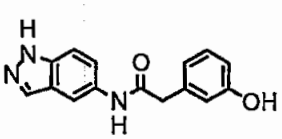
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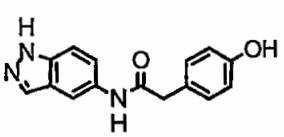
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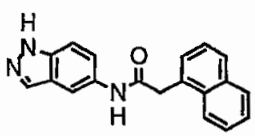
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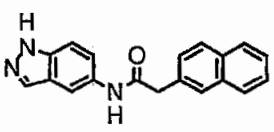
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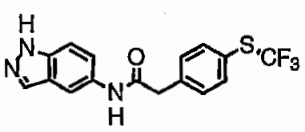
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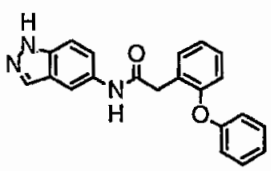
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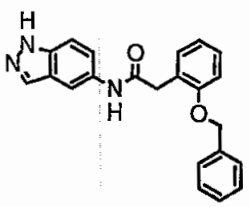
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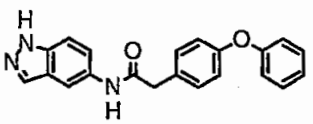
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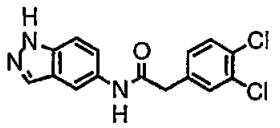
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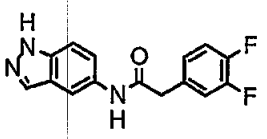
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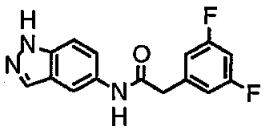
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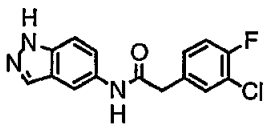
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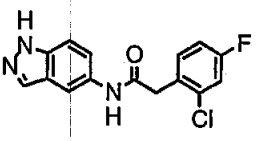
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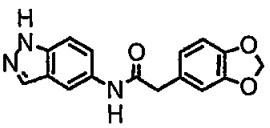
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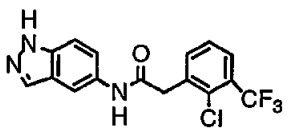
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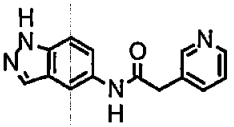
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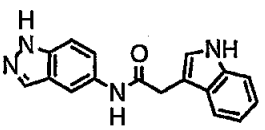
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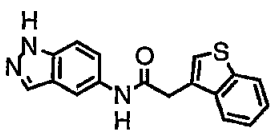
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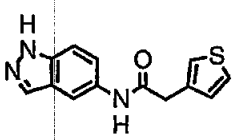
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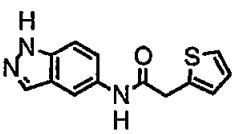
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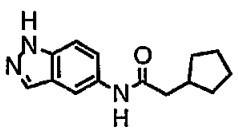
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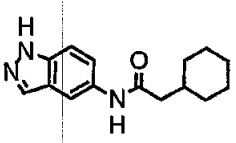
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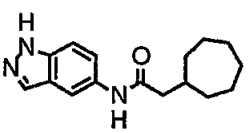
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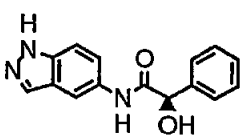
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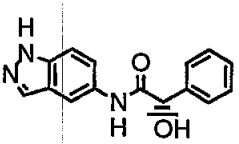
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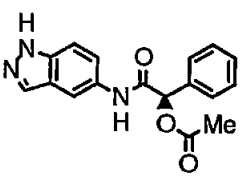
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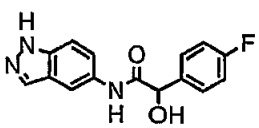
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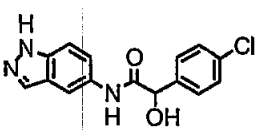
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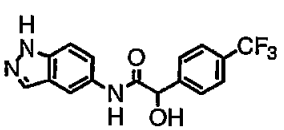
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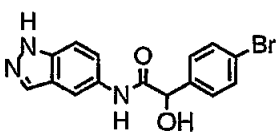
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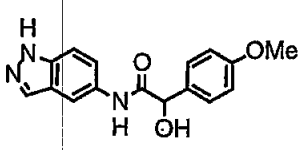
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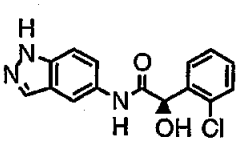
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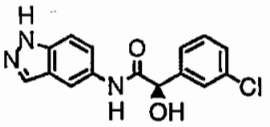
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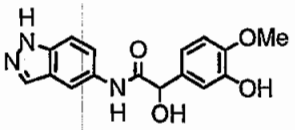
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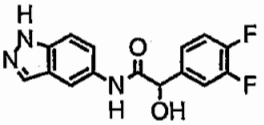
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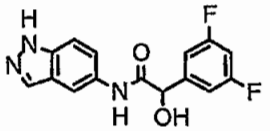
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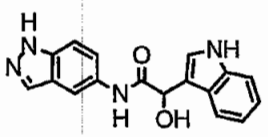
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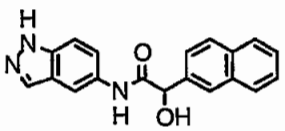
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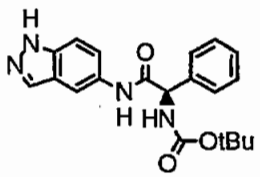
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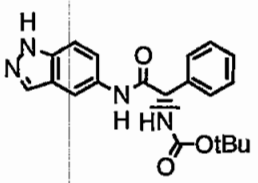
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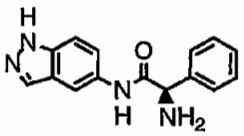
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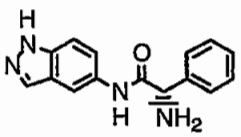
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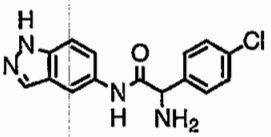
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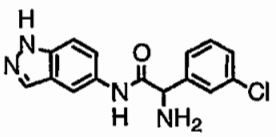
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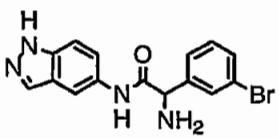
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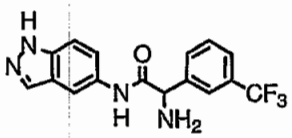
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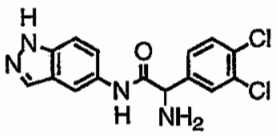
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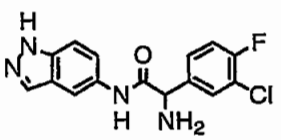
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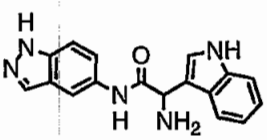
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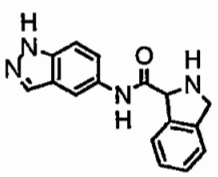
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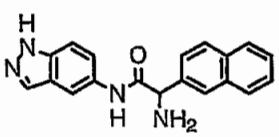
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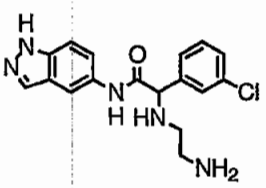
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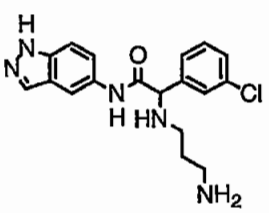
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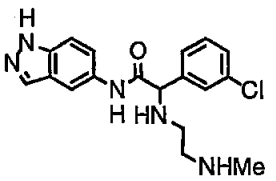
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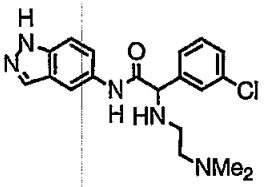
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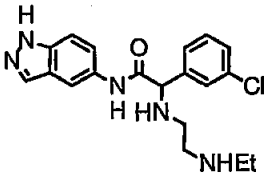
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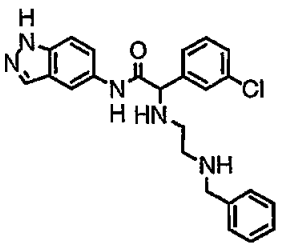
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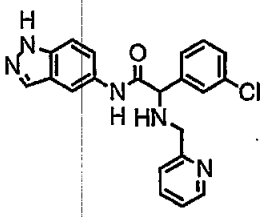
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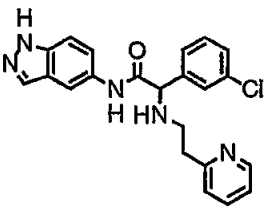
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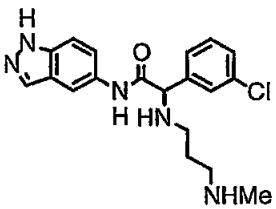
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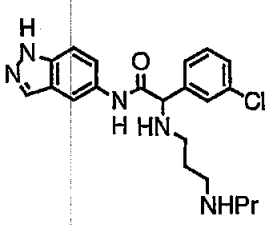
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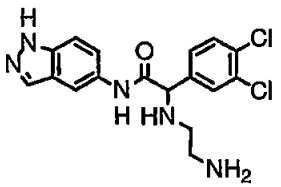
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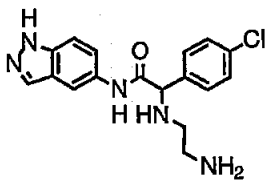
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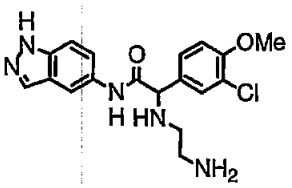
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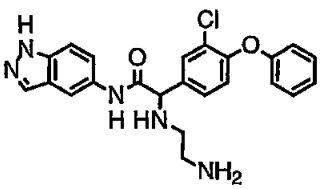
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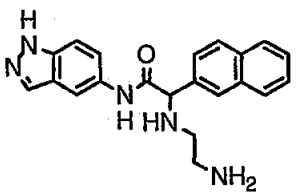
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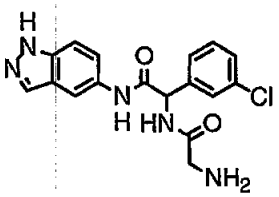
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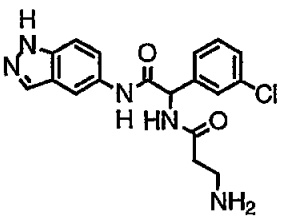
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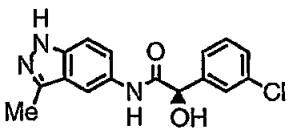
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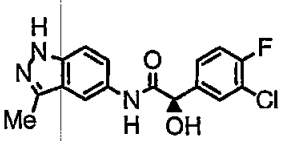
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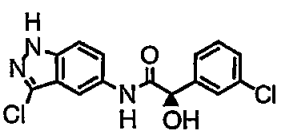
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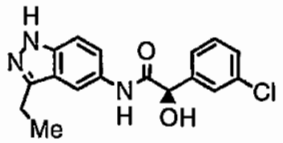
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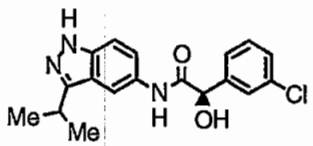
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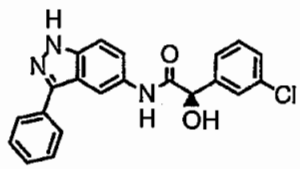
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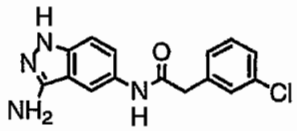
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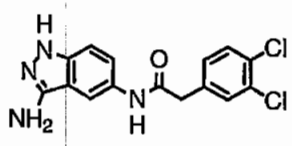
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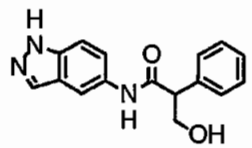
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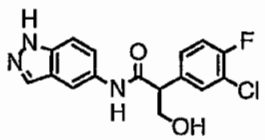
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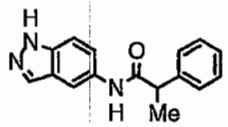
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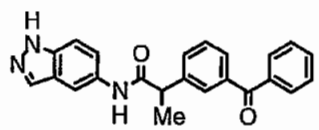
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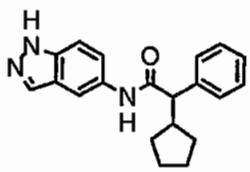
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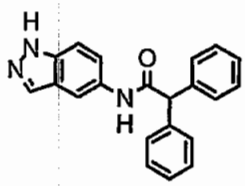
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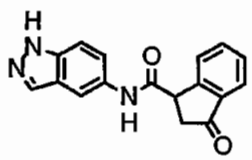
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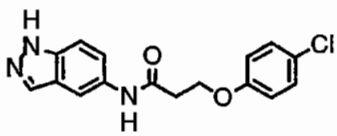
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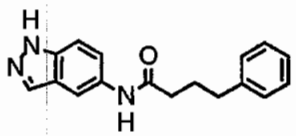
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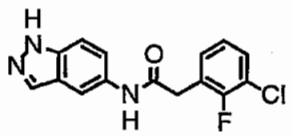
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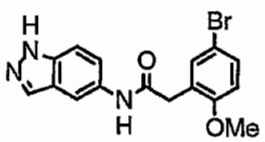
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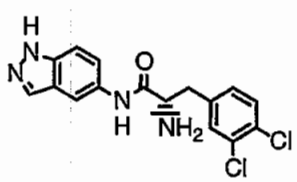
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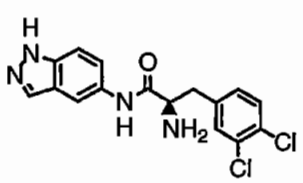
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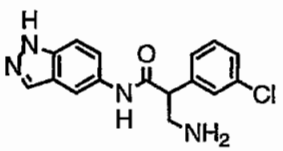
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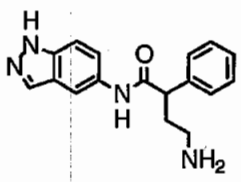
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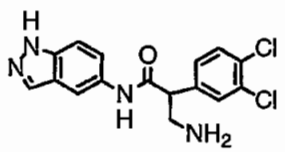
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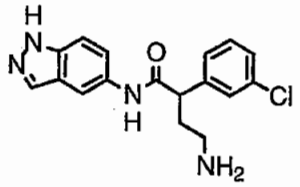
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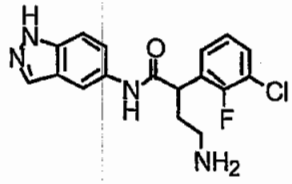
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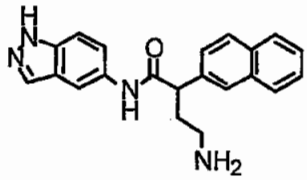
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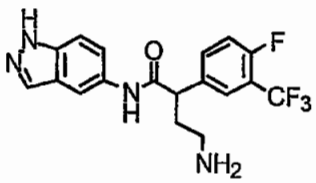
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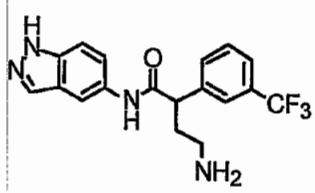
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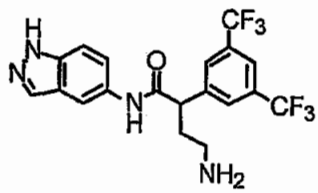
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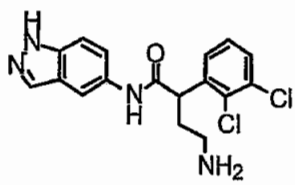
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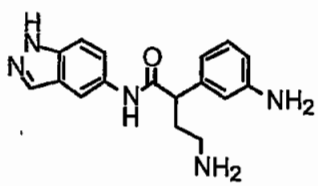
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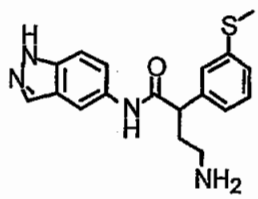
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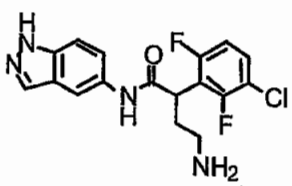
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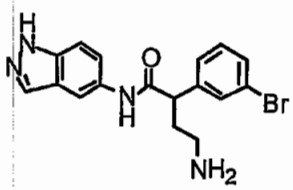
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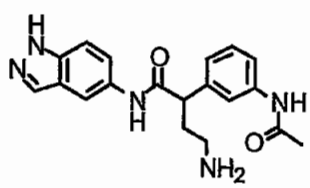
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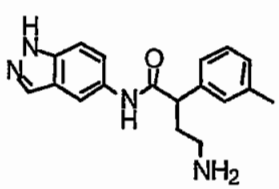
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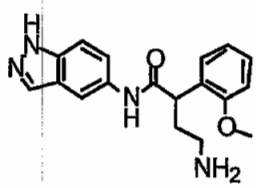
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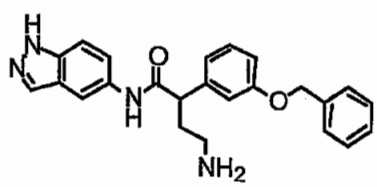
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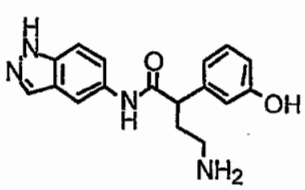
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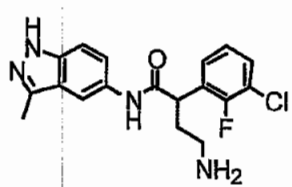
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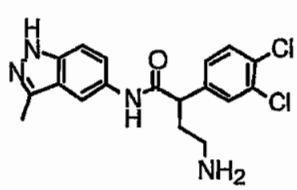
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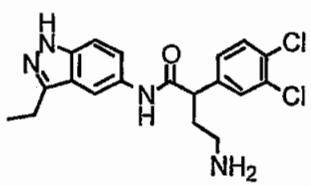
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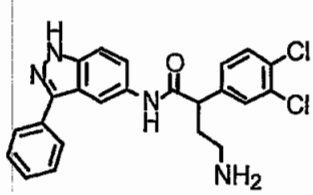
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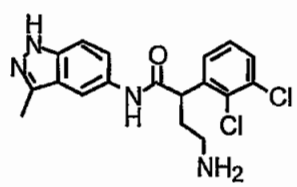
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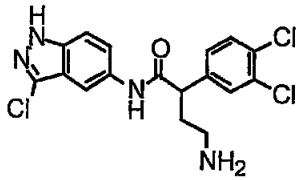
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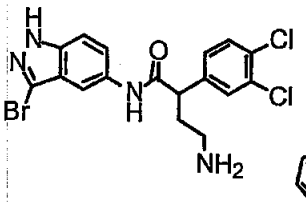
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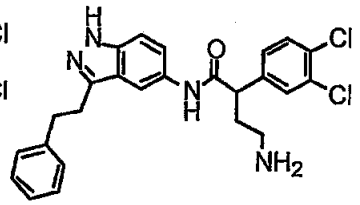
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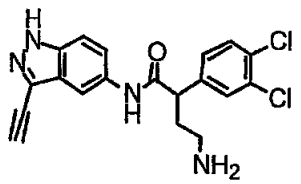
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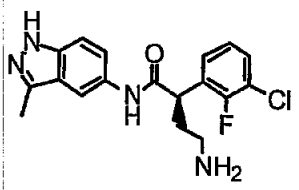
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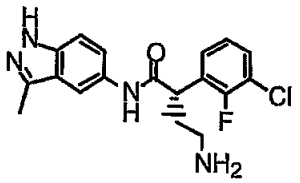
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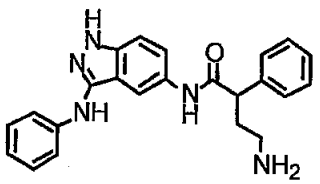
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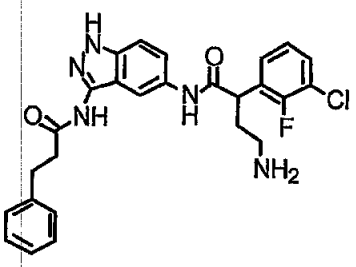
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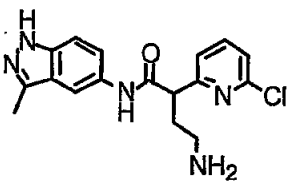
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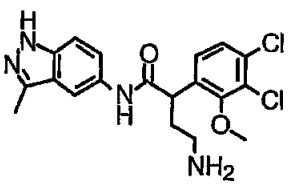
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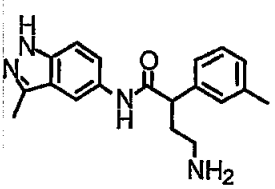
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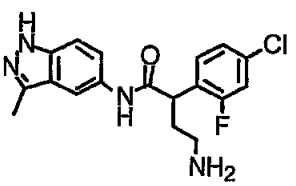
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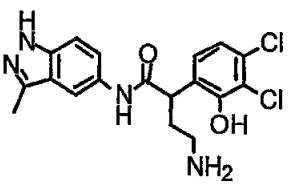
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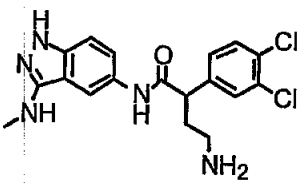
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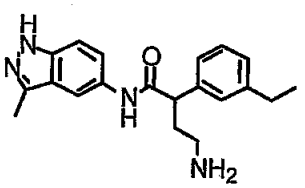
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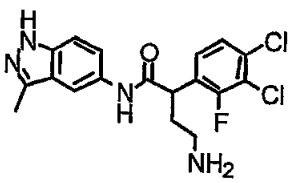
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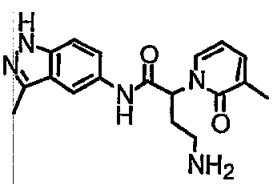
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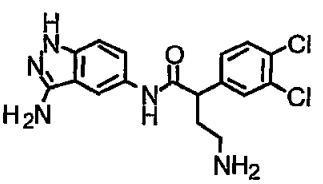
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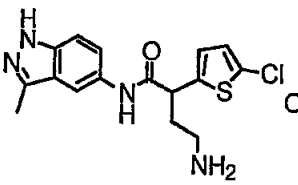
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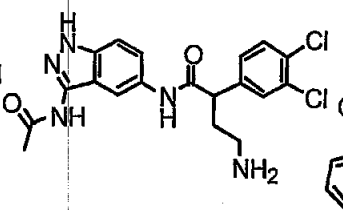
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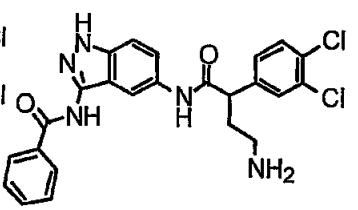
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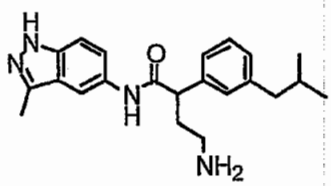
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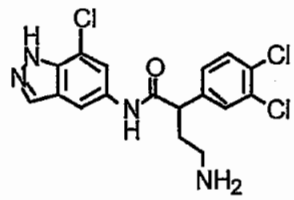
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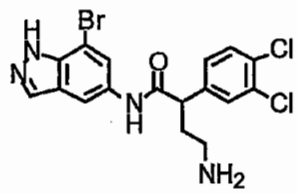
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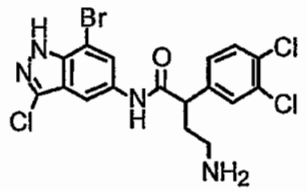
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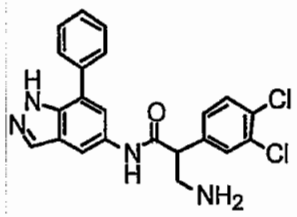
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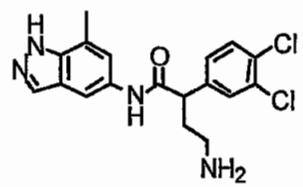
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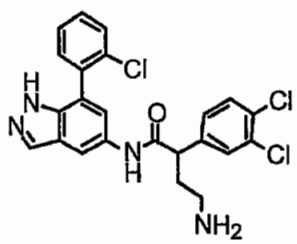
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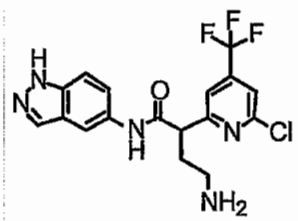
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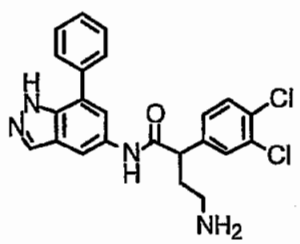
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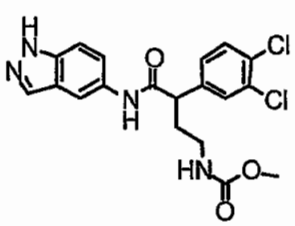
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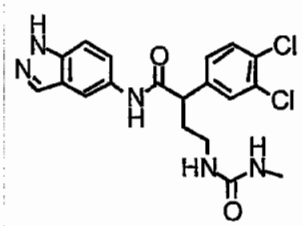
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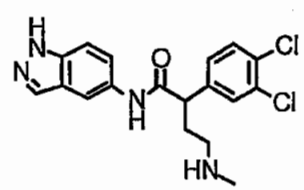
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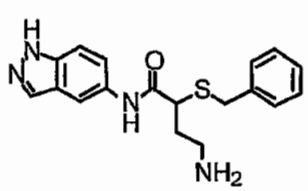
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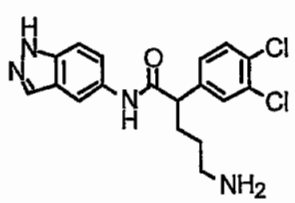
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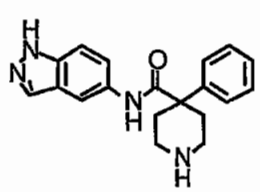
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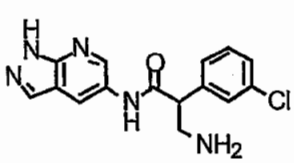
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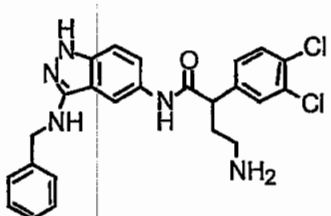
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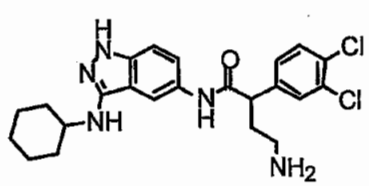
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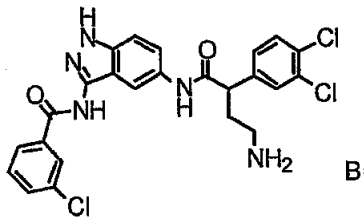
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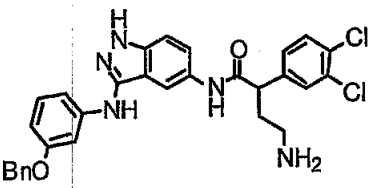
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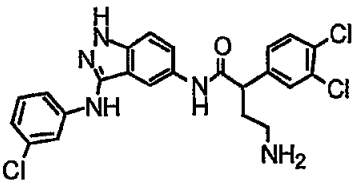
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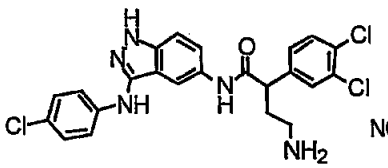
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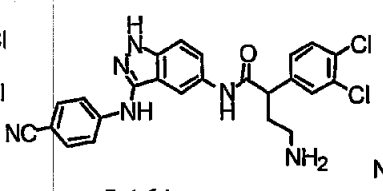
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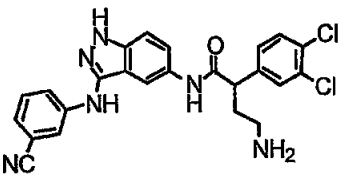
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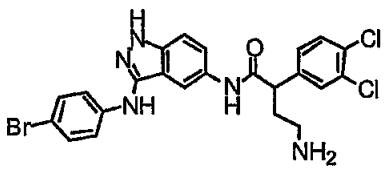
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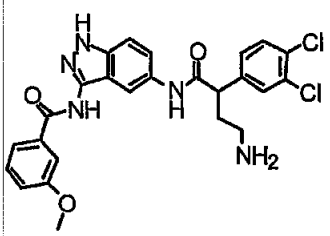
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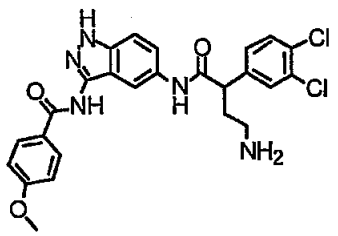
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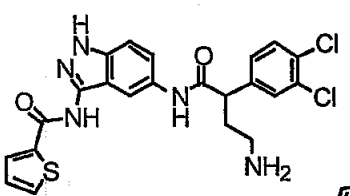
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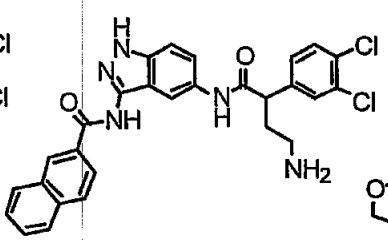
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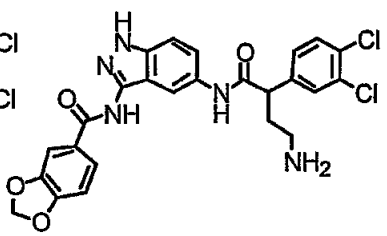
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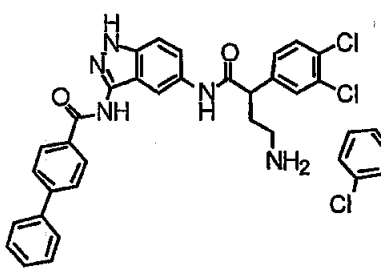
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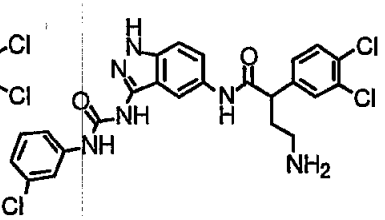
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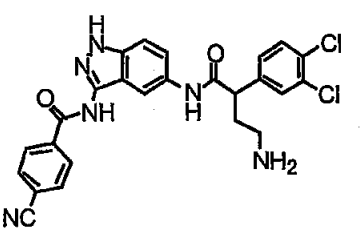
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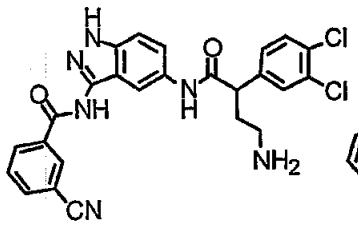
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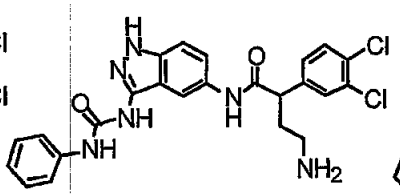
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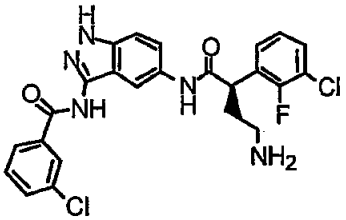
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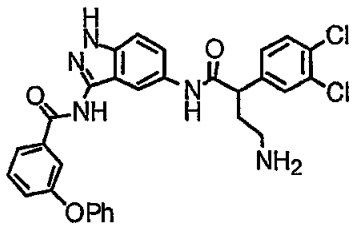
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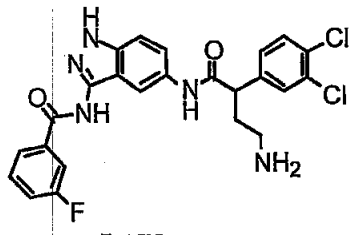


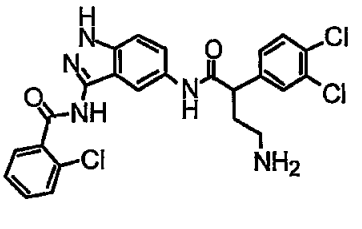
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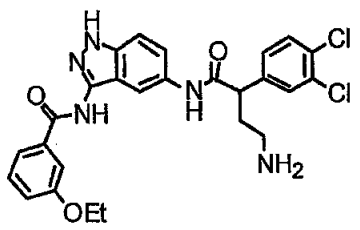


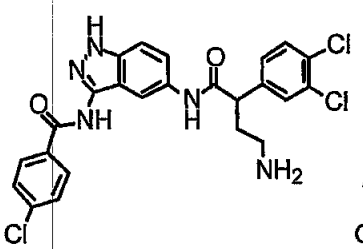
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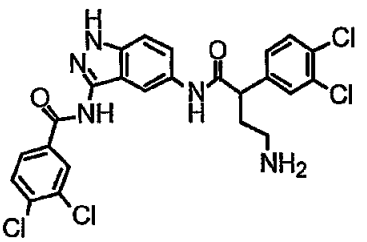

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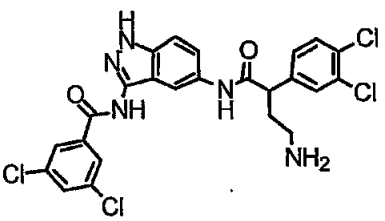

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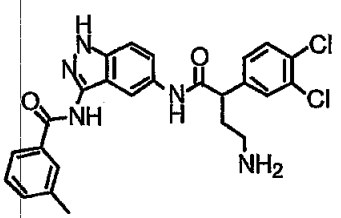

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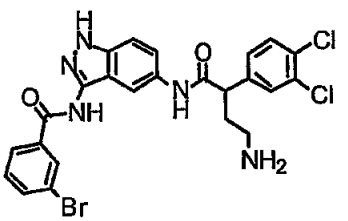

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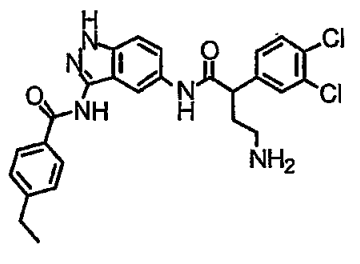

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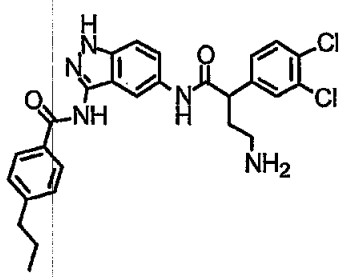

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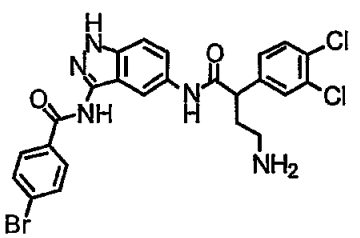

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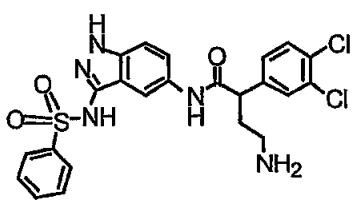

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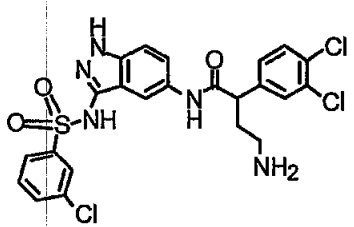

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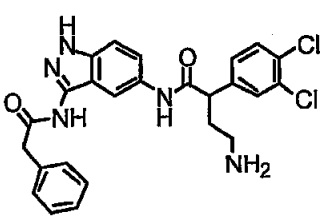

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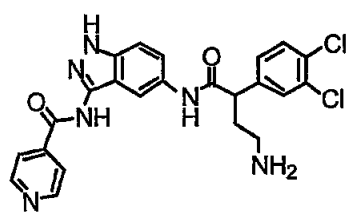

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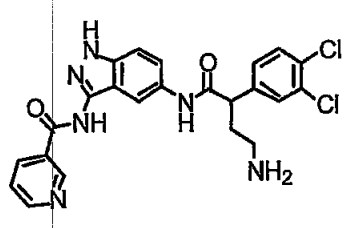

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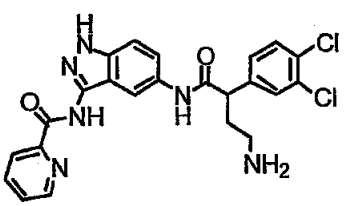

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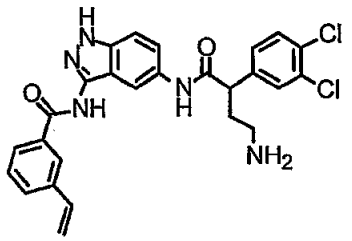

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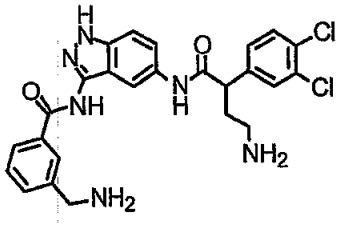

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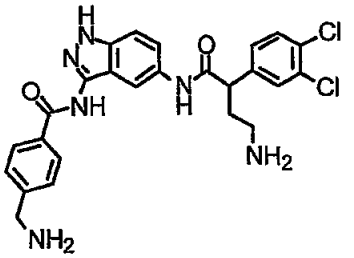

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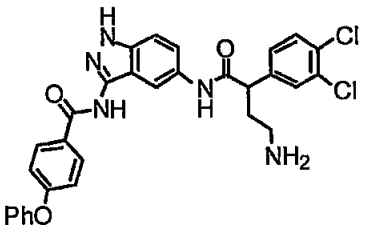
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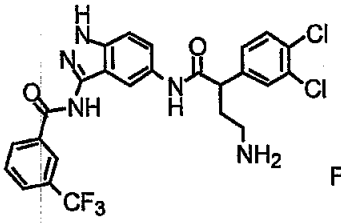
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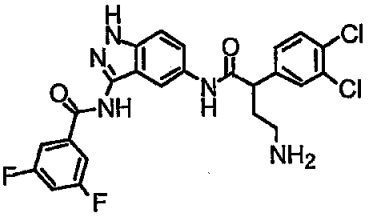
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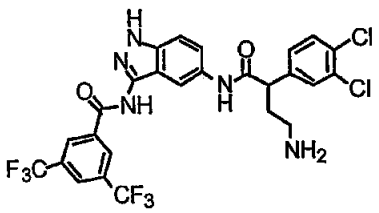
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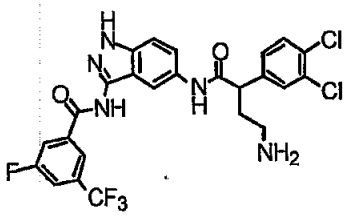
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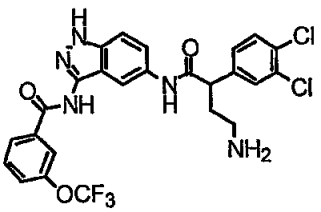
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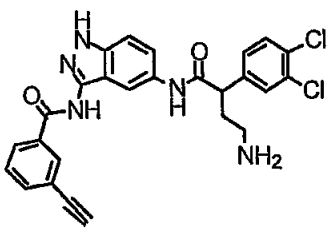
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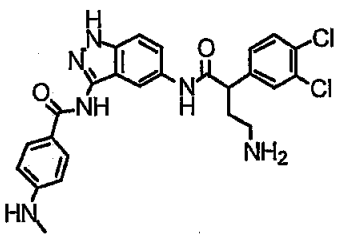
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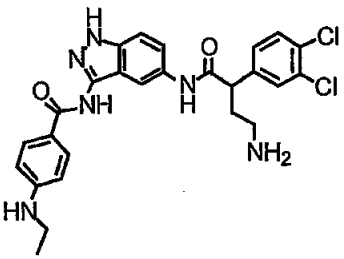
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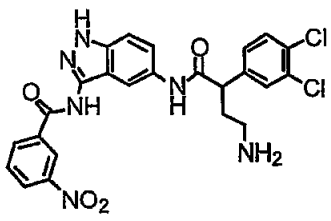
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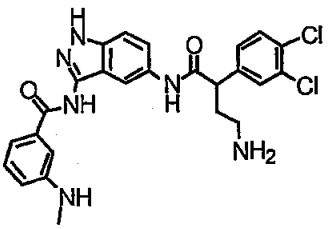
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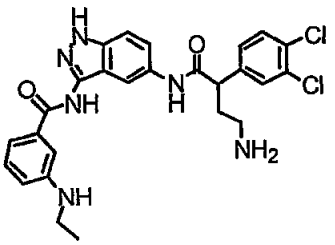
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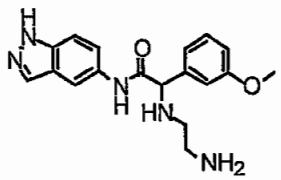
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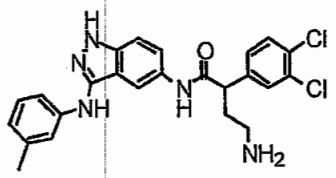
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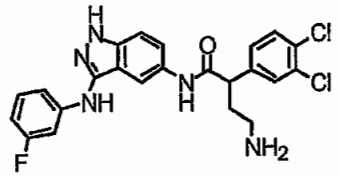
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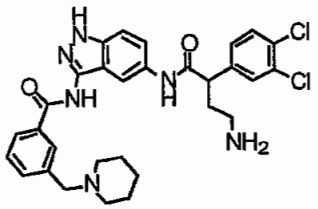
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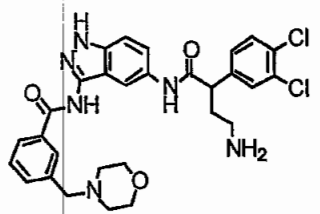
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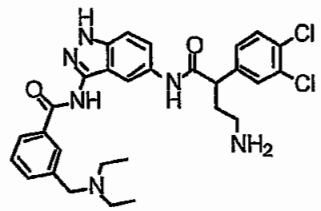
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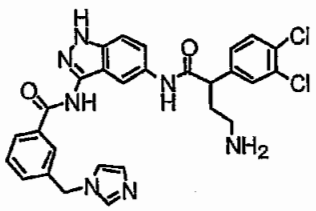
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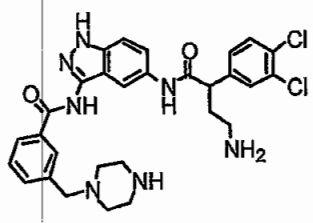
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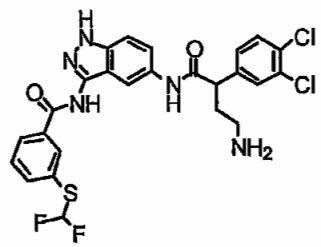
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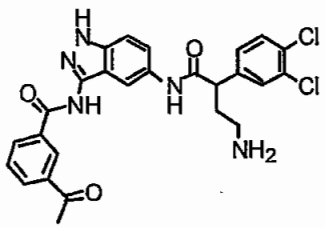
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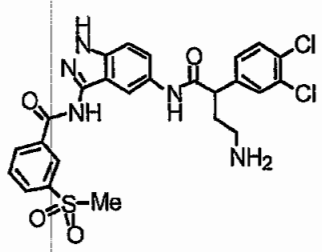
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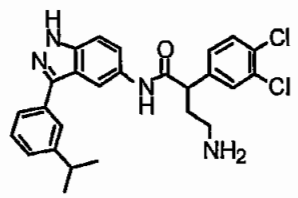
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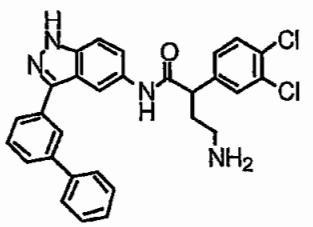
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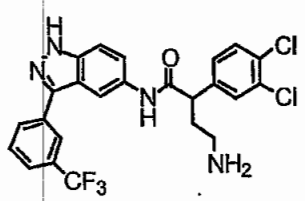
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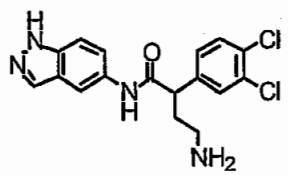
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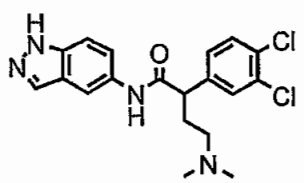
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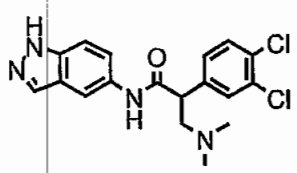
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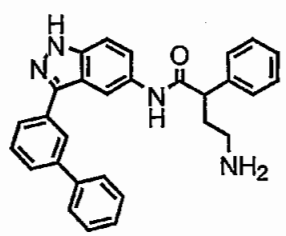
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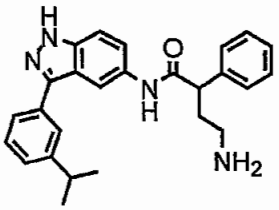
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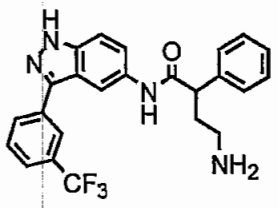
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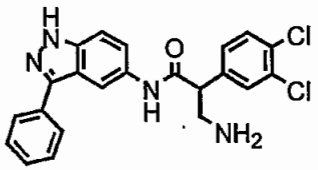
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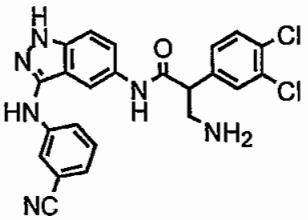
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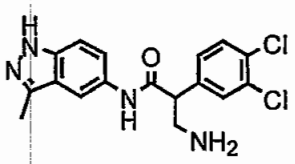
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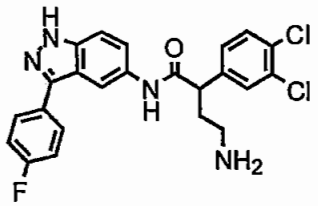
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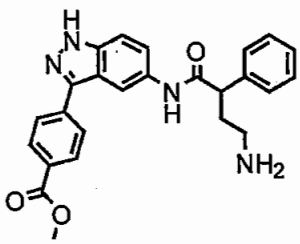
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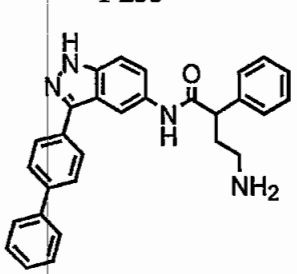
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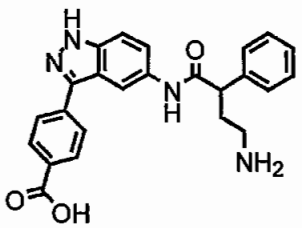
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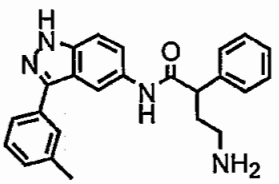
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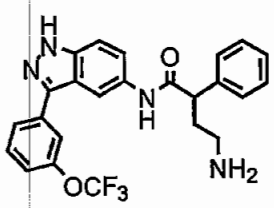
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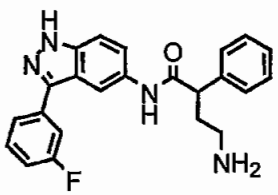
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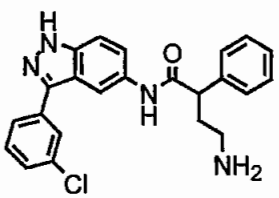
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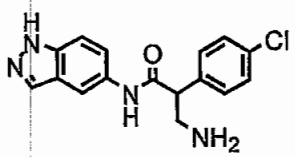
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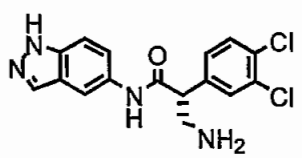
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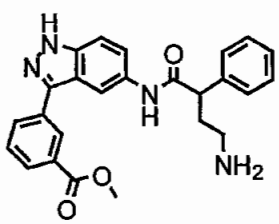
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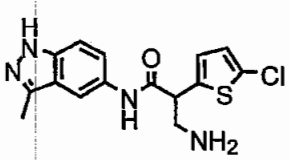
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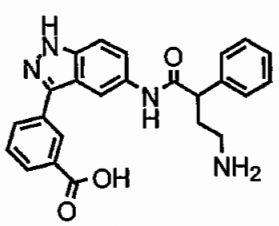
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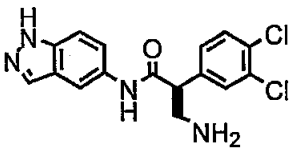
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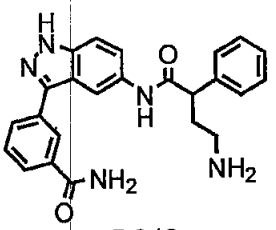
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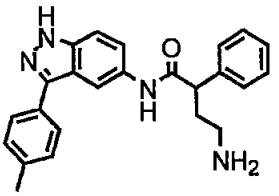
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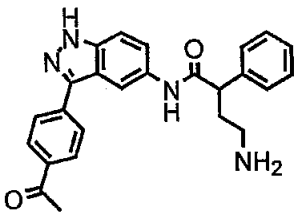
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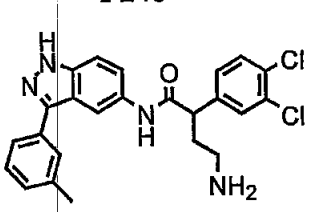
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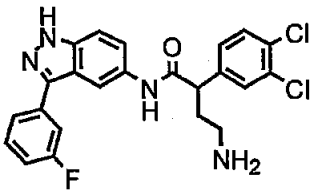
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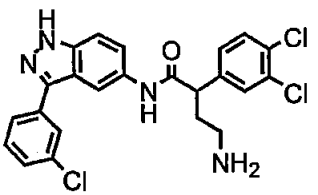
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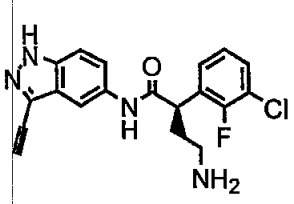
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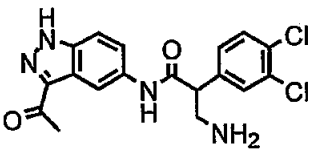
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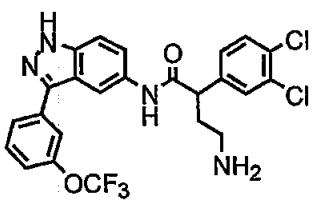
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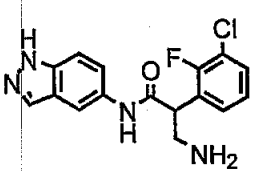
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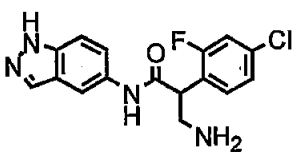
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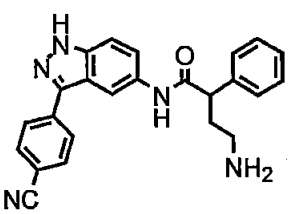
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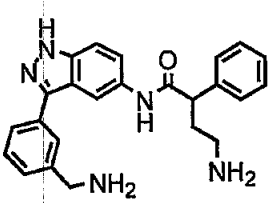
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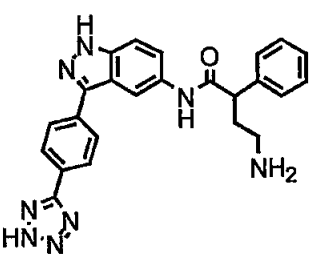
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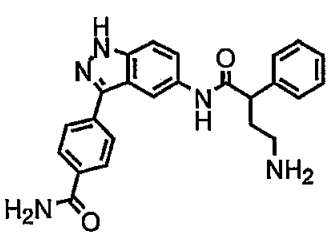
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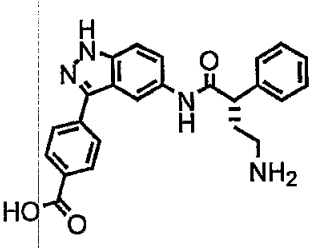
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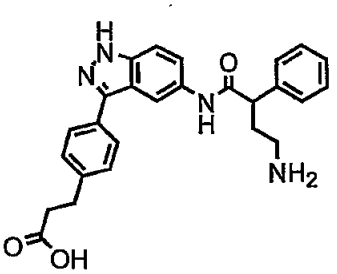
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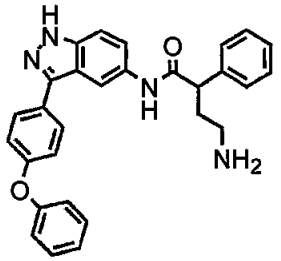
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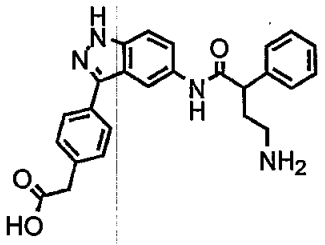
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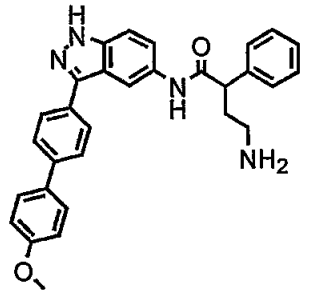
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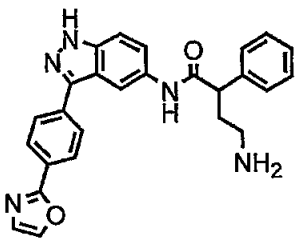
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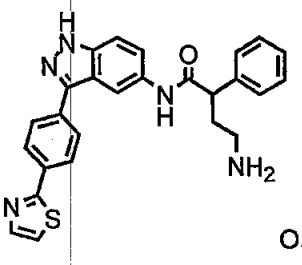
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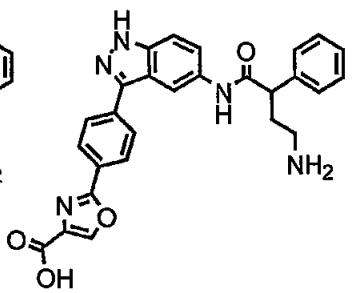
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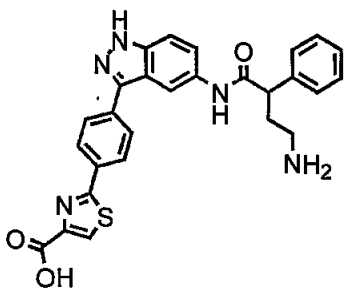
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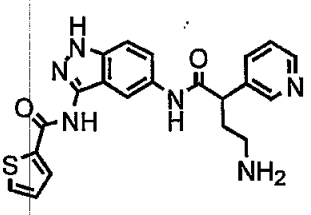
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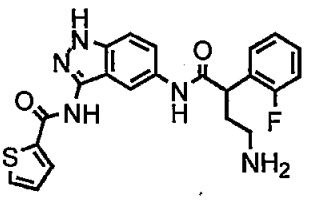
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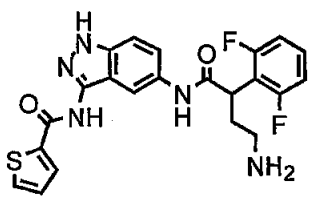
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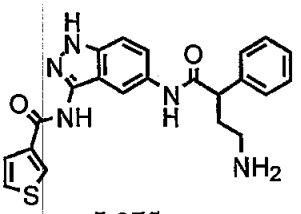
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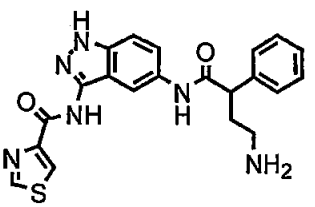
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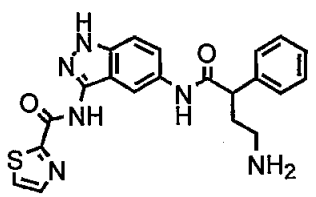
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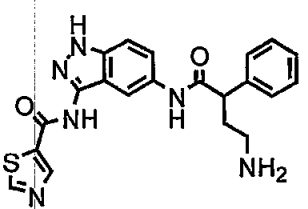
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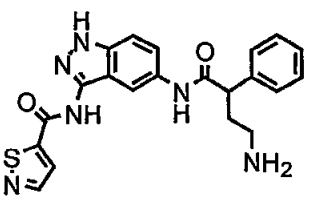
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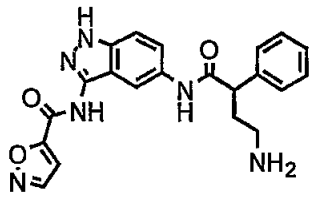
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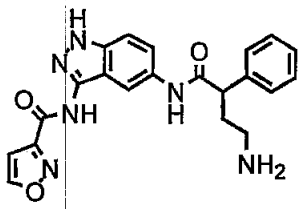
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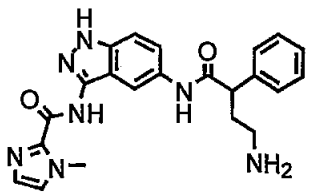
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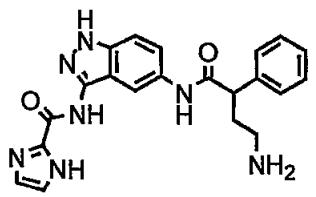
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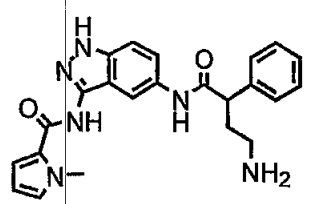
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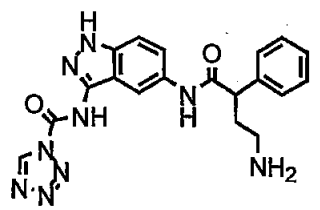
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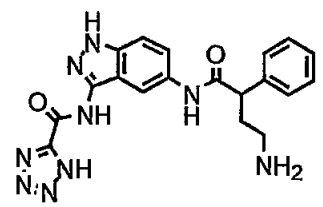
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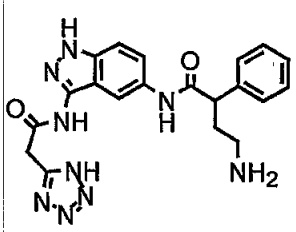
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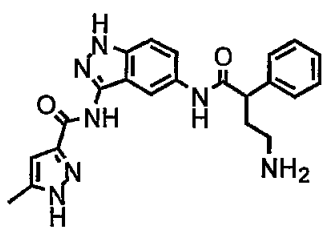
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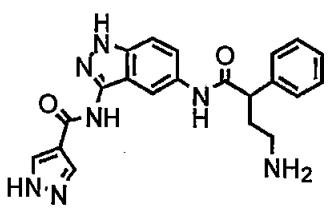
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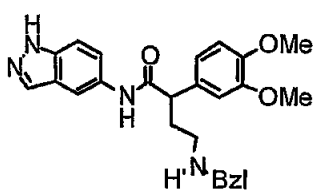
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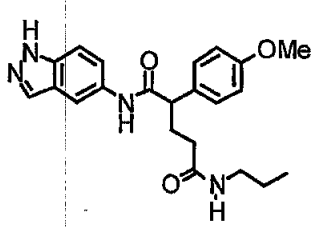
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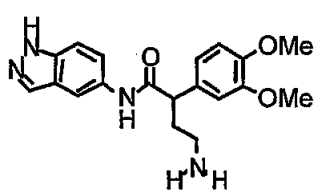
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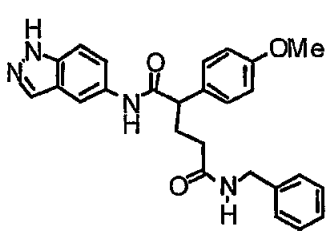
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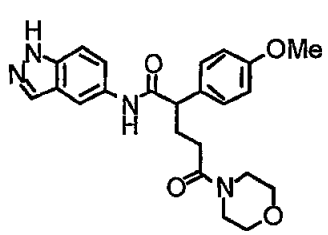
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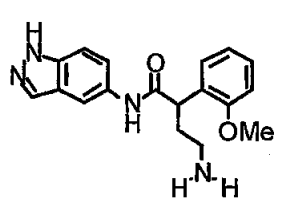
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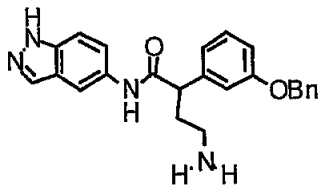
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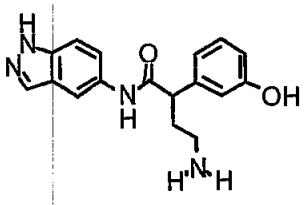
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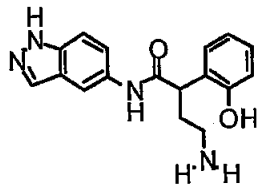
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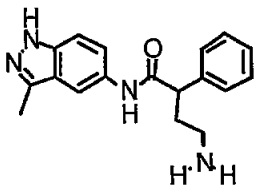
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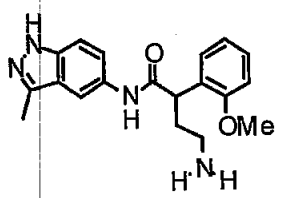
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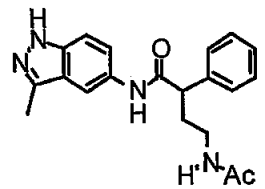
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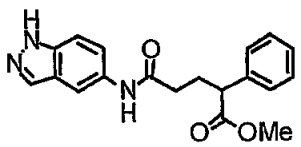
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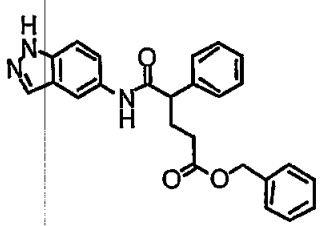
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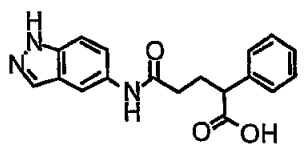
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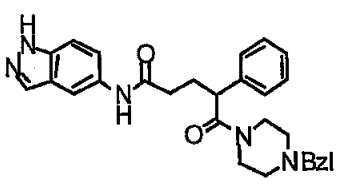
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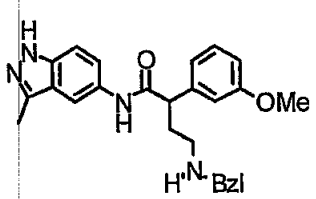
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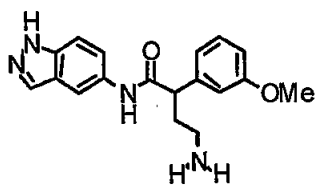
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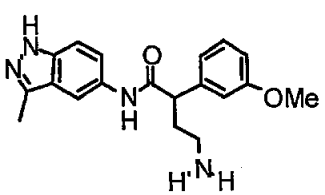
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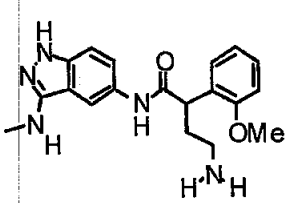
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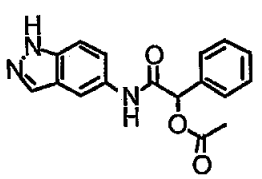
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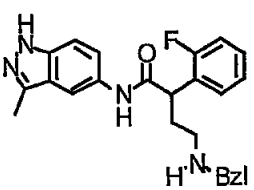
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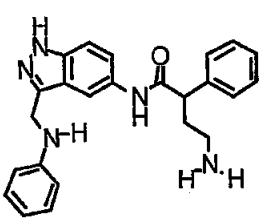
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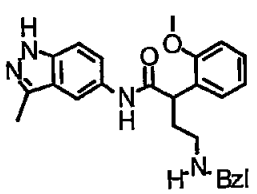
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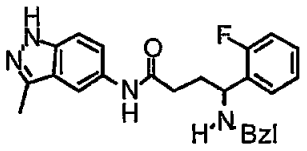
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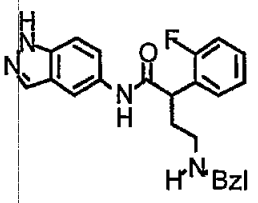
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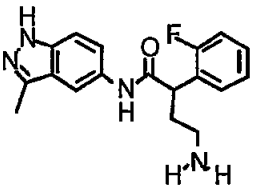
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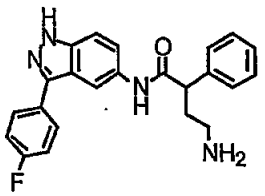
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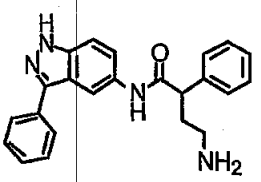
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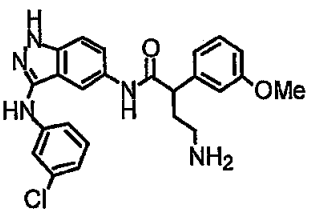
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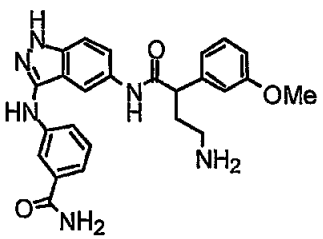
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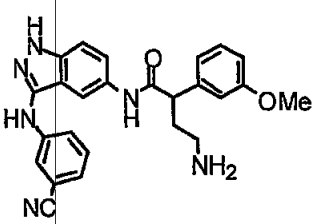
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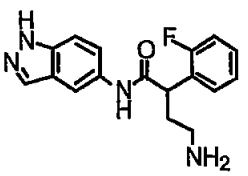
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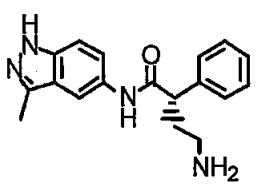
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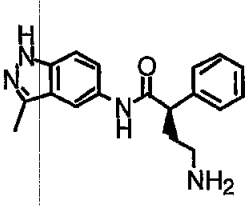
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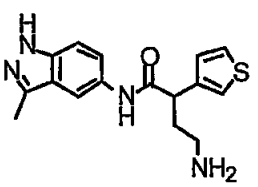
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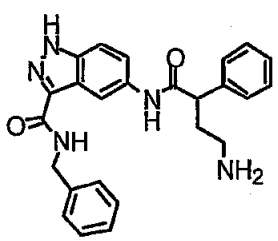
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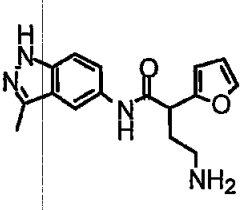
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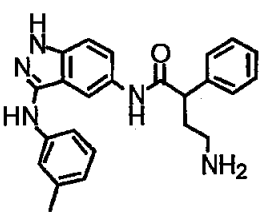
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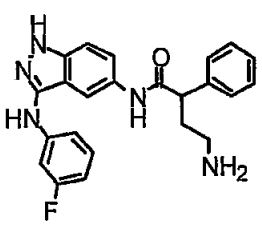
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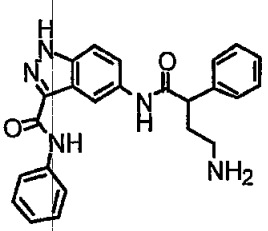
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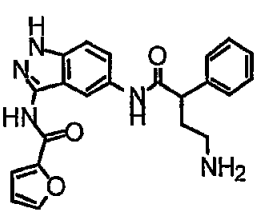
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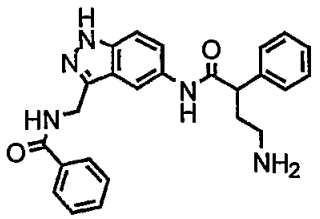
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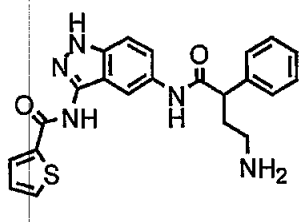
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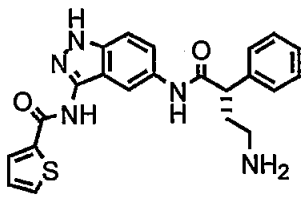
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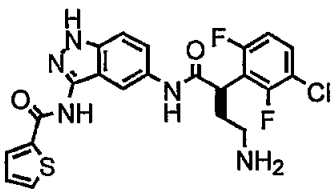
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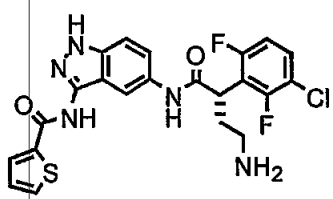
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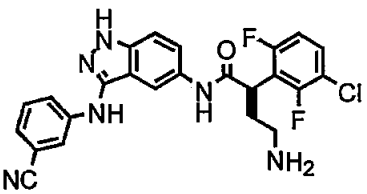
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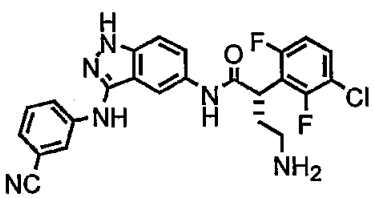
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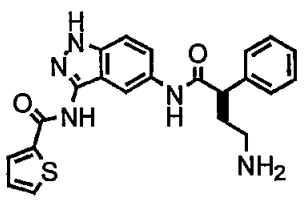
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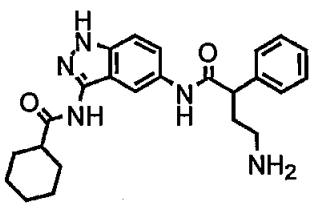
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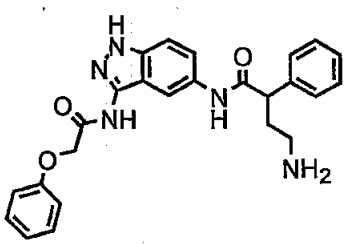
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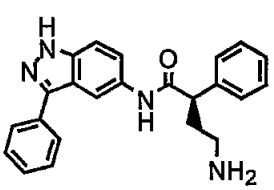
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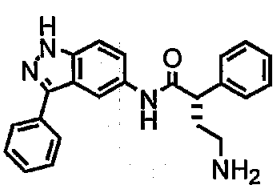
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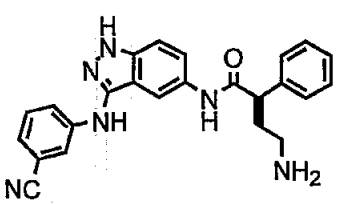
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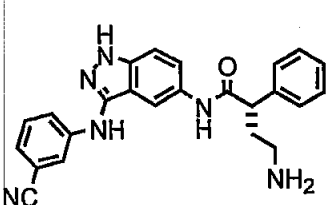
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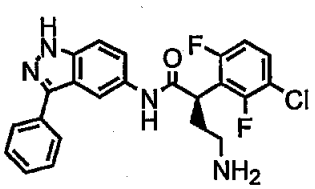
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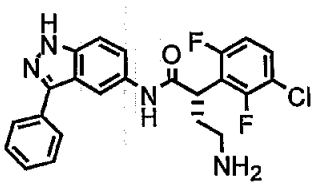
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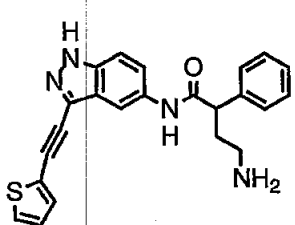
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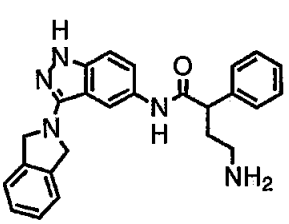
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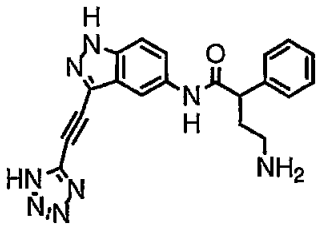
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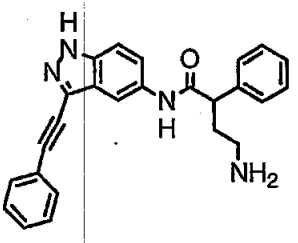
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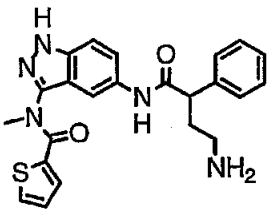
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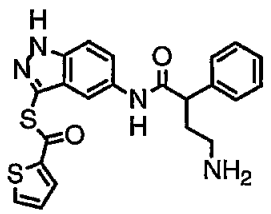
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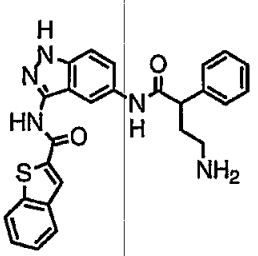
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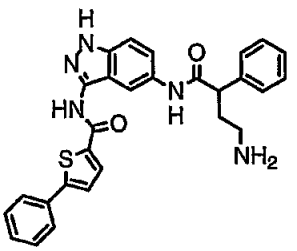
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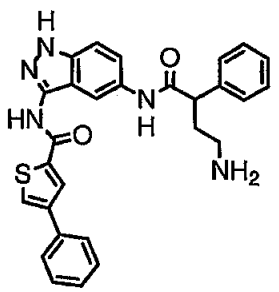
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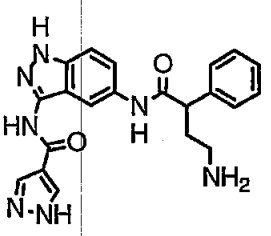
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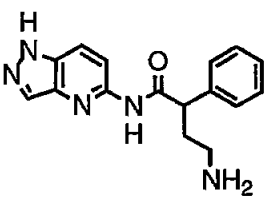
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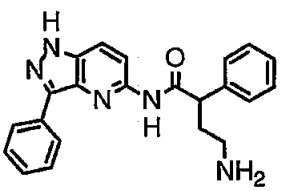
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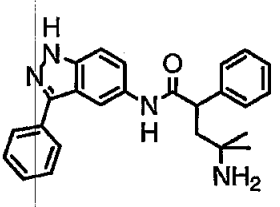
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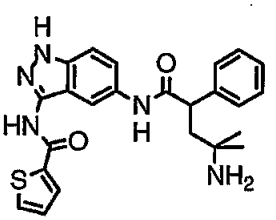
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I-1069



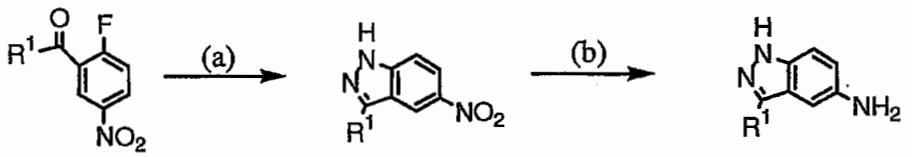
I-1070



I-1071

[0091] The compounds of the present invention may be prepared as illustrated by the Schemes I-XVII below, by the Synthetic Examples described herein, and by general methods known to those of ordinary skill in the art.

Scheme I

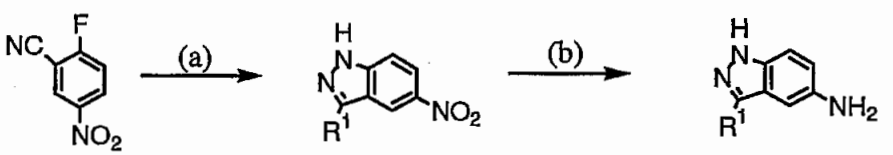


1 2 3

Reagents: (a) $N_2H_4 \cdot H_20$, BuOH, reflux; (b) $SnCl_2 \cdot 2H_2O$, BuOH, reflux.

[0092] Scheme I above shows a general method for preparing the aminoindazole compounds **3** where R^1 is other than hydrogen. When R^1 is an alkyl or aryl group, the nitro-indazole compound **2** may be prepared by methods substantially similar to those described by Henke, *et al*, *J. Med. Chem.*, 1997, **40**, 2706. The reduction of the nitro group at step (b) to afford compound **3** is achieved by the methods described by Bellamy, *et al*, Tetrahedron Lett., 1984, 25, 839. Alternatively, reduction of the nitro group of compound **2** can be achieved by treating **2** with hydrogen gas in the presence of Pd/C by methods substantially similar to those described by Boyer, *et al*, *J Chem. Res. Miniprint*, 1990, **11**, 2601. Another alternative method for achieving the reduction of the nitro group of compound **2** is by hydrolysis using a method substantially similar to that described by Lee, *et al*, *Synthesis*, 2001, **1**, 81.

Scheme II

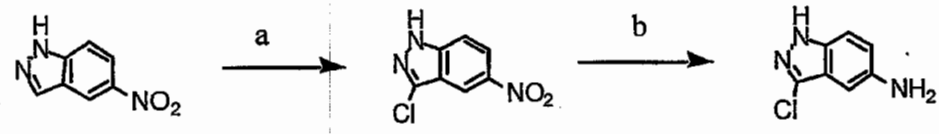


4 2 3

Reagents: (a) $N_2H_4 \cdot H_20$, BuOH, reflux; (b) $SnCl_2 \cdot 2H_2O$, BuOH, reflux.

[0093] Scheme II above shows a general method for preparing the aminoindazole compounds **3** where R^1 is an amino or alkylamino group. The nitro-indazole compound **2** may be prepared from 2-fluoro-5-nitro-benzonitrile (**1**) by methods substantially similar to those describe by Parnell, *et al*, J. Chem. Soc., 1959, 2363. Amino-indazole compound **3** may then be prepared from compound **2** as described above for Scheme I.

Scheme III

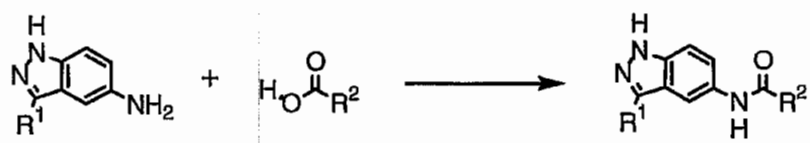


5 6 7

Reagents: (a)Cl_2, acetic acid; (b) H_2, Pd/C

[0094] Scheme III above shows a method for preparing compounds of formula **I** where R^1 is halogen. For example, 5-nitro-1*H*-indazole (**5**) may be chlorinated to afford 3-chloro-5-nitro-1*H*-indazole (**6**) using the methods described by v. Auwers, *et al*, *Justus Liebigs Ann. Chem.*, 1927, **451**, 295. Alternatively, the nitroindazole **5** can be treated with N-chlorosucciniimide to form a 3-chloro nitroindazole **6**. The reduction of **6** to form the amino compound **7** may be achieved by following the methods described by Boyer, *et al.*, *J Chem. Res. Miniprint*, 1990, **11**, 2601.

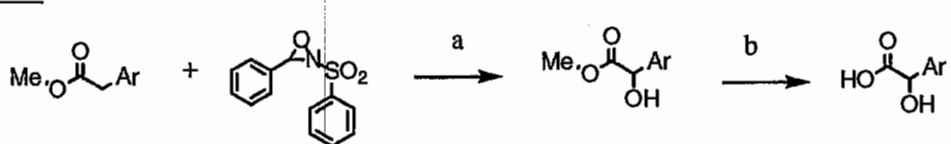
Scheme IV



3 8 Ia

[0095] Scheme IV above outlines a synthetic route for preparing compounds of formula **I**. The starting aminoindazole **3** is coupled to a carboxylic acid compound **8** to form compounds of formula **I** using standard coupling conditions known in the art. Where necessary, reactive functional groups of R^2 may be protected before coupling. In certain cases, the yield of the coupling reaction has been improved by protecting the indazole ring NH, with a Boc group.

Scheme V

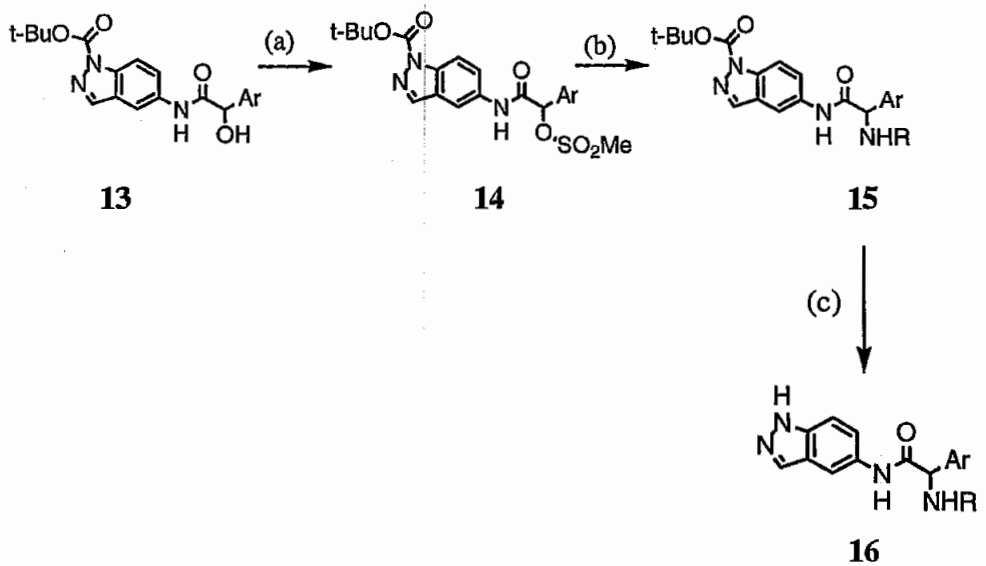


9 10 11 12

Reagents: (a) KHMDS, THF, -78° C; (b) LiOH, MeOH, H_2O

[0096] Scheme V above shows a general method for preparing α-hydroxy acids **12** used for preparing compounds of formula **Ib**, where R^3 is OH, according to the methods described in Scheme IV. The formation of the α-hydroxy ester compound **11** from **9** and **10** was achieved by methods substantially similar to those described by Hernandez, *et al*, *J. Org. Chem.*, 1995, **60**, 2683. The oxaziridine reagent **10** can be prepared according to the procedure described by Davies, *et al.*, *J. Org. Chem.*, 1988, **53**, 2087.

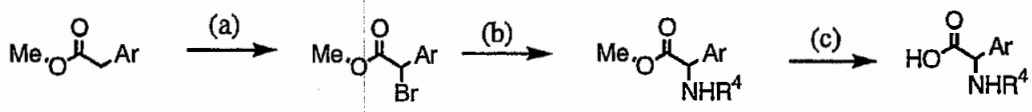
Scheme VI



Reagents: (a)MsCl, pyridine, THF; (b) NHR, pyridine, THF; (c) TFA, CH_2Cl_2

[0097] Scheme VI shows a general method for preparing compounds of formula **Ib** where R^3 is a variety of amino groups from compounds of formula **Ib** where R^3 is a hydroxy group as described above in Scheme V. Compound **13** may be treated with methanesulfonyl chloride and pyridine in THF to afford the mesyl derivative **14**. The mesyl group may then be displaced by the desired amino group to afford compound **15**. Removal of the Boc protecting group provides compound **16**. Each of these steps are well known to one of skill in the art.

Scheme VII

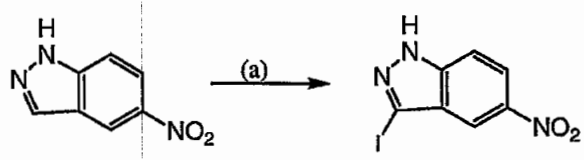


17 18 19 20

Reagents: (a)NBS, hv, CCl_4; (b) NHR, K_2CO_3, THF; (c) LiOH, THF, H_2O

[0098] Scheme VII above shows a method for preparing carboxylic acid intermediates useful for preparing compounds of formula **Ib** where R^3 is an amino group. This method may be used to prepare compounds of formula **Ib** where R^3 is a variety of amino groups of formula $N(R^4)_2$, $N(R)COT_nN(R^4)_2$, or $N(R)T_nN(R^4)_2$. Each of the above steps is well known to one of skill in the art. Carboxylic acid compound **20** may then be coupled to the amino-indazole according to Scheme IV to afford compounds of formula **Ib**.

Scheme VIII

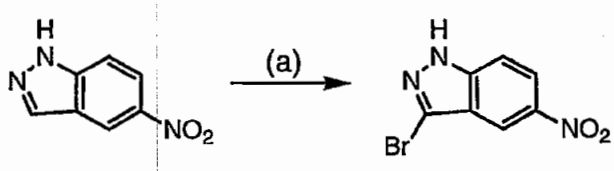


5 21

Reagents: (a), I_2, KOH, DMF, rt.

[0099] Scheme VIII above shows the preparation of 3-iodo-5-nitroindazole (**21**) from 5-nitroindazole (**5**) according to methods substantially similar to that described in published PCT application number WO 02/10137.

Scheme IX

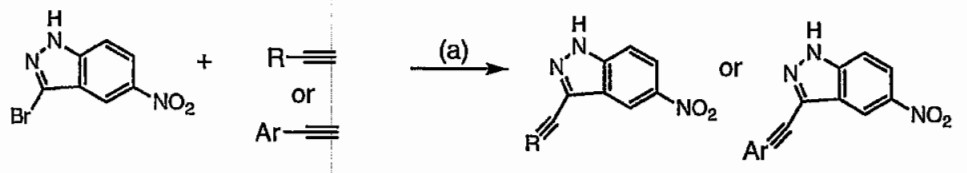


5 22

Reagents: (a) Br_2, AcOH, reflux.

[00100] Scheme IX above shows a method for the preparation of 3-bromo-5-nitroindazole, by a method substantially similar to that described by Benchidimi, *et al*, *J Het. Chem.*, 1979, **16**, 1599.

Scheme IX

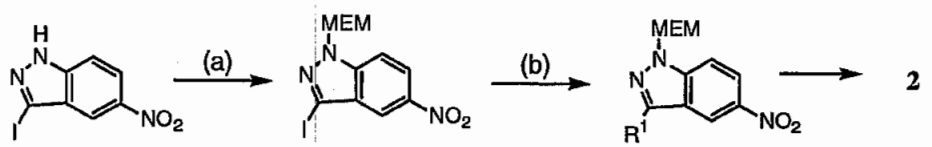


22 23 24 24'

Reagents:(a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 50°C.

[00101] Scheme IX above shows a general method for the preparation of compounds of formula I where R^1 is an alkynyl group. The bromoindazole (**22**) is coupled with propyne (**23**), by the Sonograshira coupling method, to afford 5-nitro-3-prop-1-ynyl-1*H*-indazole (**24**). One of skill in the art would recognize that a variety of alkynes are amenable to the above reaction and are useful for the preparation of a variety of compounds of formula I wherein the T moiety of the R^1 group is an alkynyl group.

Scheme X

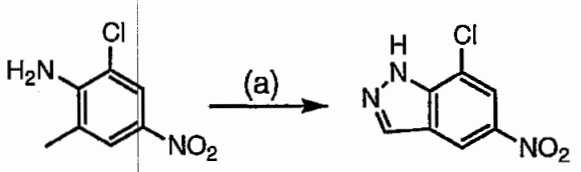


21 25 26

Reagents: (a) MEMCl, NaHMDS, THF, rt; (b) $RB(OH)_2$, $Pd(dppf)_2Cl_2$, K_2PO_4, DME, rt.

[00102] Scheme X above shows an alternative method for the preparation of nitroindazoles (**2**). The NH-group of the iodoindazole compound **21** may be protected. Although use of the MEM-protecting group is depicted above, one of skill in the art would recognize that a variety of protecting groups would be suitable for the above reaction. Other amino protecting groups are well known in the art and are described in detail in *Protecting Groups in Organic Synthesis*, Theodora W. Greene and Peter G. M. Wuts, 1991, published by John Wiley and Sons. The amino-protected iodoindazole (**25**) is coupled to a boronic acid using the Suzuki coupling methods that are well known in the art. One of ordinary skill in the art would recognize that a variety of boronic acids may be used in the Suzuki coupling thereby resulting in a variety of indazoles (**26**) where R^1 is alkyl or aryl.

Scheme XI

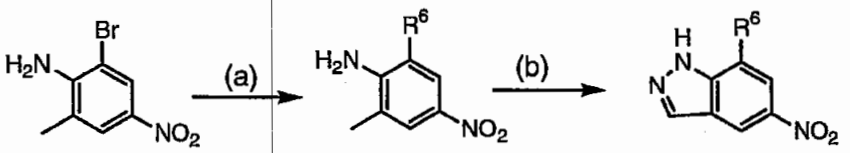


27 28

Reagents:(a) $NaNO_2$, AcOH, reflux.

[00103] Scheme XI above shows a general method for the preparation of 7-chloro-5-nitroindazole (**28**) by treating 2-chloro-6-methyl-4-nitro-phenylamine (**27**) with sodium nitrate in the presence of acetic acid.

Scheme XII

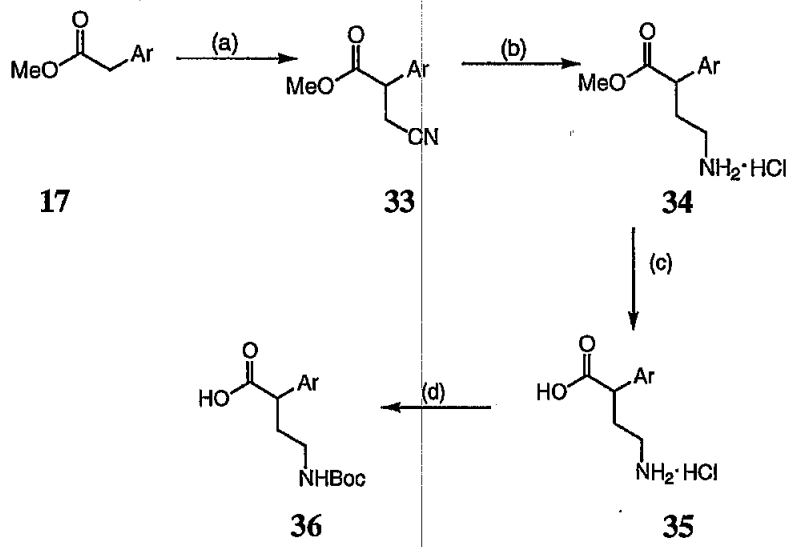


29 30 31

Reagents: (a) $R^6B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, aq. EtOH;(b) $NaNO_2$, AcOH, reflux.

[00104] Scheme XII above shows a general method for preparing compounds of formula **I** having an R^6 substituent at the 7-position (**31**). At step (a), 2-bromo-6-methyl-4-nitro-phenylamine (**29**) is coupled with a boronic acid using Suzuki coupling conditions to form the intermediate compound (**30**). One of ordinary skill in the art would recognize that a variety of boronic acids are suitable for the above reaction and would be useful in preparing a variety of compounds of formula **I** having an R^6 substituent at the 7-position of the indazole ring (**31**). The indazole ring is formed at step (b) by treating intermediate (**30**) with sodium nitrate and acetic acid at reflux.

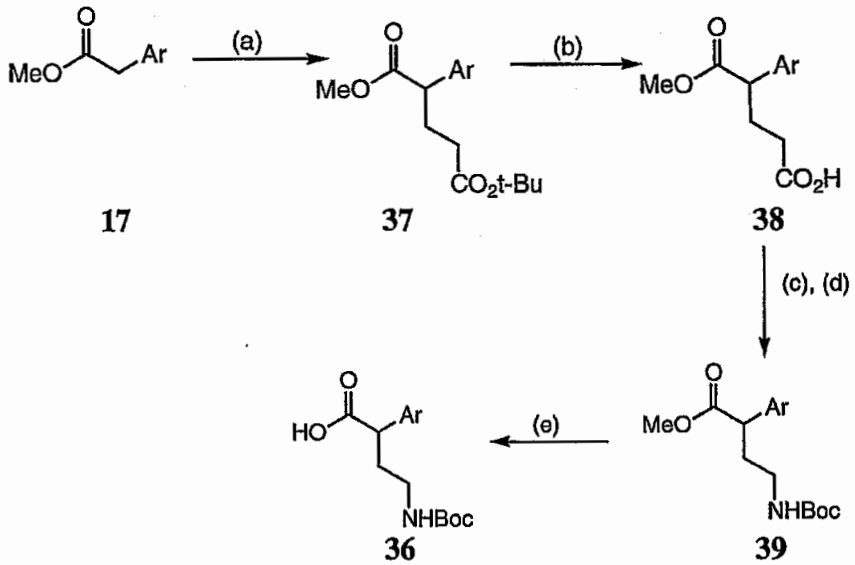
Scheme XIV



Reagents: (i) LDA, -78°C (ii) ICH_2CN, -78°C to ambient temperature, THF; (b)H_2, PtO_2, HCl, MeOH;(C) 8M HCl, reflux; (d) $(Boc)_2O$, Na_2CO_3, aq. THF, ambient temperature.

[00105] Scheme XIV above shows a general method for preparing the protected amino acid intermediates (**36**) useful for preparing compounds of formula **Ib** where R^3 is $T_nN(R^4)_2$. The cyano compound (**33**) is prepared by treating the ester (**17**) with lithiumdiisopropylamide (LDA) at -78°C then adding iodoacetonitrile. The nitrile is reduced using hydrogen in the presence of a platinum catalyst by a method substantially similar to that described by Prager, *et al*, *Aust. J. Chem.*, 1997, **50**, 813. The resulting amine (**34**) is hydrolyzed to form the acid compounds **35**. The amino groups is then protected with a BOC group by treating **35** with BOC-anhydride in the presence of aqueous sodium carbonate in tetrahydrofuran. Other amino protecting groups are well known in the art and are described in detail in *Protecting Groups in Organic Synthesis*, Theodora W. Greene and Peter G. M. Wuts, 1991, published by John Wiley and Sons.

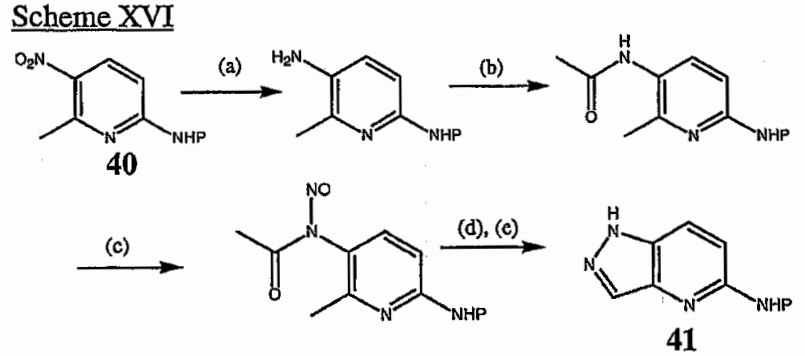
Scheme XV



Reagents: (a) *tert*-Butylacrylate, KO^{t}Bu, THF, -78°C to rt; (b) TFA, DCM; (c) DPPA, PhMe, rt; (d) ^{t}BuOH, $SnCl_2$(cat), 80°C, (e) LiOH, aq. THF.

[00106] Scheme XV above shows an alternative method for preparing the protected amino acid intermediates (**36**) useful for preparing compounds of formula **Ib** where R^3 is $T_nN(R^4)_2$. Michael addition of *tert*-butylacrylate to the anion of ester **17** affords the diester **37**. The *tert*-butyl ester of compound **37** is selectively cleaved to afford the acid intermediate **38**. The mono-ester **38** is then treated sequentially with diphenylphosphorylazide and *tert*-butanol to afford the BOC-protected amino ester **39**. Hydrolysis of ester affords the desired protected amino acid intermediate (**36**).

Scheme XVI

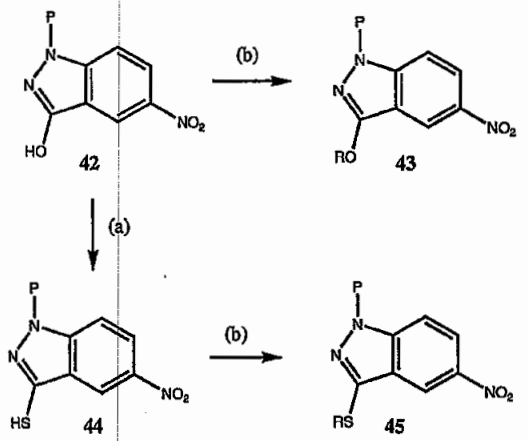


Reagents: (a) H_2, Pd/C; (b) Ac_2O; (c) NOCl; (d) benzene, reflux; (e) KOH, ethanol, reflux

[00107] Scheme XVI above shows a general method for preparing compounds of the present invention where V^3 is N. The pyridopyrazole intermediate **41**, useful for the preparation of compounds of the present invention where V^3 is N, is prepared from the

amino-protected pyridine compound **40** by methods substantially similar to those described by Foster, H. E. et. al., J. Chem. Soc., Perkin Trans 1, 1973, 2901.

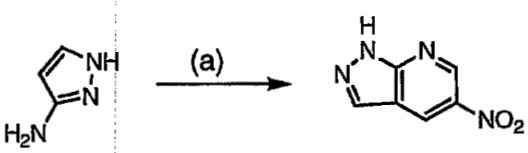
Scheme XVII



Reagents: (a) P_2S_5, xylene, reflux; (b) $NaNH_2$, RCl

[00108] Scheme XVI above shows a general method for preparing compounds of the present invention wherein a methylene unit of the T moiety of the R^1 group of formula **I** is replaced by either -O- or -S-. The formation of the indazole **42** was achieved by methods substantially similar to those described by Pfannstiel, K. *et. al.,* Ber1942, **75B**, 1096 and Vicente, J *et al.*, *Heterocycles*, 1997, 45 (1), 129. Indazole **45** was synthesized from compound **42** following a procedure outlined by Kuroda, T *et al* in JP50130759.

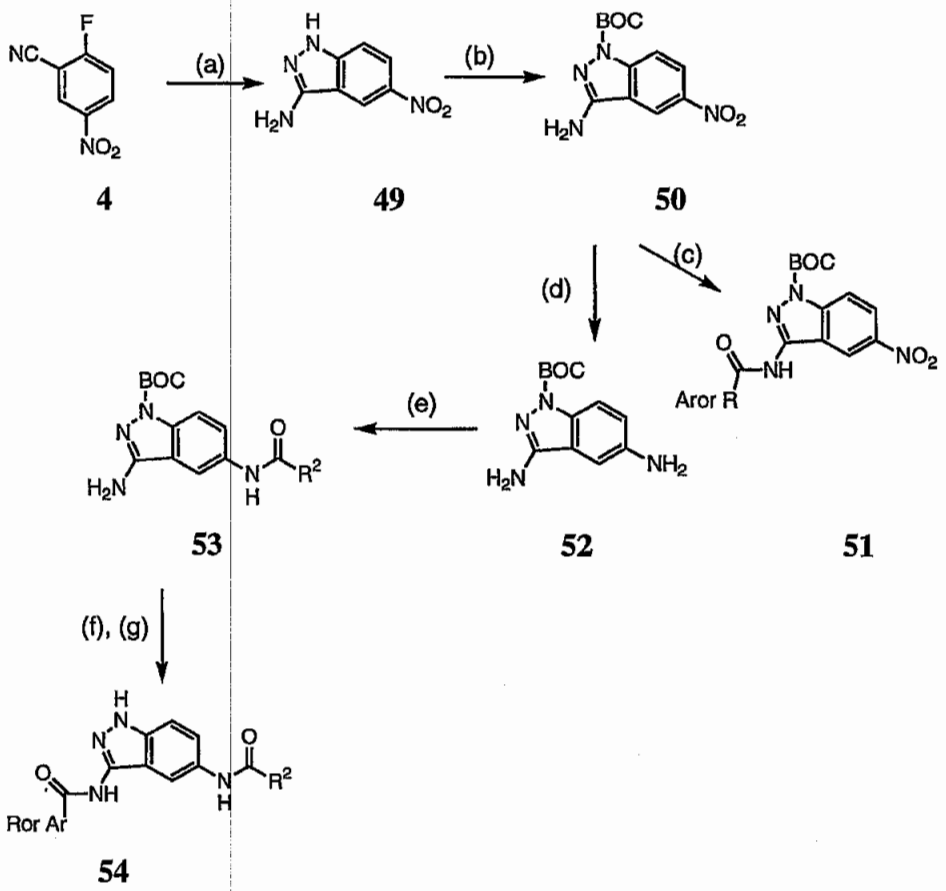
Scheme XVIII



46 **47**

[00109] Scheme XVIII above shows a general scheme for preparing compounds of formula **I** where V^1 is nitrogen by methods substantially similar to that described by Fanta, *Org. Synth. Coll.*, **4**, 844.

Scheme XIX



Reagents:(a) $N_2H_4 \cdot H_20$, BuOH, reflux; (b) $(Boc)_2O$, Et^iPr_2N, DMAP (cat), THF, rt; (c) RC(O)Cl, Py; (d) H_2, Pd/C, MeOH, rt; (e) R^2CO_2H, PyBroP, DCM; (f) RC(O)Cl, Et^iPr_2N, DCM; (g) TFA, DCM.

[00110] Scheme XVIII above shows a synthetic route for preparing compounds of the present invention where R^1 is NH_2, NHC(O)R, or NHC(O)Ar. Nitrile **4** may be treated with hydrazine to afford 3-aminoindazole **49**. Selective Boc-protection of the endocyclic nitrogen, followed by acylation of the exocyclic nitrogen affords 5-nitroindazole **51**. The nitro group may be reduced by hydrogenation (Scheme III) and the resulting amino group coupled with an acid **8** as in Scheme IV. Alternatively, hydrogenation of 5-nitroindazole **50** affords 3,5-diaminoindazole **52**. Selective acylation with acid **8** yields the indazole **53**, which may be elaborated as shown to provide indazole **54**. All of the methods used are known to those skilled in the art.

[00111] The activity of a compound utilized in this invention as an inhibitor of AKT, PKA, PDK1, p70S6K, or ROCK kinase may be assayed *in vitro, in vivo* or in a cell line according to methods known in the art. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated AKT,

PKA, PDK1, p70S6K, or ROCK. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to AKT, PKA, PDK1, p70S6K, or ROCK. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/AKT, inhibitor/PKA, inhibitor/PDK1, inhibitor/p70S6K, or inhibitor/ROCK complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where compounds are incubated with AKT, PKA, PDK1, p70S6K, or ROCK bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of AKT, PKA, PDK1, p70S6K, or ROCK kinase are set forth in the Examples below.

[00112] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in the compositions of this invention is such that is effective to measurably inhibit a protein kinase, particularly AKT, PKA, PDK1, p70S6K, or ROCK kinase, in a biological sample or in a patient. Preferably the composition of this invention is formulated for administration to a patient in need of such composition. Most preferably, the composition of this invention is formulated for oral administration to a patient.

[00113] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00114] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00115] The term "measurably inhibit", as used herein means a measurable change in AKT, PKA, PDK1, p70S6K, or ROCK activity between a sample comprising said

composition and a AKT, PKA, PDK1, p70S6K, or ROCK kinase and an equivalent sample comprising AKT, PKA, PDK1, p70S6K, or ROCK kinase in the absence of said composition.

[00116] A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a AKT, PKA, PDK1, p70S6K, or ROCK family kinase.

[00117] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[00118] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}\ alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[00119] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile

injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. 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.

[00120] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00121] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00122] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00123] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00124] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00125] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00126] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00127] The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00128] Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[00129] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[00130] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[00131] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00132] For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, Gleevec™, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

[00133] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus,

rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00134] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00135] According to another embodiment, the invention relates to a method of inhibiting AKT, PKA, PDK1, p70S6K, or ROCK kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound. Preferably, the method comprises the step of contacting said biological sample with a preferred compound of the present invention, as described herein *supra*.

[00136] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00137] Inhibition of AKT, PKA, PDK1, p70S6K, or ROCK kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[00138] Another aspect of this invention relates to a method for treating an AKT-, PKA-, PDK1-, p70S6K-, or ROCK-mediated disease in a patient, which method comprises administering to a patient in need thereof, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable composition

comprising said compound. According to a preferred embodiment, the invention relates to administering a compound of formula **I'**, or a pharmaceutically acceptable composition comprising said compound. A more preferred embodiment relates to administering a preferred compound of formula **I'**, as described herein *supra*, or a pharmaceutically acceptable composition comprising said compound.

[00139] According to another embodiment, the present invention relates to a method for treating an AKT-, PKA-, PDK1-, p70S6K-, or ROCK-mediated disease in a patient, which method comprises administering to a patient in need thereof, a therapeutically effective amount of a compound of formula **IIa, IIb**, or **V**, or a pharmaceutically acceptable composition comprising said compound. According to another embodiment, said method comprises administering to a patient in need thereof, a therapeutically effective amount of a preferred compound of formula **IIa, IIb**, or **V**, as described herein *supra*, or a pharmaceutically acceptable composition comprising said compound.

[00140] According to another embodiment, the present invention relates to a method for treating an AKT-, PKA-, PDK1-, p70S6K-, or ROCK-mediated disease in a patient, which method comprises administering to a patient in need thereof, a therapeutically effective amount of a compound of formula **III** or **IV**, or a pharmaceutically acceptable composition comprising said compound. According to another embodiment, said method comprises administering to a patient in need thereof, a therapeutically effective amount of a preferred compound of formula **III**, or **IV**, as described herein *supra*, or a pharmaceutically acceptable composition comprising said compound.

[00141] According to another embodiment, the invention provides a method for treating or lessening the severity of an AKT-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[00142] The term "AKT-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which AKT is known to play a role. The term "AKT-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with an AKT inhibitor. AKT-mediated diseases or conditions include, but are not limited to, proliferative disorders, cancer, cardiovascular disorders, rheumatoid arthritis, and neurodegenerative disorders. Preferably, said cancer is selected from pancreatic, prostate, or ovarian cancer.

[00143] According to another embodiment, the invention provides a method for treating or lessening the severity of a PKA-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[00144] The term "PKA-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which PKA is known to play a role. The term " PKA-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a PKA inhibitor. PKA-mediated diseases or conditions include, but are not limited to, proliferative disorders and cancer. According to another embodiment, the invention provides a method for treating or lessening the severity of a PDK1-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[00145] According to another embodiment, the invention provides a method for treating or lessening the severity of an PDK1-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[00146] The term "PDK1-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which PDK1 is known to play a role. The term " PDK1-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a PDK1 inhibitor. PDK1-mediated diseases or conditions include, but are not limited to, proliferative disorders, and cancer. Preferably, said cancer is selected from pancreatic, prostate, or ovarian cancer.

[00147] According to another embodiment, the invention provides a method for treating or lessening the severity of a p70S6K-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[00148] The term "p70S6K-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which p70S6K is known to play a role. The term "p70S6K-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a p70S6K inhibitor. p70S6K-mediated diseases or conditions include, but are not limited to, proliferative disorders, such as cancer and tuberous sclerosis.

[00149] According to another embodiment, the invention provides a method for treating or lessening the severity of a ROCK-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[00150] The term "ROCK -mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which ROCK is known to play a role. The term " ROCK -mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a ROCK inhibitor. Such conditions include, without limitation, hypertension, angina pectoris, cerebrovascular contraction, asthma, peripheral circulation disorder, premature birth, cancer, arteriosclerosis, spasm, retinopathy, inflammatory disorders, autoimmune disorders, AIDS, and osteoporosis.

[00151] According to another embodiment, the present invention relates to a method for treating or lessening the severity of a disease or condition selected from a proliferative disorder, a cardiac disorder, an inflammatory disorder, an autoimmune disorder, a viral disease, or a bone disorder, wherein said method comprises the step of administering an effective amount of a compound of the present invention. Preferably, said method comprises the step of administering an effective amount of a preferred compound of the present invention.

[00152] According to a preferred embodiment, the present invention relates to a method for treating or lessening the severity of a disease or condition selected from cancer, rheumatoid arthritis, asthma, HIV, angina pectoris, peripheral circulation disorder, hypertension, arteriosclerosis, or osteoporosis.

[00153] Preferably, the present invention relates to a method for treating or lessening the severity of a cancer.

[00154] More preferably, the present invention relates to a method for treating or lessening the severity of a cancer selected from brain (gliomas), breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, or thyroid.

[00155] Most preferably, the present invention relates to a method for treating or lessening the severity of pancreatic, prostate, or ovarian cancer..

[00156] In an alternate embodiment, the methods of this invention that utilize compositions that do not contain an additional therapeutic agent, comprise the additional step of separately administering to said patient an additional therapeutic agent. When these additional therapeutic agents are administered separately they may be administered

to the patient prior to, sequentially with or following administration of the compositions of this invention.

[00157] The compounds of this invention or pharmaceutical compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a compound of this invention. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

[00158] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

SYNTHETIC EXAMPLES

[00159] As used herein, the term "R_t(min)" refers to the HPLC retention time, in minutes, associated with the compound. Unless otherwise indicated, the HPLC method utilized to obtain the reported retention time is as follows:

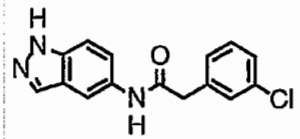
Column: XTerra C8 column, 4.6 x 150 mm

Gradient: 0-100% acetonitrile+methanol 60:40 (20mM Tris phosphate)

Flow rate: 1.51 mL/minute

Detection: 225 nm.

Example 1



I-6

2-(3-Chloro-phenyl)-N-(1H-indazol-5-yl)-acetamide (I-6): To a solution of 5-aminoindazole (1 mmol), HOBt (1 mmol) and 3-chlorophenylacetic acid (1.1 mmol) in DMF (4 mL) was added N-methylmorpholine (1.1 mmol). After stirring for 10 minutes, EDC·HCl (1.1 mmol) was added and the reaction mixture stirred overnight at ambient temperature. The reaction mixture was concentrated and the residue purified by reverse phase preparative HPLC [Waters Delta-Pak C18, 15uM, 100A column, gradient 10% - 100% B (solvent A: 0.05% TFA in water; solvent B: CH_3CN) over 10 minutes at 25 mL/min] to afford compound **I-6** (79 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d6) δ 3.68 (2H, s), 7.12-7.73 (6H, m), 8.00 (1H, s), 8.11 (1H, s), 10.10 (1H, s), 12.97 (1H, bs); MS (ES+): m/e= (M+H) 286.

Example 2

[00160] We have prepared other compounds of formula I by methods substantially similar to those described in Example 1. The characterization data for these compounds is summarized in Table 2 below and includes HPLC, LC/MS (observed) and ^{1}H NMR data.

[00161] ^{1}H NMR data is summarized in Table 2 below wherein ^{1}H NMR data was obtained at 400 MHz in deuterated DMSO, unless otherwise indicated, and was found to be consistent with structure. Compound numbers correspond to the compound numbers listed in Table 1.

Table 2. Characterization Data for Selected Compounds of Formula I

Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
1	-	6.65	2.61-2.67 (2H, m), 2.91-2.95 (2H, m), 7.19 (1H, m), 7.27-7.29 (4H, m), 7.37 (1H, d), 7.46 (1H, d), 8.00 (1H, s), 8.11 (1H, s), 9.89 (1H, s), 12.95 (1H, brs).

Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
2	320	7.90	3.8 (2H, s), 7.3-7.7 (6H, m), 8.0 (1H, s), 8.2 (1H, s), 10.3 (1H, s), 13.0 (1H, s)
3	295	6.90	3.4 (3H, s), 3.5 (2H, m), 6.7 (2H, d), 7.2 (2H, d), 7.4 (2H, q), 8.1 (1H, s), 8.2 (1H, s), 10.1 (1H, s), 13.0 (1H, s).
4	286	7.17	3.85 (2H, s), 7.29-7.49 (6H, m), 8.00 (1H, s), 8.10 (1H, s), 10.20 (1H, s), 13.00 (1H, brs).
5	286	7.48	3.66 (2H, s), 7.36-7.49 (6H, m), 8.00 (1H, s), 8.11 (1H, s), 10.18 (1H, s) 13.00 (1H, brs).
7	268	6.25	3.61 (2H, s), 6.75-6.81 (2H, m), 7.05 (1H, t), 7.15 (1H, m), 7.44-7.45 (2H, m), 8.00 (1H, s), 8,12 (1H, s), 9.54 (1H, s), 10.06 (1H, s), 13.00 (1H, brs).
8	268	5.75	4.54 (2H, s), 6.63 (1H, d), 6.76 (2H, m), 7.09-7.13 (1H, m), 7.40-7.49 (2H, m), 8.00 (1H, s), 8.12 (1H, s), 10.12 (1 H, s), 13.00 (1H, brs).
9	268	5.51	3.51 (2H, s), 6.68 (2H, d), 7.14 (2H, d), 7.42-7.45 (2H, m), 8.00 (1H, s), 8.11 (1H, s), 9.26 (1H, s), 10.06 (1H, s), 12.96 (1H, brs).
10	302	7.67	4.16 (2H, s), 7.46-7.57 (6H, m), 7.85 (1H, d), 7.94 (1H, d), 7.99 (1H, s), 8.11 (1H, s), 8.17 (1H, d), 10.33 (1H, s), 12.97 (1H, brs).
11	302	7.76	3.83 (2H, s), 7.46-7.54 (5H, m), 7.85-90 (4H, m), 8.00 (1H, s), 8.14 (1H, s), 10.25 (1H, s), 12.98(1H, brs).
12	352	8.39	3.7 (2H, s), 7.3-7.6 (4H, m), 7.7 (2H, d), 8.0 (1H, s), 8.2 (1H, s), 10.3 (1H, s), 13.0 (1H, s).
13	344	8.10	3.7 (2H, s), 6.8 (1H, d), 6.9 (2H, d), 7.0-7.5 (8H, m), 8.0 (1H, s), 8.1 (1H, s), 10.1 (1H, s), 13.0 (1H, s).
14	358	8.14	3.7 (2H, s), 5.1 (2H, s), 6.9 (1H, dt), 7.0 (1H, d), 7.2-7.5 (9H, m), 8.0 (1H, s), 8.1 (1H, s), 10.1 (1H, s), 13.0 (1H, s).
15	344	8.21	3.6 (2H, s), 7.0 (4H, d), 7.1 (1H, t), 7.3-7.5 (6H, m), 8.0 (1H, s), 8.2 (1H, s), 10.2 (1H, s), 13.0 (1H, s).
16	321	7.99	3.69 (2H,s), 7.34 (1H,d), 7.40 (1H,d), 7.48 (1H,d), 7.55-7.62 (2H,m), 8.00 (1H,s), 8.10 (1H,s), 10.20 (1H,s), 12.98 (1H,s)
17	288	7.20	3.67 (2H, s), 7.19 (1H, m), 7.38-7.49 (4H, m), 8.00 (1H, s), 8.10 (1H, s), 10.18 (1H, s), 12.98 (1H, brs).
18	288	7.23	3.71 (1H, s), 7.07 -7.13 (3H, m), 7.40 (1H, d), 7.48 (1H, d), 8.00 (1H, s), 8.10 (1H, s), 10.19 (1H, s), 12,98 (1H, brs).

Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
19	304	7.57	3.68 (2H, s), 7.36-7.42 (3H, m), 7.47 (1H, d), 7.56 (1H, m), 8.00 (1H, s), 8.10 (1H, s), 10.18 (lH, s), 12.98 (1H, brs).
20	304	7.41	3.7 (2H, s), 7.3 (1H, m), 7.4-7.6 (4H, m), 8.0 (1H, s), 8.2 (1H, s), 10.2 (1H, s), 13.1 (1H, s)
21	296	6.67	3.6 (2H, s), 6.0 (2H, s), 6.7-6.9 (3H, m), 7.4-7.5 (2H, m), 8.0 (1H, s), 8.2 (1H, s), 10.2 (1H, s), 13.0 (1H, bs)
22	356, 354	8.13	3.5 (2H, s), 7.3-7.5 (2H,q), 7.7 (2H, dd), 7.8 (1H, s), 8.0 (1H, s), 8.2 (1H, s), 10.4 (1H, s), 13.0 (1H, s).
23	253	5.40	3.71 (2H, s), 7.36-7.49 (3H, m), 7.75 (1H, m), 8.00 (1H, s), 8.10 (1H, s), 8.46 (1H, m), 8.54 (1H, s), 10.23 (1H,s), 12.98 (1H, brs).
24	291	6.88	3.74 (2H, s), 6.98 (1H, t), 7.07 (1H, t), 7.27 (1H, s), 7.35 (1H, d), 7.44-7.46 (2H, m), 7.63 (1H, d), 8.00 (1H, s), 8.12 (1H, s), 10.10 (1H, s), 10.91 (1H, brs), 12.98 (1H, brs).
25	308	7.90	3.94 (2H, s), 7.38-7.47 (4H, m), 7.61 (1H, s), 7.92 (1H, d), 7.99 (2H, m), 8.12 (1H, s), 10.29 (1H, s), 12.97 (1H, brs).
26	258	6.67	3.66 (2H, s), 7.11 (1H, m), 7.33 (1H, s), 7.42-7.50 (3H, m), 8.00 (1H, s), 8.12 (1H, s), 10.13 (1H, s), 12.97 (1H, brs).
27	258	7.90	3.87 (2H, s), 6.98 (2H, m), 7.39-7.42 (2H, m), 7.48 (1H, m), 8.01 (1H, s), 8.12 (1H, s), 10.20 (1H, s), 12.98 (1H, brs).
28	244	7.49	1.16-1.23 (2H, m), 1.51-1.61 (4H, m), 1.74-1.76 (2H, m), 2.23-2.31 (3H, m), 7.39 (1H, d), 7.45 (1H, d), 7.99 (1H, s), 8.12 (1H, s), 9.83 (1H, s), 12.98 (1H, brs).
29	258	8.00	0.96-1.02 (2H, m), 1.12-1.24 (3H, m), 1.60-1.78 (6H, m), 2.18 (2H, m), 7.38 (1H, d), 7.45 (1H, d), 7.99 (1H, s), 8.12 (1H, s), 9.83 (1H, s), 12.95 (1H, brs).
30	272	8.47	1.18-1.26 (2H, m), 1.39-1.72 (12H, m), 2.01 (1H, m), 2.22 (2H, d), 7.39 (1H, d), 7.45 (1H, d), 7.99 (1H, s), 8.13 (1H, s), 9.84 (1H, s), 12.97 (1H, brs).
31	268	6.02	5.11(1H, m), 6.41 (1H, m), 7.29 (1H, m), 7.34-7.38 (2H, m), 7.45-7.58 (4H, m), 8.00 (1H, s), 8.15 (1H, s), 9.93 (1H, s), 12.97 (1H, brs).

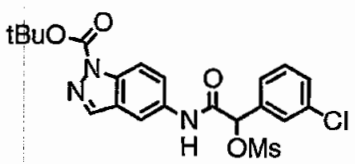
Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
32	268	6.02	5.11(1H, m), 6.41 (1H, m), 7.29 (1H, m), 7.34-7.38 (2H, m), 7.45-7.58 (4H, m), 8.00 (1H, s), 8.15 (1H, s), 9.93 (1H, s), 12.97 (1H, brs).
33	310	6.93	2.17 (3H, s), 6.00 (1H, s), 7.38-7.49 (5H, m), 7.57 (2H, m), 8.00 (1H, s), 8.07 (1H, s), 10.33 (1H, s), 12.99 (1H, brs).
34	286	6.29	5.12 (1H, m), 6.47 (1H, m), 7.19 (2H, t), 7.45 (1H, d), 7.54-7.58 (3H, m), 8.00 (1H, s), 8.14 (1H, s), 9.95 (1H, s), 12.97 (1H, brs).
35	302	6.95	5.14 (1H, m), 6.52 (1H, m), 7.42-7.47 (3H, m), 7.54-7.56 (3H, m), 8.00 (1H, s), 8.14 (1H, s), 9.56 (1H, s), 12.98 (1H, brs).
36	336	7.46	5.24 (1H, m), 6.67 (1H, m), 7.46 (1H, d), 7.55 (1H, d), 7.72-7.75 (4H, m), 8.00 (1H, s), 8.14 (1H, s), 10.03 (1H, s), 12,98 (1H, brs).
37	347	7.07	5.11 (1H, m), 6.52 (1H, m), 7.44-7.57 (6H, m), 8.00 (1H, s), 8.13 (1H, s), 9.96 (1H, s), 12.98 (1H, brs).
38	298	5.97	3.73 (3H, s), 5.04 (1H, m), 6.29 (1H, m), 7.42-7.46 (3H, m), 7.54 (1H, m), 8.00 *1H, s), 8.15 (1H, s), 9.88 (1H, s), 12,98 (1H, brs).
39	302	6.33	5.48 (1H, m), 6.64 (1H, m), 7.33-7.37 (2H, m), 7.44-7.48 (2H, m), 7.57-7.60 (2H, m), 8.00 (1H, s), 8.16 (1H, s), 10.05 (1H, s), 12.99 (1H, brs).
40	302	6.91	5.15 (1H,d), 6.59 (1H,d), 7.35-7.56 (6H,m), 7.94 (1H,s), 8.00 (1H,s), 9.86 (1H,s), 12.98 (1H,s)
41	314	4.99	3.73 (3H, s), 4.95 (1H, m), 6.20 (1H, m), 6.88 (2H, m), 6.94 (1H, s), 7.45 (1H, d), 7.55 (1H, d), 8.00 (1H, s), 8.15 (1H, s), 8.95 (1H, s), 9.83 (1H, s), 12.97 (1H, brs).
42	304	6.72	5.15 (1H, m), 6.62 (1H, m), 7.38-7.47 (3H, m), 7.53-7.55 (2H, m), 8.00 (1H, s), 8.13 (1H, S), 9.97 (1H, S), 12.98 (1H, S).
43	304	6.78	5.18 (1H, m), 6.71 (1H, m), 7.17-7.25 (3H, m), 7.46 (1H, d), 7.54 (1H, d), 8.00 (1H, s), 8.13 (1H, s), 9.99 (1H, s), 12.99 (1H, brs).
44	307	5.85	5.35 (1H, d), 6.07 (1H, d), 7.01-7.08 (1H, m), 7.10-7.18 (1H, m), 7.36 (3H, m), 7.46 (1H, d), 7.58 (1H, d), 7.75 (1H, d), 8.00 (1H, s), 8.18 (1H, s), 9.94 (1H, s), 11.01 (1H, d), 12.96 (1H, s).

Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
45	318	7.15	5.30 (1H, d), 6.58 (1H, d), 7.44-7.59 (4H, m), 7.69 (1H, d), 7.89-7.93 (2H, m), 7.99 (1H, s), 8.04 (1H, s), 8.16 (1H, s), 10.01 (1H, s), 12.97 (1H, s).
46	367	8.14	1.40 (9H,s), 5.37 (1H, m), 7.28-7.40 (4H, m), 7.46-7.52 (4H, m), 8.00 (1H, s), 8.09 (1H, s), 10.25 (1H, s), 12,98 (1H, brs).
47	367	8.14	1.40 (9H,s), 5.37 (1H, m), 7.28-7.40 (4H, m), 7.46-7.52 (4H, m), 8.00 (1H, s), 8.09 (1H, s), 10.25 (1H, s), 12,98 (1H, brs).
48	267	5.80	5.07 (1H, brs), 7.37 (1H, d), 7.44-7.53 (4H, m), 7.60 (2H, m), 8.05 (1H, s), 8.09 (1H, s), 8.73 (3H, brs), 10.58 (1H, s), 13.06 (1H, brs). TFA salt
49	267	5.80	5.07 (1H, brs), 7.37 (1H, d), 7.44-7.53 (4H, m), 7.60 (2H, m), 8.05 (1H, s), 8.09 (1H, s), 8.73 (3H, brs), 10.58 (1H, s), 13.06 (1H, brs). TFA salt
50	301	6.71	5.1 (1H, s), 7.35 (1H, d), 7.45-7.65 (5H, m), 8.10 (2H, d), 8.8 (3H, bs), 10.6 (1H, bs), 13.1 (1H, bs) TFA salt
51	301	6.69	5.13 (1H,s), 7.36 (1H,d), 7.51-7.55 (4H,m), 7.56 (1H,s), 7.72 (1H,s), 8.06-8.13 (1H,m), 8.78 (3H, brs), 10.62 (1H,s), 13.08 (1H,s) TFA salt
52	347	6.78	3.61 (2H, br s), 4.60 (1H, s), 7.30 (2H, m), 7.41 (4H, br m), 7.60 (1H, s), 7.96 (1H, s), 8.09 (1H, s), 8.16(1H, s), 10.11 (1H, br s,), 12.95 (1H, s). TFA salt
53	335	7.19	3.10 (2H, br s), 4.68 (1H, s), 7.44 (2H, m), 7.59 (2H, br m), 7.75 (1H, m), 7.88 (1H, s), 8.00 (1H, s), 8.16(1H, s), 10.18 (1H, br s,), 12.99 (1H, s). TFA salt
54	335	7.39	5.16 (1H,s), 7.36 (1H,d), 7.51-7.58 (2H,m), 7.81 (1H,d), 7.88 (1H,s), 8.06 (2H,m), 8.78 (3H, brs), 10.60 (1H,s), 13.08 (1H,brs) TFA salt
55	319	6.93	5.19 (1H,s), 7.37 (1H,d), 7.51-7.61 (3H,m), 7.85 (1H, m), 8.06-8.10 (2H,m), 8.83 (3H, brs), 10.60 (1H,s), 13.15 (1H, brs) TFA salt
56	M-H 304	5.54	-
57	279	6.70	.7 (2H, AB quartet), 5.6 (1H, s), 7.4-7.7 (6H, m), 8.10 (2H, s), 9.5 (1H, bs), 10.2 (1H, bs), 11.05 (1H, s), 13.1 (0.5H,bs) TFA salt
58	317	6.93	5.30 (1H, d), 7.40-7.45 (1H, m), 7.50-7.55(1H, m), 7.60-7.65 (2H, m), 7.69 (1H, m), 7.89-7.93 (2H, m), 7.99 (2H, s), 8.05-8.1 (2H, m), 8.95 (2H, s), 10.75 (1H, s), 13.0 (1H, br s). TFA salt
76	316	7.22	2.42 (3H, s), 5.14 (1H, m), 6.57 (1H, m), 7.37-7.40 (3H, m), 7.48-7.53 (2H, m), 7.59 (1H, s), 8.07 (1H, s), 9.95 (1H, s), 12.55 (1H, brs).

Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
77	333	7.17	2.45 (3H, s), 5.15 (1H, brs), 7.37 (1H, d), 7.44 (1H, d), 7.61 (2H,m) 7.84 (1H,d), 7.95 (1H,s), 8.76 (3H,brs), 10.58 (1H, s), 12.66 (1H,s) TFA salt
78	336	7.80	5.16 (1H,d), 6.63 (1H,d), 7.40 (2H,m), 7.50 (2H,m), 7.56 (1H,s), 7.67 (1H,m), 8.14 (1H,s), 10.14 (1H,s), 13.23 (1H,s)
79	330	7.55	1.28 (3H,t), 2.85 (2H,q), 5.14 (1H, d), 6.58 (1H, d), 7.35-7.42 (3H, m), 7.48-7.52 (2H, m), 7.59 (1H, s), 8.11 (1H, s), 9.95 (1H, s), 12.55 (1H, s).
80	344	7.91	1.33 (6H, d), 3.25 (1H, sep), 5.14 (1H, d), 6.59 (1H, d), 7.37-7.42 (3H, m), 7.49 (1H, d), 7.54-7.59 (2H, m), 8.17 (1H, s), 9.95 (1H, s), 12.51 (1H, s).
81	378	8.30	5.15 (1H, d), 6.63 (1H, d), 7.36-7.42 (3H, m), 7.52-7.54 (4H, m), 7.60 (1H, s), 7.73 (1H, d), 7.91 (2H, d), 8.52 (1H, s), 10.09 (1H, s), 13.19 (1H, s).
82	301	6.87	3.65 (2H, s), 5.25 (2H, brs), 7.16 (1H, d), 7.26 (1H, d), 7.32-7.37 (3H, m), 7.43 (1H, s), 7.94 (1H, s), 10.05 (1H, s), 11.29 (lH, brs).
83	336	7.54	3.66 (2H, s), 5.24 (2H, brs), 7.15 (1H, d), 7.25 (1H, d), 7.33 (1H, m), 7.59-7.61 (2H, m), 7.94 (1H, s), 10.06 (1H, s)< 11.29 (1H, brs).
84	282	6.15	3.56-3.58 (1H, m), 3.82-3.86 (1H, m), 4.07-4.09 (1H, m), 4.96 (1H, m), 7.25 (1H, m), 7.31-7.35 (2H, m), 7.39-7.47 (4H, m), 7.99 (1H, s), 8.16 (1H, s), 10.10 (1H, s), 12.95 (1H, brs).
85	336, 334	7.13	3.6 (1H, m), 3.87 (1H, m), 4.00 (1H, m), 5.01 (1H, bs), 7.35-7.4 (3H, m), 7.47 (1H, d), 7.6 (1H, d), 8.0 (1H, s), 8.15 (1H, s), 10.18 (1H, s)
86	266	7.23	1.4 (3H; d), 3.8 (1H, q), 7.2-7.5 (7H, m), 8.0 (1H, s), 8.2 (1H, s), 10.1 (1H, s), 13.0 (1H, s)
87	370	8.07	1.5 (3H, d), 3.9 (1H, q), 7.3-7.7 (10H, m), 7.8 (1H, s), 8.0 (1H, s), 8.2 (1H, s), 10.2 (1H, s), 13.0 (1H, s).
88	320	8.68	0.8-1.9 (9H, m), 2.6 (1H, m), 7.2-7.5 (7H, m), 8.0 (1H, s), 8.2 (1H, s), 10.1 (1H, s), 13.0 (1H, s)

Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
89	328	8.29	5.1 (1H, s), 7.2-7.5 (12H, m), 8.0 (1H, s), 8.2 (1H, s), 10.4 (1H, s), 13.1 (1H, s)
90	292	6.09	2.9 (2H, d), 4.45 (1H, t), 7.4-7.5 (3H, m), 7.7-7.8 (3H, m), 8.0 (1H, s), 8.1 (1H, d), 10.6 (1H, s), 13.0 (1H, s).
91	317	7.7	2.7 (2H, t), 4.3 (2H, t), 7.0 (2H, d), 7.3-7.5 (4H, m), 8.0 (1H, s), 8.2 (1H, s), 10.1 (1H, s), 13.0 (1H, s).
92	280	7.5	1.87 (2H, q), 2.3 (2H, t), 2.6 (2H, t), 7.1-7.3 (5H, m), 7.4-7.5 (2H, q), 8.0 (1H, s), 8.1 (1H, s), 9.9 (1H, s), 13.0 (1H, s).
93	304	7.45	3.7 (2H, s), 7.2 (1H, t), 7.3-7.6 (4H, m), 8.0 (1H, s), 8.1 (1H, s), 10.3 (1H, s), 13.0 (1H, s).
94	362, 360	7.68	3.6 (2H, s), 3.8 (3H, s), 7.0 (1H, t), 7.4-7.5 (4H, m), 8.0 (1H, s), 8.1 (1H, s), 10.1 (1H, s), 13.0 (1H, s).
95	351, 349	7.46	3.07 (2H, m), 3.21 (2H, m), 4.15 (1H, m), 7.26 (1H, d, J=8.0Hz), 7.34 (1H, d, J=8.7Hz), 7.53 (2H, m), 7.60(1H, m), 8.06(2H, d, J=7.45Hz), 8.30(3H, br s), 10.46 (1H, s), 13.09 (1H, s) TFA salt
96	351, 349	7.46	3.08 (2H, m), 3.21 (2H, m), 4.16 (1H, m), 7.26 (1H, d, J=8.4Hz), 7.35 (1H, d, J=8.5Hz), 7.50 (2H, m), 7.69(1H, m), 8.06(2H, d, J=6.6Hz), 8.25(3H, br s), 10.46 (1H, s), 13.09 (1H, s). TFA salt

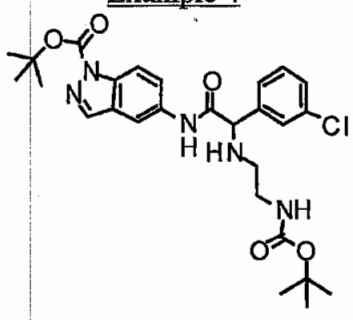
Example 3



5-[2-(3-Chloro-phenyl)-2-methanesulfonyloxy-acetylamino]-indazole-1-carboxylic acid *tert*-butyl ester: 5-Amino-indazole-1-carboxylic acid *tert*-butyl ester was prepared following the procedure outlined by S.J. Brickner, WO9002744. 5-Amino-indazole-1-carboxylic acid *tert*-butyl ester was then coupled with 2-(3-chlorophenyl)-2-hydroxyacetic acid following the procedure as described in Example 1 to afford 5-[2-(3-chloro-phenyl)-2-hydroxy-acetylamino]-indazole-1-carboxylic acid *tert*-butyl ester. To a solution of 5-[2-(3-chloro-phenyl)-2-hydroxy-acetylamino]-indazole-1-carboxylic acid *tert*-butyl ester (7.47 mmol) in dry THF (20 mL) at 0° C was added pyridine (37.33 mmol, 5 equivalents) followed by methanesulfonyl chloride (22.40 mmol, 3 equivalents) added in a dropwise fashion. The resultant solution was stirred at ambient temperature

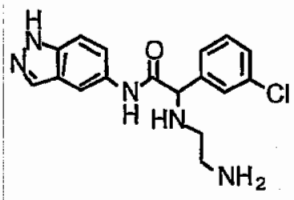
overnight. The reaction mixture was then concentrated *in vacuo* and the resulting oil was partitioned between EtOAc and brine. The organic layer was washed with brine (thrice), dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the title compound (3.58 g, qunatitative yield), which was used without further purification.

Example 4



5-[2-(2-*tert*-Butoxycarbonylamino-ethylamino)-2-(3-chloro-phenyl)-acetylamino]-indazole-1-carboxylic acid *tert*-butyl ester: To a solution of 5-[2-(3-chloro-phenyl)-2-methanesulfonyloxy-acetylamino]-indazole-1-carboxylic acid *tert*-butyl ester (1.49 mmol) in dry THF (4 mL) was added pyridine (4.48 mmol, 3 equivalents) followed by followed by a dry THF solution of (2-amino-ethyl)-carbamic acid *tert*-butyl ester (3 equivalents, ~0.5 mL/mmol). The resulting solution was refluxed at 60°C overnight. The reaction mixture was then concentrated *in vacuo* and the resulting oil was partitioned between EtOAc and brine. The organic layer was washed with brine (thrice), dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using eluting with EtOAc:hexane (60:40) to afford the title compound in 85% yield.

Example 5



I-59

2-(2-Amino-ethylamino)-2-(3-chloro-phenyl)-*N*-(1*H*-indazol-5-yl)-acetamide (I-59): To 5-[2-(2-*tert*-butoxycarbonylamino-ethylamino)-2-(3-chloro-phenyl)-acetylamino]-indazole-1-carboxylic acid *tert*-butyl ester (1.26mmol) was added trifluoroacetic acid

(5mL) and the reaction mixture was stirred for 1.5 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by reverse phase preparative HPLC [Waters Delta-Pak C18, 15uM, 100A column, gradient 10% - 100% B (solvent A: 0.05% TFA in water; solvent B: CH_3CN) over 10 minutes at 25 mL/min] to afford compound the title compound (172mg, 82%). ^{1}H NMR (400 MHz, DMSO-d6) δ 2.5-5.5(9H, br m), 6.9-7.3(1H, m), 7.4-8.2(8H, m), 9.2-10.8(1H, br m), 13.0(1H, br s); MS (ES+): m/e= 344.4(100%), 346.4(40%)

Example 6

[00162] We have prepared other compounds of formula **I** by methods substantially similar to those described in Examples 1, 3, 4, and 5. The characterization data for these compounds is summarized in Table 3 below and includes HPLC, LC/MS (observed) and ^{1}H NMR data.

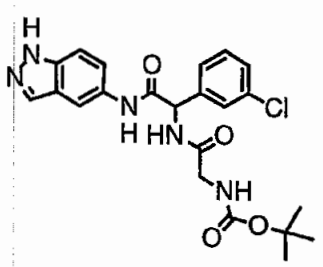
[00163] ^{1}H NMR data is summarized in Table 3 below wherein ^{1}H NMR data was obtained at 400 MHz in deuterated DMSO, unless otherwise indicated, and was found to be consistent with structure. Compound numbers correspond to the compound numbers listed in Table 1.

Table 3. Characterization Data for Selected Compounds of Formula **I**

Compound No	M+1 (obs)	R_t(min)	^{1}H NMR
60	-	6.0	2.0(2H, m), 2.8-3.2(4H, m), 5.2(1H, br s), 7.4(1H, m), 7.6(4H, m), 7.8(4H, m), 8.1(1H, m), 9.6-9.8(2H, br s), 10.8(1H, br s), 12.9-13.3(1H, br s) TFA salt
61	358	5.8	2.6-2.7(3H, s), 2.9-3.4(4H, m), 5.1(1H, br s), 7.4(1H, m), 7.5-7.6(4H, m), 7.7(1H, s), 8.1(2H, m), 10.5-10.7(1H, br s), 12.7-13.3(1H, br s) TFA salt
62	372.5	6.1	2.8-3.4(10H, m), 4.7-4.9(1H, br s), 7.3-7.7(6H, m), 8.0-8.2(2H, m), 10.2-10.5(1H, br s), 12.7-13.3(1H, br s) TFA salt

Compound No	M+1 (obs)	R_t(min)	^{1}H NMR
63	372	6.0	1.2(3H, m), 2.8-3.3(6H, m), 5.0(1H, br s), 7.4(1H, m), 7.6(4H, m), 7.7(1H, s), 8.0-8.1(2H, m), 10.5-10.8(1H, br s), 12.8-13.3(1H, br s) TFA salt
64	434	7.5	2.8-3.4(4H, m), 4.2-4.3(2H, s), 4.7-5.1(1H, br s), 7.3-7.6(10H, m), 7.7(1H, s), 8.1(2H, m), 10.4-10.6(1H, br s), 12.9-13.1(1H, br s) TFA salt
65	392	7.6	4.2-4.4(2H, m), 5.2(1H, s), 7.3(1H, m), 7.4-7.6(6H, m), 7.7(1H, m), 7.9(1H, m), 8.0-8.1(2H, m), 8.7(1H, m), 9.6-10.5(1H, br s), 10.6(1H, s), 12.9-13.2(1H, br s) TFA salt
66	406	7.7	3.2(3H, br s), 3.4(1H, br s), 5.2(1H, s), 7.5(3H, m), 7.6(4H, m), 7.8(2H, m), 8.1(2H, m), 8.6(1H, s), 9.6-9.9(1H, br s), 10.7(1H, s), 12.8-13.2(1H, br s) TFA salt
67	372	6.0	3.2(3H, br s), 3.4(1H, br s), 5.2(1H, s), 7.5(3H, m), 7.6(4H, m), 7.8(2H, m), 8.1(2H, m), 8.6(1H, s), 9.6-9.9(1H, br s), 10.7(1H, s), 12.8-13.2(1H, br s) TFA salt
68	400	6.6	0.9-1.0(3H, m), 1.5-1.6(2H, m), 2.0(2H, m), 2.7-3.1(6H, m), 5.2(1H, br s), 7.4(1H, m), 7.6(5H, m), 7.7-7.8(1H, m), 8.1(2H, m), 8.4-8.6(2H, br s), 9.7-9.9(1H, br s), 12.9-13.1(1H, br s) TFA salt

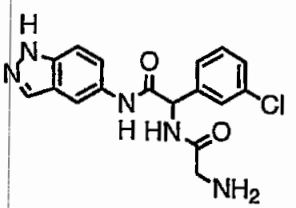
Example 7



({[(3-Chloro-phenyl)-(1*H*-indazol-5-ylcarbamoyl)-methyl]-carbamoyl}-methyl)-carbamic acid *tert*-butyl ester: To a solution of 2-amino-2-(3-chloro-phenyl)-*N*-(1*H*-indazol-5-yl)-acetamide (0.17 mmol) and *tert*-butoxycarbonylamino-acetic acid (0.17 mmol) in THF (2 mL) was added HOBt (0.18 mmol). The reaction mixture was cooled to 0°C and EDC (0.18 mmol) was added and the reaction mixture was left to stir overnight. The reaction mixture was then concentrated *in vacuo* and the residue was was partitioned between EtOAc and brine. The organic layer was washed with brine, dried over sodium

sulphate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc:hexanes (80:20) to give the title compound in 55% yield.

Example 8



I-74

2-(2-Amino-acetylamino)-2-(3-chloro-phenyl)-*N*-(1*H*-indazol-5-yl)-acetamide (I-74): To a solution of ({[(3-chloro-phenyl)-(1*H*-indazol-5-ylcarbamoyl)-methyl]-carbamoyl}-methyl)-carbamic acid *tert*-butyl ester (0.09 mmol) in dichloromethane (2.5 mL) at 0°C was added trifluoroacetic acid (2.5 mL) and the reaction mixture was stirred for 1 hour. The reaction mixture was concentrated *in vacuo* to afford compound the title compound (9 mg, 24%). ^{1}H NMR (400 MHz, DMSO-d6) δ 3.8(2H, m), 5.8(1H, m), 7.4-7.7(5H, m), 7.9-8.2(4H, m), 9.3-9.4(1H, m), 10.6(1H, s), 13.0(1H, br s); MS (ES+): m/e= 358.3(40%), 134.3(100%).

Example 9

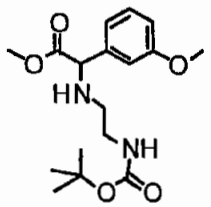
[00164] We have prepared other compounds of formula **I** by methods substantially similar to those described in Examples 7 and 8. The characterization data for these compounds is summarized in Table 4 below and includes HPLC, LC/MS (observed) and ^{1}H NMR data.

[00165] ^{1}H NMR data is summarized in Table 4 below wherein ^{1}H NMR data was obtained in at 400 MHz deuterated DMSO, unless otherwise indicated, and was found to be consistent with structure. Compound numbers correspond to the compound numbers listed in Table 1.

Table 4. Characterization Data for Selected Compounds of Formula 1

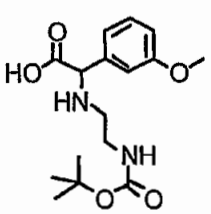
Compound No I-	M+1 (obs)	R_t(min)	^{1}H NMR
75	344, 346	7.22	2.3-2.4(2H, m), 2.8(2H, m), 3.7(1H, s), 7.3-7.6(6H, m), 8.0-8.2(2H, m), 8.8-9.0(1H, br s), 10.4(1H, m), 12.8-13.0(1H, br s)

Example 10



(2-*tert*-Butoxycarbonylamino-ethylamino)-(3-methoxy-phenyl)-acetic acid methyl ester: To a solution of (3-methoxy-phenyl)-acetic acid methyl ester (19.6 mmol) in CCl_4 was added *N*-bromosuccinimide (19.6 mmol) and the reaction mixture was irradiated for 2 hours. The reaction mixture was then concentrated *in vacuo* to afford the intermediate bromo-(3-methoxy-phenyl)-acetic acid methyl ester. To a solution of bromo-(3-methoxy-phenyl)-acetic acid methyl ester in THF (30 mL) under an atmosphere of nitrogen was added a solution of (2-amino-ethyl)-carbamic acid *tert*-butyl ester (20.6 mmol) in THF (20 mL) followed by K_2CO_3 (39.2 mmol, 2 equivalents). The reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was partitioned between water (50 mL) and EtOAc (2 x 50mL), the combined organics were dried (sodium sulfate) and concentrated *in vacuo* to afford an oil. The oil was purified by silica gel column chromatography using as eluent EtOAc:petrol (1:1) to give the title compound as an oil in 53% yield.

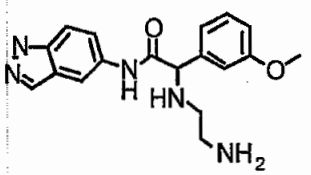
Example 11



(2-*tert*-Butoxycarbonylamino-ethylamino)-(3-methoxy-phenyl)-acetic acid: To a solution of (2-*tert*-butoxycarbonylamino-ethylamino)-(3-methoxy-phenyl)-acetic acid methyl ester (10.4 mmol) in THF:H_2O (3:1, 40 mL) was added LiOH (10.9 mmol) and

the reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was concentrated *in vacuo* then diluted with H_20 and neutralised with 2M HCl solution and the resulting precipitate was collected by filtration to afford the title compound in 46% yield.

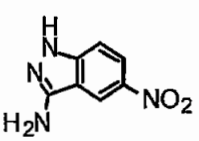
Example 12



I-1017

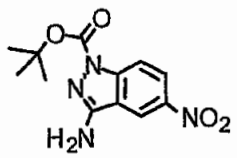
2-(2-Amino-ethylamino)-*N*-(1*H*-indazol-5-yl)-2-(3-methoxy-phenyl)-acetamide (I-1017): 5-Aminoindazole was coupled with (2-tert-butoxycarbonylamino-ethylamino)-(3-methoxy-phenyl)-acetic acid according to the method described in Example 1. The BOC protecting group was then removed according to the method described in Example 8 to afford compound **I-1017**. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.02-3.14 (4H, m), 3.80 (3H,s), 4-5 (1H, vbr s), 5.11 (1H, brs), 7.05 (1H,d), 7.20 (2H,m), 7.40 (2H,m), 7.52 (1H,d), 7.5-8 (2H, brs), 8.05 (1H,s), 8.07 (1H,s), 8.2-10.1 (1H, brs), 10.68 (1H,brs), 13.15 (1H,brs); MS (ES+): m/e= 340.

Example 13



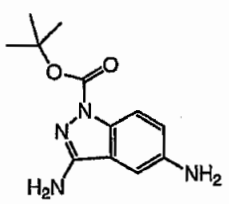
5-Nitro-1*H*-indazole-3-ylamine: Hydrazine monohydrate (17.5 mL, 362 mmol) was added to a hot (50°C) solution of 2-fluoro-5-nitrobenzonitrile (30g, 181 mmol) in EtOH (500 mL). The mixture was heated at reflux for 4 hours then allowed to cool to room temperature, whereupon the product precipitated from solution. The filtrate was concentrated and the residue partitioned between EtOAc and saturated ammonium chloride solution. The organic phase was separated, dried over magnesium sulfate and concentrated to obtain further product. The combined product (32.2g, quant.) was taken on to the following step without further purification.

Example 14



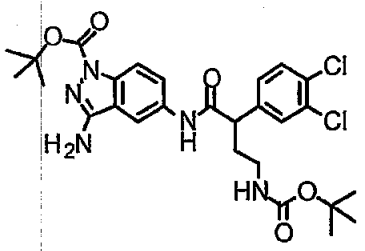
3-Amino-5-nitroindazole-1-carboxylic acid *tert*-butyl ester: Dimethylaminopyridine (4g, 36 mmol) was added to a solution of 5-nitro-1*H*-indazol-3-ylamine (32.2 g, 181 mmol), *tert*-butyldicarbonate (39.4 g, 181 mmol) and triethylamine (25 mL, 181 mmol) in THF (1 L) at room temperature under nitrogen. After stirring for 30 minutes, the reaction mixture was concentrated and the residue partitioned between EtOAc and saturated ammonium chloride solution. The layers were separated and the organic phase washed with brine, dried ($MgSO_4$), and concentrated to an orange solid. Recrystallisation from ethyl acetate provided the title product as a yellow solid (25g, 50%). ^{1}H NMR (400 MHz, DMSO) 1.60 (9H, s), 6.75 (2H, brs), 8.10 (1H, d), 8.36 (1H, d), 8.96 (1H, s); MS (ES-) m/e=277.

Example 15



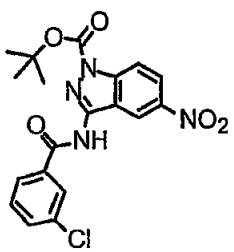
3,5-Diamino-indazole-1-carboxylic acid *tert*-butyl ester: 3-Amino-5-nitroindazole-1-carboxylic acid *tert*-butyl ester (3g, 10.8 mmol) was dissolved in MeOH (50 mL) and the solution degassed (3x alternating vacuum/nitrogen purges). Palladium on charcoal 10% w/w (300 mg) was added and the nitrogen atmosphere replace by hydrogen. After 3 hours, the mixture was filtered through a pad of Celite® and the filtrate concentrated to afford the title compound as a highly viscous oil (2.17g, 81%). ^{1}H NMR (400 MHz, DMSO)1.55 (9H, s), 5.07 (2H, brs), 6.04 (2H, brs), 6.79-6.82 (2H, m), 7.62 (1H, brs). MS (ES+) m/e=249.

Example 16



3-Amino-5-[4-*tert*-butoxycarbonylamino-2-(3,4-dichloro-phenyl)-butyrylamino]-indazole-1-carboxylic acid *tert*-butyl ester: To a stirred solution of 3,5-diamino-indazole-1-carboxylic acid *tert*-butylester (2.17g, 8.75 mmol), PyBroP (4.1 g, 8.75 mmol) and 4-*tert*-butoxycarbonylamino-2-(3,4-dichloro-phenyl)-butyric acid (3g, 8.75 mmol) in dichloromethane (100 mL) was added diisopropylethylamine (3.0 mL, 17.5 mmol) at 0°C. The resulting mixture was allowed to warm to room temperature over 4 hours then was concentrated and the residue partitioned between EtOAc and ammonium chloride (saturated, aqueous). The organic phase was separated and washed with sodium bicarbonate (saturated, aqueous), then dried (sodium sulfate) and concentrated to a brown foam. Purification by column chromatography (silica, 20% petroleum ether-EtOAc gave the title compound as a light brown solid (2.92g, 58%); ^{1}H NMR (400 MHz, DMSO) 1.36 (9H, s), 1.56 (9H, s), 1.80-1.90 (1H, m), 2.10-2.20 (1H, m), 2.89 (2H, m), 6.29 (2H, brs), 6.87 (1H, t), 7.38 (1H, d), 7.45 (1H, d), 7.61-7.65 (2H, m), 7.90 (1H, m), 8.19 (1H, s), 10.30 (1H, s); MS (ES+) m/e=578.

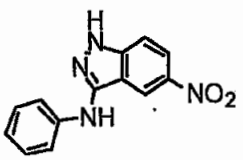
Example 17



3-(3-Chlorobenzoylamino)-5-nitroindazole-1-carboxylic acid *tert*-butyl ester: 3-Amino-5-nitroindazole-1-carboxylic acid *tert*-butyl ester (600 mg, 2 mmol) was dissolved in dry pyridine (15 mL) under nitrogen. The solution was cooled on an ice bath and 3-chlorobenzoyl chloride (0.3 mL, 2 mmol) added. After 6 hours, the mixture was diluted with EtOAc, washed with 1M hydrochloric acid solution (x3) and brine then dried over magnesium sulfate and concentrated to a solid. Purification by column

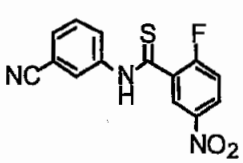
chromatography (silica, 7:3 petrol-EtOAc) afforded the title compound as a solid (300 mg, 39%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.77 (9H, s), 7.52 (1H, t), 7.62 (1H, d), 7.90 (1H, d), 8.07 (1H, m), 8.32 (1H, d), 8.45 (1H, d), 9.22 (1H, brs), 9.32 (1H, s); MS (ES+) m/e=417.

Example 18



(5-Nitro-1*H*-indazol-3-yl)-phenylamine: 2-Fluoro-5-nitro-*N*-phenyl benzamide (100mg, 0.38 mmol) was suspended in EtOH (10 mL) and the mixture heated to 50°C. To the resulting solution was added hydrazine monohydrate (0.1 mL, 1.9 mmol). The mixture was heated at reflux for 30 minutes, at which time LC-MS showed complete conversion to the aryl hydrazine (ES+ m/e= 273). The mixture was allowed to cool to room temperature, concentrated and the residue partitioned between EtOAc and saturated ammonium chloride solution. The layers were separated and the organic phase was dried over sodium sulfate and concentrated to a yellow foam. The residue was dissolved in phosphorous oxychloride (5 mL) and the mixture heated at 90°C for 30 minutes, then allowed to cool to room temperature and stirred overnight. The reaction mixture was concentrated and the residue partitioned between EtOAc and saturated sodium bicarbonate. The organic phase was dried over sodium sulfate and concentrated to afford the title compound as a red solid (80 mg, 83%); ^{1}H NMR (400 MHz, DMSO) 6.88 (1H, t), 7.31 (2H, t), 7.51 (1H, d), 7.74 (2H, t), 8.17 (1H, dd), 9.24 (1H, s), 9.42 (1H, s), 12.74 (1H, s); MS (ES+) m/e=255.

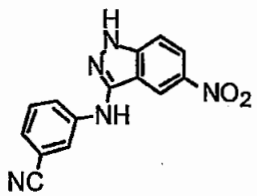
Example 19



***N*-(3-Cyano-phenyl)-2-fluoro-5-nitro-thiobenzamide:** To a solution of N-(3-Cyano-phenyl)-2-fluoro-5-nitro-benzamide (10.0g; 0.035 mol) in toluene (100mL) was added Lawson's reagent (7.84g; 0.019 mol) and the solution refluxed for 16 hours. The reaction

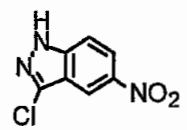
mixture was concentrated *in vacuo* and purified by flash chromatography, eluting with 30% ethyl actetate/ petroleum ether to afford the title compound as a yellow solid (8.56g; 81%). ^{1}H NMR (400MHz, CDCl3) δ_H 7.60-7.75 (2H, m), 7.80 (1H, m), 8.15 (1H, d), 8.40-8.50 (1H, m), 8.50 (1H, s), 8.50-8.55 (1H, m), 12.45 (1H, br). Mass Spectrum (ES-) m/e= 300.22.

Example 20



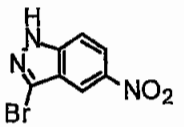
3-(5-Nitro-1*H*-indazol-3-ylamino)-benzonitrile: To a solution of *N*-(3-Cyano-phenyl)-2-fluoro-5-nitro-thiobenzamide (8.56g; 0.028 mol) in *n*-butanol (300mL) was added hydrazine hydrate (2.54 mL; 0.053 mol) and the solution refluxed for 3 hours. The reaction mixture was concentrated *in vacuo* and triturated with hot ethanol to afford the title compound as a red solid (4.93g; 62%). ^{1}H NMR (400MHz, DMSO-d6) δ_H 7.30 (1H, d), 7.45-7.60 (2H, m), 7.90 (1H, d), 8.20 (1H, d), 8.25 (1H, s), 9.20 (1H, s), 9.85 (1H, s). Mass Spectrum (ES-) m/e= 278.28.

Example 21



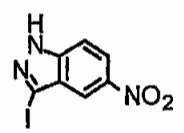
3-Chloro-5-nitroindazole: 5-Nitroindazole (5g, 30.7 mmol) was suspended in glacial AcOH (150 mL) and the mixture heated to 50°C. *N*-Chlorosuccinimide (4.9g, 36.8 mmol) was added and the mixture heated at relux (solution forms) for 1hour. The reaction mixture was concentrated and partitioned between EtOAc and brine. The organic phase was washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated to a yellow solid. Recrystallisation from EtOH provided the title compound as a pale yellow solid (2.63g, 43%); ^{1}H NMR (400 MHz, DMSO) δ 7.73 (1H, d), 8.21 (1H, dd), 8.51 (1H, d), 13.97 (1H, brs); MS (ES-) m/e=196.

Example 22



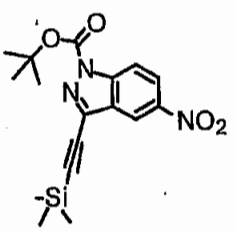
3-Bromo-5-nitroindazole: 5-Nitroindazole (10 g, 61.3 mmol) was dissolved in acetic acid (170 mL) and the mixture heated to 80°C. Bromine (3.1 mL, 60.7 mmol) was added slowly and the mixture heated to reflux. After 2 hours, the reaction mixture was allowed to cool to room temperature, and the resulting precipitate filtered off. Additional product was isolated by concentrating the filtrate, partitioning the residue between chloroform and saturated sodium bicarbonate solution, separating and drying the organic phase over sodium sulfate. Concentration gave a solid which was combined with the original precipitate to give the title compound as a yellow solid (11.4g, 77%). ^{1}H NMR δ 7.74 (1H, d), 8.21 (1H, dd), 8.40 (1H, d), 14.06 (1H, brs); MS (ES-) m/e=240.

Example 23



3-iodo-5-nitro-1*H*-indazole: To a solution of 5-nitro-1*H*-indazole (10.0g, 62.3 mmol) in DMF (120 ml) was added potassium hydroxide (12.9g, 230.4 mmol) followed by iodine (31.1g, 122.6 mmol) portion wise over 5 minutes. The resulting mixture was stirred at room temperature for 14 hours and then poured onto 10% sodium metabisulfite (100 ml) and extracted into ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compounds as a pale orange solid (17.5 g). ^{1}H NMR (400MHz, DMSO-d6) δ 7.77 (1H, d), 8.26 (1H, d), 8.34 (1H, s), 14.15 (1H, s). MS (ES+) m/e = 290.

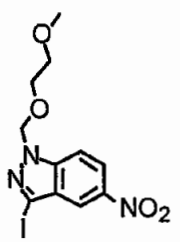
Example 24



5-Nitro-3-(trimethylsilylethynyl)-indazole-1 carboxylic acid *tert*-butyl ester:

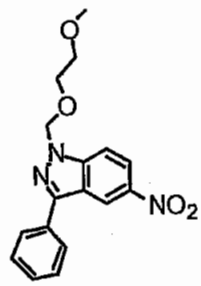
3-Bromo-5-nitro-indazole-1-carboxylic acid *tert*-butyl ester (2g, 5.8 mmol) was dissolved in dry DMF (30 mL) under nitrogen and triethylamine (1.6 mL, 1.6 mmol) added. Copper iodide (20 mg, 0.12 mmol), trimethylsilylacetylene (2.5 mL, 17.4 mmol) palladium bis-triphenylphosphine dichloride (84 mg, 0.12 mmol) and a further 1.6 mL of triethylamine were added and the mixture heated at 50°C overnight. The reaction mixture was allowed to cool to room temperature and concentrated. The residue was taken up in EtOAc and filtered through a plug of Celite®. The filtrate was washed with saturated ammonium chloride solution and dried over sodium sulfate then concentrated to a black foam. Purification by chromatography (silica, 1:1 petrol-EtOAc) gave the title compound as a black solid (940 mg, 45%); MS (ES+) m/e=360.

Example 25



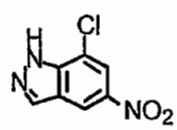
3-iodo-1-(2-methoxyethoxymethyl)-5-nitro-1*H*-indazole: To a solution of 3-iodo-5-nitro-1*H*-indazole (10.0g, 34.6 mmol) in THF (50 ml) was added sodium bis(trimethylsilyl)amide (1M in THF, 48.4 mmol, 48.4 ml) and the solution stirred at room temperature for 20 minutes. 2-methoxyethoxymethyl chloride (4.9g, 39.1 mmol, 4.5 ml) was added and the solution stirred at room temperature for 15 hours. The reaction was quenched with ammonium chloride (30 ml, saturated aqueous) and extracted into ethyl acetate (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (1:1 EtOAc:hexanes) to give the title compound as an orange solid (6.0g). ^{1}H NMR (400MHz, $CDCl_3$) δ 3.35 (3H, s), 3.50 – 3.52 (2H, m), 3.68 – 3.70 (2H, m), 5.86 (1H, s), 7.69 (1H, d), 8.38 (1H, d), 8.53 (1H, s). MS (ES+) m/e = 378.

Example 26



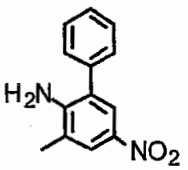
3-iodo-1-(2-methoxyethoxymethyl)-5-nitro-3-phenyl-1*H*-indazole: To a mixture of 3-iodo-1-(2-methoxyethoxymethyl)-5-nitro-1*H*-indazole (0.50g, 1.32 mmol), phenyl boronic acid (0.22 g, 1.80 mmol), potassium phosphate (1.26 g, 5.94 mmol) and 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II), complex with dichloromethane (0.15g, 0.18 mmol) was added dry dimethoxyethane (8.0 ml) and then heated at 85 °C for 18 hours. Ammonium chloride solution (30 ml, saturated aqueous) was added and extracted into ethyl acetate (3 x 30 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (3% MeOH in DCM) to afford the title compound as a yellow solid (0.35g, 81%). ^{1}H NMR (400MHz, $CDCl_3$) δ 3.37 (3H, s), 3.51 – 3.53 (2H, m), 3.73 – 3.75 (2H, m), 5.93 (1H, s), 7.50 – 7.54 (1H, m), 7.57 – 7.61 (2H, m), 7.73 (1H, d), 7.98 (2H, dd), 8.37 (1H, dd), 9.00 (1H, s).

Example 27



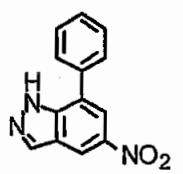
7-Chloro-5-nitro-1*H*-indazole: To a solution of 2-chloro-6-methyl-4-nitroaniline (5.49g, 29.4 mmole) in acetic acid (150mL) was added sodium nitrite (2.03g, 29.4 mmole) pre-dissolved in water (5mL). The resulting brown slurry was stirred overnight at room temperature, then at 60°C for a further 4 hours. The bulk of the solvent was removed by evaporation *in-vacuo* and the resulting black residue re-dissolved in EtOAc (100mL) and washed in brine (2x70mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give a mixture of starting material and product 91mg(1.49g). The crude mixture was taken through to the next step; ^{1}H NMR (400MHz, DMSO) δ 8.25(1H, s), 8.50(1H, s), 8.85(1H, s), 14.30(1H, br s).MS (ES+): m/e=198 (minus Boc).

Example 28



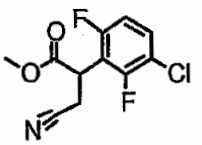
3-Methyl-5-nitro-biphenyl-2-ylamine: A mixture of 2-bromo-6-methyl-4-nitroaniline (100mg, 0.43mmole), phenyl boronic acid (81mg, 0.66mmole), 2M $Na_2CO_{3(aq)}$ (660µL), $Pd(PPh_3)_4$ (4mg, 0.0033mmole) in DME(2.4mL) containing 1.0:1.3 EtOH/H_2O (1.4mL) was placed in a microwave tube and degassed for 5 minutes. The tube was then capped and irradiated with microwaves (CEM Discover) for 20 minutes at 110 °C. The crude reaction mixture was diluted with dichloromethane (10mL) and washed with saturated $NaHCO_3$ solution (3x20mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in-vacuo* to afford a crude solid, this was then purified further by flash chromatography (100% dichloromethane) to yield the desired pure (91mg) as a bright yellow solid.. ^{1}H NMR (400MHz, CDCl3) δ 2.25(3H, s), 4.42(2H, br s), 7.39(3H, m), 7.50(2H, m), 7.97(1H, s), 8.12(1H, s). MS (ES+): m/e=229, (ES-): m/e=227.

Example 29



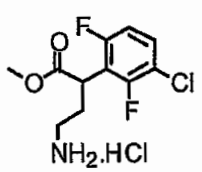
5-Nitro-7-phenyl-1*H*-indazole: To a solution of 3-Methyl-5-nitro-biphenyl-2-ylamine (91mg, 0.39mmole) in pre-heated glacial acetic acid (4mL) was added 0.44M sodium nitrite solution (1mL), in a dropwise fashion. The resulting mixture was stirred overnight at room temperature. The crude product was concentrated *in-vacuo* and the residue re-dissolved in EtOAc (20mL) and washed with saturated $NaHCO_3$ (2x20mL) and brine (1x20mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in-vacuo* to yield the desired product (67mg) as a yellow powder. ^{1}H NMR (400MHz, CDCl3) δ 7.50(1H, m), 7.58(2H, m), 7.69(2H, m), 8.33(2H, m), 8.75(1H, s), 10.55(br s). MS (ES+): m/e=240, (ES-): m/e=238.

Example 30



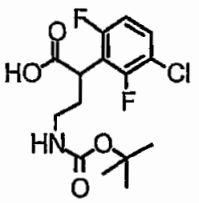
2-(3-Chloro-2,6-difluorophenyl)-3-cyanopropionic acid methyl ester: Butyllithium (4.1 mL of 2.5M solution in hexanes,10.3 mmol) was added to a solution of diisopropylamine (1.4 mL, 10.3 mmol) in THF (15 mL) under nitrogen at 0°C. After 15 minutes the reaction mixture was cooled to –78°C and a solution of 3-chloro-2,6-difluorophenylacetic acid methyl ester (2.15 g, 9.8 mmol) in THF (15mL) was added. After 30 minutes, iodoacetonitrile (3.5 mL, 49 mmol) was added rapidly to the reaction mixture. The reaction mixture was allowed to warm to 0°C and ammonium chloride solution added (10 mL, saturated aqueous). The reaction mixture was concentrated and the residue partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc and the combined organics were dried over magnesium sulfate then concentrated to afford a black oil. The crude product was purified by column chromatography (silica, 25%EtOAc-petrol to EtOAc) to afford the title compound as a pale yellow oil (1.51g, 59%); ^{1}H NMR (400 MHz, DMSO) δ 3.06 (1H, dd), 3.19 (1H, dd), 3.67 (3H, s), 4.64 (1H, dd), 7.29 (1H, t), 7.70 (1H, m).

Example 31



4-Amino-2-(3-chloro-2,6-difluorophenyl)-butyric acid methyl ester hydrochloride: To a solution of 2-(3-Chloro-2,6-difluorophenyl)-3-cyanopropionic acid methyl ester (784mg, 3.0 mmol) and concentrated hydrochloric acid (0.63 mL, 7.55 mmol) in MeOH (5 mL) was added platinum dioxide (69 mg, 0.3 mmol) under nitrogen. The reaction mixture was degassed (5x vacuum cycles) and the nitrogen atmosphere replaced with hydrogen (5x vacuum cycles). The mixture was stirred for 3.5 hours, then filtered through a pad of Celite®, washing with MeOH. The filtrate was concentrated and used in the next step without further purification.

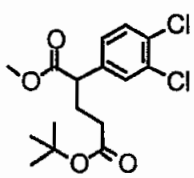
Example 32



4-*tert*-Butylcarbonylamino-2-(3-chloro-2,6-difluorophenyl)-butyric acid:

4-Amino-2-(3-chloro-2,6-difluorophenyl)-butyric acid methyl ester hydrochloride (685 mg, 2.28 mmol) was dissolved in 8M hydrochloric acid solution (10 mL) and the mixture heated at reflux overnight. The mixture was allowed to cool to room temperature, then concentrated. The residue was dissolved in a solution of sodium bicarbonate (1.2g, 11.4 mmol) in water (15 mL) and THF added (15 mL). The mixture was cooled to 0°C and di-*tert*-butyldicarbonate (648 mg, 2.97 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 5.5 hours, then concentrated. After dilution with water, the mixture was extracted with ether, then the aqueous phase acidified to pH 4.5 using 2M HCl. The acidified aqueous phase was extracted with EtOAc (x3) and the combined extracts dried (magnesium sulfate) and concentrated. The residue was purified by chromatography (silica, 5% MeOH-DCM) to afford the title compound as a wax (512mg, 65% two steps); MS (ES-) m/e=348.

Example 33

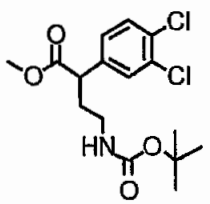


2-(2,4-Dichlorophenyl)-pentanedioic acid 5-*tert*-butyl ester 1-methyl ester:

Potassium *tert*-butoxide (767 mg, 6.85 mmol) was added to a solution of methyl 3,4-dichlorophenylacetate (15g, 68 mmol) in THF (100 mL) at 0°C under nitrogen. After 15 minutes, the resulting yellow solution was cooled to –78°C and *tert*-butylacrylate (11.0 mL, 75 mmol) added over 10 minutes. The reaction mixture was allowed to reach room temperature and stirred overnight. The mixture was concentrated and partitioned between EtOAc and saturated ammonium chloride solution. The aqueous phase was extracted with EtOAc and the combined organics washed with brine, dried (magnesium sulfate) and

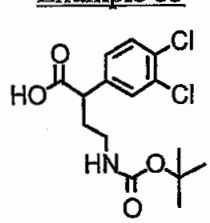
concentrated to a yellow oil. Purification by column chromatography (silica, 5% ether-petrol) gave the title compound as a pale yellow oil (15.5g, 65%).

Example 34



4-*tert*-Butoxycarbonylamino-2-(3,4-dichlorophenyl)-butyric acid methyl ester: 2-(2,4-Dichlorophenyl)-pentanedioic acid 5-*tert*-butyl ester 1-methyl ester (13g, 45 mmol) was dissolved in toluene (130 mL) at 0°C under nitrogen. Diphenylphosphoryl azide (10.6 mL, 49 mmol) and triethylamine (6.8 mL, 49 mmol) were added and the mixture allowed to warm to room temperature over 3 hours. After a further 2 hours, the reaction mixture was concentrated and the residue taken up in EtOAc. The organic phase was washed with 1w/w% citric acid solution and brine then dried over magnesium sulfate. Concentration at 30°C gave the acyl azide as a yellow oil which was immediately dissolved in *tert*-butanol (130 mL) at room temperature. Tin tetrachloride (0.31 mL, 2.68 mmol) was added and the mixture heated at 80°C for 45 minutes, during which time nitrogen gas was evolved. Upon cooling to room temperature, saturated sodium bicarbonate solution (30 mL) was added and the reaction mixture concentrated. The residue was extracted EtOAc (x3) and the combined extracts washed with brine, dried over magnesium sulfate and concentrated to a yellow oil. Purification by column chromatography (silica, 20% EtOAc-petrol) gave the title compound as a colourless oil (12.8g, 79%); MS (ES-) m/e=360.

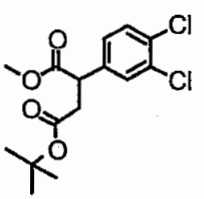
Example 35



4-*tert*-Butoxycarbonylamino-2-(3,4-dichlorophenyl)-butyric acid: To a solution of 4-*tert*-butoxycarbonylamino-2-(3,4-dichlorophenyl)-butyric acid methyl ester (12.3g, 34 mmol) in THF (80 mL)/water (20 mL) was added lithium hydroxide (1.63 g, 68 mmol) at

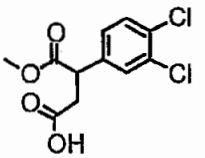
0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated and the residue diluted with water. After extraction with EtOAc, the aqueous phase was acidified to pH 5 by the addition of 2M aqueous hydrochloric acid solution. The aqueous phase was extracted with EtOAc and the extracts dried over magnesium sulfate. Concentration gave the title compound as a pale brown foam (11.54g, 98%); ^{1}H NMR (400 MHz, DMSO) δ 1.35 (9H, s), 1.74-1.81 (1H, m), 2.03-2.10 (1H, m), 2.81 (2H, m), 3.61 (1H, t), 6.86 (1H, m), 7.28 (1H, dd), 7.54 (1H, dd), 7.59 (1H, d), 12.60 (1H, brs); MS (ES-) m/e=346.

Example 36



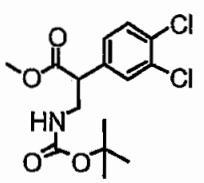
(3,4-Dichloro-phenyl)-succinic acid 4-*tert*-butyl ester 1-methyl ester : 2.5M ^{n}Butyllithium in hexanes (37.5 ml, 0.094 mol) was added, in a dropwise fashion, to a solution of diisopropylamine (14.45 ml, 0.103 mol) in tetrahydrofuran (300 ml) at 0°C. The solution was stirred at 0°C for 20 minutes. The mixture was then cooled to –70°C and a solution of (3,4-dichloro-phenyl)-acetic acid methyl ester (20.54 g, 0.094 mol) in tetrahydrofuran (50 ml) was added dropwise *via* cannula. The reaction mixture was stirred at –70°C for 30 minutes. After this time, *tert*-butyl bromoacetate (45.42 ml, 0.281 mol) was added in a dropwise fashion. The cooling bath was removed and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (100 ml). THF was partially removed *in vacuo* and the mixture was extracted with EtOAc (3 x 200 ml). The combined organic extrats were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography using as eluent petrol : ether (9:1) to give the title compound in 92% yield.). ^{1}H NMR (400 MHz, DMSO-d6) δ 1.34 (9H, s), 2.65 (1H, dd), 2.98 (1H, dd), 3.60 (3H, s), 4.08 (1H, m), 7.31 (1H, m), 7.58-7.62 (2H, m); MS (ES^+) : m/e = 333.2 (5%); MS (ES^-) : m/e = 331.2 (100%), 333.2 (65%), 335.2 (10%).

Example 37



2-(3,4-Dichloro-phenyl)-succinic acid 1-methyl ester : Trifluoroacetic acid (100 ml) was added to a mixture of 2-(3,4-dichloro-phenyl)-succinic acid 4-*tert*-butyl ester 1-methyl ester (23.64 g, 0.071 mol) and dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 3 hours then concentrated *in vacuo*. The crude mixture was kept under *vacuo* for several hours before being used without further purification in the next step.). ^{1}H NMR (400 MHz, DMSO-d6) δ 2.66 (1H, dd), 3.01 (1H, dd), 3.59 (3H, s), 4.08 (1H, m), 7.30 (1H, m), 7.56-7.61 (2H, m); MS (ES^+) : m/e = 277.1 (100%), 279.1 (65%), 281.0 (10%); MS (ES^-) : m/e = 275.1 (50%), 277.1 (30%), 279.1 (5%).

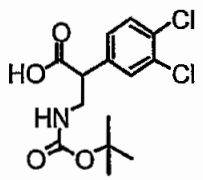
Example 38



3-*tert*-Butoxycarbonylamino-2-(3,4-dichloro-phenyl)-propionic acid methyl ester : To a solution of 2-(3,4-dichloro-phenyl)-succinic acid 1-methyl ester (0.071 mol) in toluene (200 ml) at 0°C were successively added diphenylphosphoryl azide (16.82 ml, 0.078 mol) and triethylamine (14.83 ml, 0.106 mol). The mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with 1% citric acid (100 ml) and extracted with EtOAc (3 x 150 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was dissolved in *tert*-butanol (200 ml). Tin(IV) chloride (0.5 ml, 0.004 mol) was added and the mixture was heated to 80°C for 1 hour (N_2 evolving). The reaction mixture was cooled down to room temperature, quenched with a saturated solution of $NaHCO_3$. *Tert*-Butanol was removed in vacuo and the mixture was extracted with EtOAc (3x 150 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography using as eluent petrol : EtOAc (9 : 1) to give the title compound (17.35 g) in 70% yield.). ^{1}H NMR (400 MHz, DMSO-d6) δ 1.31

(9H, s), 3.25-3.40 (1H, m), 3.41-3.52 (1H, m), 3.61 (3H, s), 3.90 (1H, t), 6.95 (1H, t), 7.26 (1H, m); 7.52 (1H, s), 7.60 (1H, d); MS (ES^+) : m/e = 348.2 (7%); MS (ES^-) : m/e = 457.2 (100%), 459.2 (70%), 461.2 (15%).

Example 39



3-*tert*-Butoxycarbonylamino-2-(3,4-dichloro-phenyl)-propionic acid : To 3-*tert*-Butoxycarbonylamino-2-(3,4-dichloro-phenyl)-propionic acid methyl ester (17.11 g, 0.049 mol) in tetrahydrofuran-water (200 ml of each) was added lithium hydroxide (1.18 g, 0.049 mol). The reaction mixture was stirred at room temperature for 6 hours. THF was removed *in vacuo* and the pH was adjusted to pH 4 with 2M hydrochloric acid. The aqueous phase was extracted with EtOAc (3x 100 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The title compound was obtained as a foam in 89% yield (14.67 g). ^1H NMR (400 MHz, DMSO-d6) δ 1.30 (9H, s), 3.22-3.35 (1H, m), 3.35-3.50 (1H, m), 3.76 (1H, t), 6.84 (1H, t), 7.24 (1H, m); 7.48 (1H, s), 7.58 (1H, d), 12.85 (1H, s); MS (ES^+) : m/e = 334.2 (8%); MS (ES^-) : m/e = 332.2 (100%), 334.1 (65%), 336.1 (10%).

Example 40

[00166] We have prepared other compounds of formula **I** by methods substantially similar to those described in Examples 1 through 39. The characterization data for these compounds is summarized in Table 5 below and includes HPLC, LC/MS (observed) and ^1H NMR data.

[00167] ^1H NMR data is summarized in Table 5 below wherein ^1H NMR data was obtained at 400 MHz in deuterated DMSO, unless otherwise indicated, and was found to be consistent with structure. Compound numbers correspond to the compound numbers listed in Table 1.

Table 5. Characterization Data for Selected Compounds of Formula I

Compound No	M+1 (obs)	R_t(min)	^{1}H NMR
69	376	6.56	2.9-3.3(4H, m), 4.8(1H, br s), 7.45-7.50(1H, m), 7.55-7.65 (2H, m), 7.70-7.75(1H, d), 7.80(1H, s), 7.90-7.95(3H, m), 8.08(1H, s), 8.1(1H, s), 10.6-10.7(1H, br s), 13.0-13.2(1H, br s) TFA salt
70	344	5.88	3.1-3.3(4H, m), 5.2(1H, br s), 7.3-7.4(2H, m), 7.6-7.7(2H, s), 7.7-7.9 (2H, br s), 8.15-8.2 (2H, d), 9.7-10.0(1H, br s), 10.6-10.7(1H, br s), 13.1-13.3(1H, br s) TFA salt
71	374	5.68	2.99 (1H, brs), 3.11 (3H, brs), 3.88 (3H,s), 5.09 (1H, brs), 7.29 (1H,d), 7.38 (1H,d), 7.53 (2H,m), 7.69, (1H,s), 7.85 (3H, brs), 8.06 (1H,s), 8.09 (1H,s), 9.75 (1H, v brs), 10.69 (1H, brs), 13.08 (1H, brs) TFA salt
72	436	7.31	3.1-3.3(4H, m), 5.2(1H, br s), 7.0-7.1(2H, m), 7.15-7.30(2H, m), 7.40-7.50 (2H, m), 7.52-7.60 (2H, m), 7.80(1H, s), 8.0-8.1(3H, m), 8.08(1H, s), 8.1(1H, s), 8.17(1H, s), 10.6-10.7(1H, br s), 13.0-13.2(1H, br s) TFA salt
73	360	6.28	3.1-3.3(4H, m), 5.3(1H, br s), 7.3-7.7(8H, m), 8.0-8.1(3H, m), 8.08(1H, s), 8.1(2H, m), 8.17(1H, s), 9.6-9.8(2H, br s), 10.7-10.8(1H, br s), 13.0-13.2(1H, br s) TFA salt

Example 41

[00168] We have prepared other compounds of formula **I** by methods substantially similar to those described in Examples 1 through 39 and by the general synthetic Schemes I-XV. The characterization data for these compounds is summarized in Table 6 below and includes HPLC, LC/MS (observed), IR, and ^{1}H NMR data.

[00169] ^{1}H NMR data is summarized in Table 6 below wherein ^{1}H NMR data was obtained at 400 MHz in deuterated DMSO, unless otherwise indicated, and was found to be consistent with structure. Compound numbers correspond to the compound numbers listed in Table 1.

Table 6. Characterization data for Selected Compounds of Formula I

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
97	317	6.0	1.2-2.0(2H, br s), 2.8-2.9(1H, m), 3.2-3.3(1H, m), 3.7-3.8(1H, m), 7.2-7.6(6H, m), 8.0-8.2(2H, m), 10.0-10.3(1H, br s), 12.8-13.1(1H, br s)	1648.3
98	296	5.2	1.3(1H, m), 1.8-1.9(1H, m), 2.1-2.2(1H, m), 2.6-2.9(1H, m), 3.7-3.9(1H, m), 7.2-7.5(7H, m), 7.9-8.0(1H, s), 8.0-8.1(1H, s), 10.0-10.1(1H, m), 12.9-13.1(1H, br s)	1655.1
99		6.8	1.7-2.4(2H, br s), 2.8(1H, m), 3.3(1H, m), 3.7-3.8(1H, m), 7.3-7.5(3H, m), 7.6-7.7(2H, m), 8.0(1H, s), 8.2(1H, s), 10.1-10.3(1H, br s), 12.8-13.1(1H, br s)	1646.6
100	331	5.9	1.7-1.8(1H, m), 2.0-2.3(1H, m), 2.5-2.6(2H, m), 3.9(1H, m), 7.2-7.6(6H, m), 8.0(1H, s), 8.1(1H, s), 10.0-10.3(1H, br m), 12.6-13.2(1H, br s)	1646.1
101	347	5.84	1.94-2.00 (1H,m), 2,28-2.32 (1H,m), 2.76-2.85 (2H, m), 4.12 (1H,t), 7.27 (1H,t), 7.36-7.53 (3H,m), 7.55 (1H,t), 7.74 (3H, brs), 8.02 (1Hs), 8.11 (1H,s), 10.19 (1H,s), 13.05 (1H, brs)	3291, 1671, 1509, 1458, 1200, 1136, 837, 799, 722
102	345	6.4	1.6-2.2(2H, br m), 1.8-2.0(1H, m), 2.2-2.3(1H, m), 2.6(2H, m), 4.0-4.1(1H, m), 7.3-8.2(1H, m), 10.1-10.2(1H, br s), 12.6-1.32(1H, br s)	1651
103	382	6.7	1.8-2.0(1H, m), 2.1-2.3(1H, m), 2.4-2.5(2H, m), 4.0(1H, m), 7.4-7.6(3H, m), 7.7-7.9(2H, m), 8.0-8.2(2H, m), 10.1-10.3(1H, br s), 12.6-13.4(1H, br s)	1655
104	364	6.4	1.7-1.9(1H, m), 2.1-2.3(1H, m), 2.4-3.6(2H, m), 4.0(1H, m), 7.4-7.8(6H, m), 7.9-8.1(2H, m), 10.1-10.3(1H, br s), 12.8-13.2(1H, br s)	1655
105	429	7.52	2.01-2.14 (1H, m), 2.30-2.42 (1H, m), 2.60-3.73 (1H, m), 2.75-2.86 (1H, m), 4.08 (1H, t), 7.37 (1H, d), 7.48 (1H, d), 8.01 (1H, s), 8.05-8.15 (4H, m), 10.38 (1H, s), 13.03 (1H, br s)	3279, 3045, 1681, 1647, 1550, 1447, 1380, 1306, 1277, 1181, 1141, 1125, 947, 898, 872, 845.
106	363	6.2	1.7-1.9(1H, m), 2.1-2.3(1H, m), 2.6-2.7(2H, m), 3.0-3.2(1H, m), 4.2-4.4(1H, m), 7.3-7.6(5H, m), 7.9-8.2(2H, m), 10.0-10.4(1H, br m), 12.8-13.2(1H, br s)	1648
107	308	4.24	1.80-1.95 (1H, m), 2.12-2.25 (1H, m), 2.60-2.80 (2H, m), 3.57 (1H, t), 5.11 (2H, s), 6.44 (1H, m), 6.54 (1H, d), 6.59 (1H, s), 6.80-7.20 (3H, m), 7.35-7.50 (2H, m), 8.00 (1H, s), 8.13 (1H, s), 10.01 (1H, s), 12.98 (1H, br s)	670, 1599, 1558, 1539, 1504, 1201, 1135, 847, 837, 801.
108	339	5.89	1.87-2.05 (1H, m), 2.22-2.35 (1H, m), 2.60-2.85 (2H, m), 3.72 (1H, t), 6.95-7.50 (7H, m), 7.71 (3H, br s), 8.01 (1H, s), 8.11 (1H, m), 8.00 (1H, s), 10.13 (1H, s), 13.00 (1H, br s) TFA salt	3263, 3056, 2918, 1669, 1590, 1509, 1475, 1436, 1377, 1197, 1136, 949, 879, 841.

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
109	363	5.61	1.82-1.95 (1H, m), 2.30-2.80 (3H, m), 4.10-4.23 (1H, m), 7.15-7.25 (1H, m), 7.30-7.40 (1H, m), 7.46 (1H, d), 7.55-7.68 (1H, m), 8.00-8.05 (2H, m), 9.98 (1H, br s), 12.99 (1H, br s)	3258, 2942, 1672, 1597, 1557, 1507, 1473, 1443, 1313, 1276, 1201, 1134, 1010, 946, 877, 834, 804.
110	375	6.01	1.95-2.10 (1H, m), 2.40-2.50 (1H, m), 2.70-2.90 (2H, m), 4.06-4.10 (1H, m), 7.14 (1H, t, J 8.0 Hz), 7.30-7.43 (3H, m), 7.57 (1H, s), 7.83 (1H, s), 8.19 (1H, s), 10.12 (1H, s), 12.29 (1H, br).	1672.2, 1508.3, 1201.4, 1136.1
111	352	4.43	1.40-2.90 (9H, m), 3.70 (1H, t), 7.00-8.10 (8H, m), 9.90-10.15 (2H, m), 12.90-13.00 (1H, m)	3254, 2958, 2931, 2863, 1727, 1670, 1648, 1605, 1557, 1506, 1489, 1442, 1377, 1273, 1228, 1200, 1178, 1131, 1070, 997, 946, 881, 830
112	309	5.68	($CDCl_3$) 1.91-2.01 (1H, m), 2.22-2.32 (1H, m), 2.31 (3H, s), 2.62-2.78 (2H, m), 3.75 (1H, t, J 7.2 Hz), 7.08-7.10 (1H, m), 7.20-7.27 (3H, m), 7.38-7.47 (2H, m), 8.00 (1H, s), 8.12 (1H, s), 10.10 (1H, br), 12.97 (1H, br)	1673.4, 1507.4, 1201.6, 1137.97
113	325	5.33	1.78-1.90 (1H, m), 2.08-2-20 (1H, m), 2.60-2.74 (2H, m), 3.85 (3H, s), 4.10-4.19 (1H, m), 4.95 (2H, br hump), 6.85 (1H, t), 7.05 (1H, d), 7.29 (1H, t), 7.36-7.50 (3H, m), 8.00 (1H, s), 8.12 (1H, s), 9.95 (1H, s), 13.00 (1H, br s)	1673, 1598, 1563, 1507, 1464, 1291, 1245, 1202, 1132, 1025, 946, 874, 838, 801, 754, 738
114	401	6.96	1.77-1.87 (H, m), 2.15-2.25 (1H, m), 2.50-2.70 (2H, m), 3.75-3.81 (1H, m), 4.25 (2H, br hump), 5.09 (2H, s), 6.92 (1H, d), 7.01 (1H, d), 7.08 (1H, s), 7.20-7.50 (8H, m), 7.98 (1H, s), 8.10 (1H, s), 10.09 (1H, s), 13.00 (1H, br s)	1660, 1596, 1563, 1507, 1484, 1451, 1316, 1262, 1202, 1026, 946, 879, 838, 801, 762, 737, 721, 678
115	311	4.47	1.85-1.96 (1H, m), 2.18-2.30 (1H, m), 2.60-2.82 (2H, 2xm), 3.62-3.70 (1H, m), 6.66 (1H, d), 6.79-6.85 (2H, m), 7.10 (1H, t), 7.24 (2H, br s), 7.42 (1H,d), 7.48 (1H, d), 7.99 (1H, s), 8.10 (1H, s), 9.48 (1H, br s), 10.07 (1H, s), 13.04 (1H, br s)	1673, 1631, 1591, 1510, 1462, 1201, 1137, 949, 874, 839, 800, 723
116	361	5.90	1.95-2.00 (1H,m), 2.28-2.32 (1H, m), 2.43 (3H,s), 2.77-2.85 (2H, m), 4.11 (1H, t), 7.27 (1H,t), 7.33-7.46 (3H, m), 7.55 (1H, t), 7.72 (3H, brs), 8.06 (1H, s), 10.18 (1H, s), 12.60 (1H, brs). TFA salt	3037, 1741, 1712, 1474, 1364, 1283, 1155, 1107, 912

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
117	377	6.99	1.99-2.04 (1H,m), 2,26-2.32 (1H, m), 2.42 (3H,s), 2.67-2.70 (1H,m), 2.76-2.80 (1H,m), 3.78 (1H,t), 7.31-7.40 (3H,m), 7.62-7.71 (5H,m), 8.04 (1H,s), 10.19 (1H,s), 12.6 (1H, brs). TFA salt	3039, 1670, 1199, 1134, 1032, 839, 789, 722
118	391	7.35	1.28 (3H, t), 1.99-2.02 (1H, m), 2.26-2.29 (1H, m), 2.67-2.70 (1H, m), 2.77-2.82 (1H, m), 2.85 (2H, q), 3.78 (1H,t), 7.33-7.41 (3H, m), 7.66-7.71 (5H, m), 8.06 (1H, s), 10.18 (1H, s), 12.6 (1H, brs). TFA salt	2981, 1670, 1510, 1200, 1135, 1033, 799, 723
119	439	8.07	1.99-2.02 (1H, m), 2.28-2.31 (1H, m), 2.67-2.70 (1H, m), 2.77-2.81 (1H, m), 3.81 (1H, t), 7.41 (2H, m), 7.49-7.56 (4H, m), 7.66-7.68 (2H, m), 7.73 (3H, brs), 7.89 (2H, d), 8.45 (1H, s), 10.31 (1H, s), 13.2 (1H, brs). TFA salt	2922, 1670, 1497, 1201, 1134, 1033, 799, 722
120	379	6.4	1.7-1.9(1H, m), 2.1-2.3(1H, m), 2.5(3H, s), 2.6-2.7(2H, m), 3.0(1H, m), 4.2-4.4(1H, m), 7.3-7.4(3H, m), 7.5-7.6(2H, m), 8.1(1H, s), 10.1-10.5(1H, br m), 12.4-12.8(1H, br s)	1649.6 cm-1
121	397	7.35	1.74-1.80 (1H, m), 2.09-2.16 (1H, m), 3.92 (1H, t), 7.39-7.52 (3H, m), 7.58-8.12 (2H, m), 8.13 (1H, s), 10.39 (1H, brs).	3271, 1648, 1472, 1431, 1303, 1029, 789
122	441	7.49	1.77-1.80 (1H, m), 2.13-2.15 (1H, m), 2.90-2.92 (1H, m), 3.96 (1H, t), 7.40-7.52 (4H, m), 7.60-7.66 (2H, m), 8.06 (1H, s), 10.42 (1H, brs).	2921, 1661, 1498, 1471, 1033, 805
123	476	8.22	1.75-1.77 (1H,m), 2.08-2.49 (1H, m), 3.01-3.04 (2H, m), 3.12-3.16 (2H, m), 3.91 (1H, t), 7.15-7,25 (1H, m), 7.26-7.7.27 (4H, m), 7.38-7.41 (3H, m), 7.63 (1H, d), 7.65 (1H, s), 8.07 (1H, s), 10.22 (1H, brs), 12.7 (1H, brs).	3277, 1646, 1560, 1507, 1059, 1032
124	387	7.09	1.81-1.90 (1H, m), 2.16-2.33 (1H, m), 2.91 (1H, m), 3.96 (1H, t), 4.50 (1H, s), 7.40-7.45 (2H, m), 7.51-7.53 (1H, m), 7.60-7.67 (2H, m), 8.21 (1H, s), 10.45 (1H, brs).	3278, 1660, 1559, 1495, 1471, 1033, 1133, 808
125	363	6.1	1.3-1.7(2H, br s), 1.7-1.8(1H, m), 2.1-2.2(1H, m), 2.4(3H, s), 2.5-2.6(2H, m), 4.2(1H, m), 7.2(1H, m), 7.4(2H, m), 7.5-7.6(2H, m), 8.1(1H, s), 10.1-10.3(1H, br s), 12.4-12.7(1H, br s)	-
126	363	6.1	1.3-1.7(2H, br s), 1.8(1H, m), 2.1-2.2(1H, m), 2.4-2.5(3H, s), 2.5-2.7(2H, m), 4.2(1H, m), 7.2-7.7(5H, m), 8.1(1H, s), 10.1-10.4(1H, br s), 12.4-12.7(1H, br s)	1646.2
127	454	7.81	1.76-1.99 (1H, m), 2.14-2.16 (1H, m), 3.88-3.92 (1H, m), 6.78 (1H, t), 7.27 (4H, m), 7.28-7.29 (1H, m), 7.61-7.67 (4H, m), 8.32 (1H, s), 8.84 (1H, s), 10.14 (1H, brs), 11.93 (1H, brs).	3290, 1658, 1602, 1553, 1497, 1473, 1317, 1030, 807, 749

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
128	510	7.50	.74-1.77 (1H, m), 2.07-2.3 (1H, m), 2.69 (2H, t), 2.94 (2H, t), 3.17 (3H,m), 3.90 (1H, t), 4.11 (1H, m) 7.18 (1H,m), 7.29-7.41 (6H, m), 7.47 (1H, m), 7.61-7.65 (2H, m), 7.97 (1H, m), 10.18 (1H, brs), 10.28 (1H, s), 13.2 (1H, brs).	3256, 1660, 1555, 1497, 1471, 1317, 1023, 698
129	344	5.36	1.88 - 1.97 (1H, m), 2.12 - 2.21 (1H, m), 2.43 (3H, s), 2.54 - 2.59 (2H, m), 4.02 (1H, dd), 7.37 - 7.42 (3H, m), 7.51 (1H, d), 7.85 (1H, t), 8.08 (1H, s), 10.23 (1H, brs), 12.52 (1H, brs)	3247, 2925, 1665, 1578, 1557, 1516, 1440, 1306, 1158, 1127, 984, 810, 769
130	407	6.99	1.81 - 1.90 (1H, m), 2.15 - 2.24 (1H, m), 2.43 (3H, s), 2.66 (2H, t), 3.88 (3H, s), 4.17 (1H, dd), 7.39 (2H, s), 7.46 (1H, d), 7.52 (1H, d), 8.03 (1H, s), 10.11 (1H, brs), 12.53 (1H, brs)	3257, 2904, 1650, 1552, 1506, 1465, 1393, 1312, 1204, 1189, 1132, 1015, 861, 799
131	323	5.90	($CDCl_3$) 1.88-1.98 (1H, m), 2.21-2.31 (1H, m), 2.31 (3H, s), 2.43 (3H, s), 2.60-2.75 (2H, m), 3.75 (1H, t, J 7.2 Hz), 7.08-7.10 (1H, m), 7.20-7.27 (3H, m), 7.37 (2H, s), 8.06 (1H, s), 10.08 (1H, br), 12.53 (1H, br).	670.7, 1511.7, 1136.6
132	359	6.22	1.85 (1H, m), 2.25 (1H, m), 2.6-2.8 (2H, m), 4.15(1H, m), 4.2-4.6 (2H, br s), 7.30 (1H, m), 7.40 (2H, s), 7.55 (1H, m), 7.65 (1H, m), 8.10 (1H, s), 10.25 (1H, s)	1665,1487, 1308, 898, 666
133	393	6.60	1.91 - 1.99 (1H, m), 2.16 - 2.23 (1H, m), 2.43 (3H, s), 2.84 - 2.87 (1H, m), 4.09 (1H, dd), 6.41 (1H, brs), 6.92 (1H, d), 7.32 - 7.37 (2H, m), 8.08 (1H, s), 12.46 (1H, brs)	3380, 3288, 1675, 1568, 1516, 1475, 1440, 1399, 1322, 1291, 1184, 1137, 922, 805, 764
134	392	6.46	1.95-2.06 (1H, m), 2.22-2.35 (1H, m), 2.62-2.71 (1H, m), 2.74-2.82 (1H, m), 2.82 (3H, d), 3.78 (1H, t), 7.17 (1H, d), 7.23 (1H, dd), 7.39 (1H, dd), 7.62 (2H, br s), 7.64-7.68 (2H, m), 7.93 (1H, s), 10.03 (1H, s), 11.31 (1H, s)	3265, 3015, 2970, 2933, 1736, 1671, 1561, 1518, 1470, 1365, 1304, 1229, 1202, 1133, 1031, 953, 874, 836.
135	337	6.45	($CDCl_3$) 1.19 (3H, t, J 7.6 Hz), 1.91-2.03 (1H, m), 2.27-2.33 (1H, m), 2.43 (3H, s), 2.62 (2H, q, J 7.6 Hz), 2.68-2.83 (2H, m), 3.73 (1H, t, J 7.9 Hz), 7.13-7.40 (6H, m), 7.69 (3H, br), 8.05 (1H, s), 10.08 (1H, s), 12.53 (1H, br). TFA salt	1673.1, 1201.4, 1137.4
136	387	7.0	1.7-1.9(1H, m), 2.1-2.3(1H, m), 2.4-2.5(3H, s), 2.6-2.7(2H, m), 4.2(1H, m), 7.4(2H, m), 7.5-7.6(2H, m), 8.0-8.1(1H, s), 10.1-10.4(1H, br s), 12.4-12.7(1H, br s)	652.7, 1727.2
137	340	4.84	(D_4-MeOH) 2.19 (3H, s), 2.26 - 2.35 (1H, m), 2.54 (3H, s), 2.54 - 2.62 (1H, m), 2.91- 3.03 (2H, m), 5.73 (1H, t), 6.44 (1H, t), 7.39 - 7.47 (3H, m), 7.64 (1H, d), 8.01 (1H, s)	3237, 3053, 1660, 1644, 1542, 1501, 1434, 1373, 1317, 1204, 1127, 835, 794, 764, 718
138	378	6.15	1.8-1.95(1H, m), 2.15-2.3(1H, m), 2.55-2.7(2H, m), 3.8-3.85(1H, m), 5.25(2H, s), 5.55(2H, br s), 7.15(1H,d), 7.25(1H,d), 7.4(1H, d), 7.6-7.7(2H, m), 7.9(1H, s), 10.1(1H, br s), 12.4-12.7(1H, br s)	1659, 1535, 1201

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
139	349	6.19	1.8-1.95(1H, m), 2.1-2.3(1H, m), 2.4-2.5(3H, s), 2.6-2.7(2H, m), 4.1(1H, m), 6.85(1H, m), 6.95(1H, m), 7.3-7.4(2H, m), 8.0-8.05(1H, s), 10.1-10.2(1H, br s), 12.4-12.7(1H, br s)	3237, 1655, 1511, 1183
140	420	6.16	1.8-1.95(1H, m), 2.1-2.3(1H, m), 2.4-2.5(3H, s), 2.5-2.7(2H, m), 4.0-4.1(1H, m), 7.3-7.4(2H, m), 7.45-7.5(1H, m), 7.6-7.75(2H, m), 7.95-8.0(1H, s), 10.1-10.15(1H, br s), 10.35-10.4(1H, brs), 12.5-12.8(1H, br s)	3200, 1661, 1558, 799
141	482	7.24	1.7-1.85(1H, m), 2.1-2.25(1H, m), 2.5-2.7(2H, m), 3.9-4.0(1H, m), 7.3-7.4(2H, m), 7.45-7.7(5H, m), 7.95-8.0(1H, s), 8.0-8.1(2H, m), 10.1-10.2(1H, br s), 10.7-10.85(1H, brs), 12.5-12.8(1H, br s)	3250, 1637, 1536, 1313, 799
142	365	7.34	($CDCl_3$) 0.86-0.88 (6H, m), 1.79-1.85 (1H, m), 1.91-2.00 (1H, m), 2.2.25-2.33 (1H, m), 2.43 (3H, s), 2.43-2.46 (2H, m), 2.64-2.78 (2H, m), 3.30 (2H, br), 3.74 (1H, t, J 7.4 Hz), 7.06-7.37 (6H, m), 8.03 (1H, s), 10.07 (1H, s), 12.53 (1H, br).	1673.3, 1201.6, 1183.8, 1137.6
143	398	7.29	1.92-2.04 (1H,m), 2,16-2.32 (1H, m), 2.52-2.67 (1H,m), 2.70-2.80 (1H,m), 3.73 (1H,t, J=7.4Hz), 7.34 (1H,m), 7.52-7.76 (6H,br m), 7.93 (1H,s), 8.12 (1H,s), 10.26 (1H,s), 13.60 (1H, brs).	1670, 1512, 1201, 1135
144	443	7.23	1.75-1.83(1H, m), 2.07-2.20(1H, m), 2.40-2.58(2H, m), 3.92(1H,.m), 7.37(1H, d, J=8.4Hz), 7.59(1H, d, J=8.3Hz), 7.61(1H, s), 7.73(1H, s), 8.00 (1H, s), 8.12(1H, s), 10.20-10.59(1H, br m), 13.19-13.59(1H, br s).	1654, 1582, 1545, 1506, 1472, 1031
145	477	7.93	1.80(1H, m), 2.18 (1H, m), 2.50-2.68 (2H, br m), 3.80(1H, m), 7.35(1H, m), 7.59(3H, m), 7.80(1H, s), 8.01(1H, s).	1670, 1585, 1549, 1502, 1472
146	427	8.05	3.04(1H, dd, J=6.2, 12.7Hz), 3.31(1H, m), 3.91(1H, m), 6.12(2H,.br s), 7.35-7.48(2H, m), 7.51(3H, m), 7.66(4H, m), 8.10(2H, d, J=12.7), 10.31 (1H, s), 13.12(1H, br s).	1672, 1600, 1562, 1202, 1135
147	377	6.81	1.85-2.10 (1H, m), 2.20-2.30 (1H, m), 2.47 (3H, s), 2.55-2.80 (2H, m), 3.77 (1H, t), 7.16 (1H, s), 7.38 (1H, dd), 7.60-7.73 (4H, m), 7.90 (1H, s), 7.99 (1H, s), 10.10 (1H, s), 13.09 (1H, s)	3255, 2922, 1704, 1677, 1651, 1553, 1513, 1473, 1322, 1195, 1135, 1085, 1032, 942, 866, 841
148	473	7.91	1.95-2.05 (1H, m), 2.20-2.35 (1H, m), 2.60-2.85 (2H, m), 3.79 (1H, t), 7.34 (1H, m), 7.39 (1H, dd), 7.43-7.75 (8H, m), 8.09 (1H, s), 8.13 (1H, m), 10.26 (1H, s), 12.93 (1H, s)	3073, 2943, 1671, 1561, 1508, 1472, 1419, 1326, 1202, 1135, 1058, 1033, 945, 874, 835.
149	398	6.34	2.15 - 2.24 (1H, m), 2.35 - 2.44 (1H, m), 2.78 - 2.86 (2H, m), 4.12 (1H, t), 7.39 (1H, dd), 7.49 (1H, d), 7.72 (3H, brs), 7.86 (1H, s), 8.02 (1H, d), 8.09 (1H, s), 10.27 (1H, s), 13.03 (1H, brs)TFA salt	3268, 3099, 2950, 1670, 1563, 1506, 1404, 1327, 1178, 1143, 943, 881, 840, 799, 71

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
150	440	7.74	1.85(1H, m), 2.18 (1H, m), 2.52-2.70 (2H, m), 3.88(1H, m), 7.40(2H, m), 7.43(3H, m), 7.64(4H, m), 8.09(2H, s,), 10.31 (1H, br s), 13.10(1H, br s).	1667, 1600, 1558, 1492
151	421	8.11	1.79-1.89 (1H, m), 2.24-2.30 (1H, m), 3.09-3.22 (2H, m), 3.55 (3H, s), 3.60-3.63 (1H, m), 5.85 (1H, br), 7.20-7.35 (4H, m), 7.47 (1H, s), 7.85 (1H, s), 8.00 (1H, s), 9.36 (1H, br), 11.87 (1H, br).	3291.5, 1691.3, 1652.8, 1551.8, 1509.1, 1272.7
152	420	7.55	1.50-1.55 (1H, m), 1.90-1.99 (1H, m), 2.35 (3H, d, J 4.6 Hz), 2.74-2.79 (1H, m), 2.91-2.96 (1H, m), 3.38-3.42 (1H, m), 5.10-5.20 (1H, br), 5.35-5.45 (1H, br), 6.90-7.15 (4H, m), 7.20-7.30 (1H, s), 7.53 (1H, s), 7.77 (1H, s), 9.74 (1H, s), 9.36 (1H, br), 12.13 (1H, br).	1737.4, 1647.81, 1580.0, 1365.6
153	378	6.59	1.91(1H, m), 2.21 (1H, m), 2.41 (3H, s), 2.53-2.70 (2H, br m), 3.88(1H, m), 6.59-7.10 (1H, br s), 7.38(2H, m), 7.43(1H, m), 7.62(2H, m), 7.99(1H, s), 8.09(1H, s), 10.31 (1H, br s), 12.98(1H, br s).	1666, 1597, 1561, 1506, 1469
154	341	5.80	1.94-2.00 (1H,m), 2,28-2.32 (1H,m), 2.76-2.95 (2H, m), 3.58 (1H, t), 3.85 (2H, d), 7.20-7.40 (4H, m), 7.38 (1H, d), 7.55 (1H,d), 7.75 (3H, brs), 8.02 (1Hs), 8.11 (1H,s), 10.19 (1H,s), 13.05 (1H, brs).	1666,1198, 1135, 830, 799, 718
155	381	6.8	1.1-1.4(2H, m), 1.6-1.8(1H, m), 2.0-2.1(1H, m), 2.4-3.6(2H, m), 3.7-3.8(1H, m), 7.3-7.7(5H, m), 7.9-8.2(2H, m), 10.1-10.2(1H, m), 12.8-13.2(1H, br s)	-
156	321	5.17	1.80-1.95 (2H, m), 2.50-2.65 (2H, m), 2.68-2.80 (2H, m), 2.85-2.98 (2H, m), 7.22-7.28 (1H, m), 7.35-7.50 (5H, m), 7.95-8.02 (2H, m), 9.25 (1H, br s), 12.99 (1H, br s)	1649, 1597, 1503, 1446, 1239, 944
157	316	5.71	3.17 (1H, m), 3.43-3.61 (1H, m), 4.08(1H, m), 7.37-7.41(4H, br m), 7.89(3H, br s), 8.12(1H, s), 8.49(1H, s), 8.56(1H, s), 10.58(1H, s), 11.60(1H, br s).	1672, 1511, 1201, 1135
158	468	7.89	1.75-1.95 (1H, m), 2.10-2.25 (1H, m), 2.57-2.70 (1H, m), 2.90-3.10 (1H, m), 3.83 (1H, t), 4.43 (2H, d), 6.48 (1H, t), 7.10-7.23 (3H, m), 7.29 (2H, t), 7.37-7.47 (3H, m), 7.58-7.67 (2H, m), 8.06 (1H, s), 10.02 (1H, s), 11.29 (1H, s	3277, 3097, 2938, 2884, 1647, 1553, 1509, 1474, 1436, 1399, 1356, 1311, 1236, 1203, 1183, 1134, 1073, 1030, 991, 958, 873, 833, 811.
159	460	8.19	1.15-1.30 (6H, m), 1.55-1.65 (1H, m), 1.65-1.90 (3H, m), 1.95-2.05 (2H, m), 2.10-2.20 (1H, m), 2.53-2.60 (1H, m), 3.42-3.47 (1H, m), 3.83 (1H, t), 5.62 (1H, d), 7.10-7.20 (2H, m), 7.39 (1H, dd), 7.60-7.66 (2H, m), 8.03 (1H, s), 9.98 (1H, s), 11.20 (1H, s)	3288, 2928, 2853, 1662, 1557, 1470, 1449, 1317, 1201, 1182, 1132, 1031, 840, 805
160	516	7.78	1.75-1.9(1H, m), 2.1-2.25(1H, m), 2.5-2.65(2H, m), 3.85-3.9(1H, m), 7.35-7.45(2H, m), 7.45-7.75(5H, m), 7.95-8.0(1H, s), 8.0-8.05(1H, m), 8.10(1H, s), 10.3(1H, br s), 10.8-10.95(1H, brs), 12.7-12.8(1H, br s	1662, 1546, 741

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
161	561	8.90	1.78(1H, m), 2.11 (1H, m), 2.48 (1H, m), 2.93(1H, br m), 3,88 (1H, m), 5.07(2H, s), 6.44(1H, m), 7.11 (2H, br m), 7.27(3H, br m), 7.40(6H, br m), 7.60 (2H, m), 8.30(1H, s), 8.82(1H, s), 10.09(1H, s), 11.94 (1H, br s)	1603, 1558, 1533,1474
162	490	8.57	1.78(1H, m), 2.12 (1H, m), 2.50 (2H, m), 3,90 (1H, m), 6.81(1H, m), 7.20 (2H, br m), 7.30(1H, m), 7.38 (1H, m), 7.46 (1H, m), 7.59 (1H, m), 7.67(1H, m), 7.87(1H, s), 8.34(1H, s), 9.11(1H, s), 10.13(1H, br s), 12.04 (1H, br s)	1598, 1541, 1480
163	490	8.58	1.85-1.95(1H, m), 2.15-2.3(1H, m), 2.5-2.7(2H, m), 3.87-3.95(1H, m), 5.7-6.2 (2H, br s), 7.20-7.35(4H, m), 7.4-7.45(1H, m), 7.6-7.75(4H, s), 8.35(1H, s), 9.05(1H, s), 10.3(1H, br s), 12.7-12.8(1H, br s	1660, 1548, 1491
164	479	7.82	2.00-2.08 (1H, m), 2.24-2.33 (1H, m), 2.64-2.69 (1H, m), 2.75-2.82 (1H, m), 3.80 (1H, t, J 7.5 Hz), 7.32-7.41 (3H, m), 7.65-7.73 (6H, m), 8.33 (1H, s), 9.56 (1H, s), 10.22 (1H, br), 12.32 (1H, br)	2220.9, 1670.9, 1606.7, 1541.7, 1201.2, 1183.8, 1135.5
165	479	8.03	1.78-1.90 (1H, m), 212-2.21 (1H, m), 2.53-2.61 (2H, m), 3.89 (1H, t, J 7.7 Hz), 7.20-7.45 (5H, m), 7.63-7.68 (2H, m), 7.84-7.86 (1H, m), 8.18 (1H, m), 8.39 (1H, m), 9.36 (1H, s), 10.19 (1H, br), 12.14 (1H, br).	2229.9, 1668.8, 1602.4, 1559.8, 1476.3, 1201.5, 1134.4
166	534	8.60	1.83-1.92 (1H, m), 215-2.24 (1H, m), 2.53-2.67 (2H, m), 3.86 (1H, t, J 7.5 Hz), 7.29-7.41 (5H, m), 7.60-7.67 (4H, m), 8.32 (1H, s), 9.05 (1H, s), 10.17 (1H, br), 12.03 (1H, br)	2220.9, 1669.3, 1548.0, 1488.5
167	512	7.40	1.93 - 2.03 (1H, m), 2.21 - 2.30 (1H, m), 2.63 - 2.79 (2H, m), 3.77 (H, t), 3.85 (3H, s), 7.19 (1H, dd), 7.37 (1H, dd), 7.43 - 7.48 (2H, m), 7.54 (1H, dd), 7.63 - 7.70 (7H, m), 7.94 (1H, d), 10.22 (1H, s), 10.77 (1H, s), 12.79 (1H, s) TFA salt	3247, 3063, 1685, 1537, 1470, 1434, 1317, 1291, 1189, 1143, 1040, 846, 799, 718
168	512	7.30	1.93 - 2.02 (1H, m), 2.20 - 2.30 (1H, m), 2.61 - 2.79 (2H, m), 3.77 (1H, t), 3.85 (3H, s), 7.07 - 7.10 (2H, m), 7.37 (1H, dd), 7.43 (1H, d), 7.54 (1H, dd), 7.63- 7.70 (5H, m), 7.92 (1H, d), 8.06 (1H, d), 10.21 (1H, s), 10.61 (1H, s), 12.75 (1H, s). TFA salt	3196, 3058, 1670, 1639, 1598, 1542, 1511, 1470, 1321, 1260, 1204, 1184, 1132, 1040, 830, 794
169	488	7.13	1.94 - 2.03 (1H, m), 2.21 - 2.31 (1H, m), 2.61 - 2.80 (2H, m), 3.78 (1H, t), 7.24 - 7.27 (1H, m), 7.38 (1H, dd), 7.43 (1H, d), 7.56 (1H, dd), 7.64 -7.70 (5H, m), 8.80 (1H, dd), 7.95 (1h, d), 10.23 (1H, s), 10.87 (1H, s), 12.81 (1H, s) TFA salt	3222, 3088, 1670, 1562, 1475, 1419, 1332, 1286, 1194, 1132, 1030, 840, 794, 712
170	532	8.10	1.87-2.00 (1H, m), 2.15-2.38 (1H, m), 2.60-2.77 (2H, m), 3.79 (1H, t), 6.56 (1H, s), 7.35-7.39 (1H, m), 7.42-7.47 (1H, m), 7.54-7.70 (6H, m), 8.00-8.16 (5H, m), 8.72 (1H, s), 10.24 (1H, s), 10.94 (1H, s), 12.80 (1H, s)	3257, 3226, 1658, 1541, 1472, 1322, 1294, 1233, 1202, 1133, 1031, 958, 867, 830.
171	526	7.31	1.93-2.02 (1H, m), 2.18-2.31 (1H, m), 2.62-2.80 (2H, m), 3.77 (1H, t), 6.15 (2H, s), 6.55 (1H, s), 7.08 (1H, d), 7.35-7.44 (2H, m), 7.51-7.70 (6H, m), 7.91 (1H, s), 10.21 (1H, s), 10.60 (1H, s), 12.76 (1H, s)	3265, 1655, 1605, 1541, 1503, 1473, 1439, 1400, 1359, 1324, 1294, 1259, 1133, 1037, 931, 875, 812.

Compd. No	M+1 (obs)	R_t	^1H NMR	IR (cm^{-1})
172	558	8.46	1.94-2.04 (1H, m), 2.18-2.32 (1H, m), 2.58-2.70 (1H, m), 2.70-2.83 (1H, m), 3.78 (1H, t), 7.37 (1H, dd), 7.42-7.47 (2H, m), 7.50-7.56 (3H, m), 7.62-7.71 (5H, m), 7.79 (2H, d), 7.87 (2H, d), 7.97 (1H, d), 8.17 (2H, d), 10.23 (1H, s), 10.83 (1H, s), 12.80 (1H, s) TFA salt	1736, 1673, 1637, 1544, 1374, 1365, 1228, 1216, 1205, 1137.
173	531	8.38	1.78-1.80 (1H, m), 2.10-2.14 (1H, m), 2.89 (1H, m), 3.77 (0.5H, t), 3.93 (0.5H, t), 7.05 (1H, m), 7.31-7.41 (5H, m), 7.48 (1H, m), 7.60-7.65 (1H, m), 7.66 (1H, s), 7.78 (1H, s), 8.14 (1H, m), 9.40 (1H, brs), 9.67 (1H, brs), 10.2 (0.5H, brs), 10,25 (0.5H, brs), 12.6 (1H, brs)	3257, 1672, 1593, 1529, 1477, 1312, 774
174	507	7.22	1.94-2.02 (1H, m), 2.20-2.30 (1H, m), 2.61-2.79 (2H, m), 3.78 (1H, t, J 7.5 Hz), 7.36-7.67 (5H, m), 7.97-8.22 (5H, m), 10.23 (1H, br), 11.08 (1H, br), 12.86 (1H, br).	2232.8, 1667.8, 1546.7, 1201.5, 1134.8
175	507	7.22	1.91-1.99 (1H, m), 2.20-2.30 (1H, m), 2.60-2.76 (2H, m), 3.81 (1H, t, J 7.6 Hz), 7.36-7.81 (6H, m), 7.98-8.49 (4H, m), 8.32 (1H, s), 10.26 (1H, br), 11.03 (1H, br), 12.84 (1H, br).	2232.0, 1667.9, 1547.6, 1202.0, 1134.5
176	497	7.83	1.75-1.78 (1H, m), 2.09-2.15 (1H, m), 2.80-2.89 (1H, m), 3.92 (1H, t), 7.00 (1H, t), 7.29-7.41 (4H, m), 7.47-7.52 (3H, m), 8.17 (1H, s), 9.29 (1H, brs), 9.57 (1H, brs), 10.22 (1H, brs), 12.45 (1H. brs).	3263, 1638, 1560, 1497, 1312, 1031, 692
177	500	7.38	1.75-1.90 (1H, m), 2.10-2.25 (1H, m), 2.50-2.65 (2H, m), 4.10-4.15 (1H, m), 7.18-7.25 (1H, m), 7.35-7.7 (6H, m), 7.6-7.75 (4H, br s), 7.95-8.15 (3H, m), 10.2 (1H, br), 10.9 (1H, br), 12.8 (1H, br).	1663, 1541, 1458
178	574	8.54	1.70-1.90 (1H, m), 2.05-2.18 (1H, m), 2.40-2.60 (2H, m), 3.72-3.92 (1H, m), 7.10 (2H, d), 7.19 (1H, t), 7.28 (1H, d), 7.35-7.46 (4H, m), 7.50-7.70 (5H, m), 7.86 (1H, d), 7.92 (1H, s), 10.24 (1H, s), 10.78 (1H, s), 12.76 (1H, s)	3491, 3291, 3069, 2954, 2871, 1674, 1647, 1549, 1488, 1474, 1439, 1325, 1296, 1279, 1232, 1198, 1133, 1032, 954, 892, 879.
179	500	7.47	1.78 (1H, m), 2.05 (1H, m), 3.90 (1H, m), 7.35 (1H, d, J=8.30Hz), 7.42 (1H, d, J=8.9Hz) 7.46 (2H, m), 7.60 (3H, m), 7.83 (1H, m), 7.90 (3H, m), 10.20 (1H, br s), 10.70-10.8 (1H, s), 12.56-12.94 (1H, br s).	1587, 1551, 1473, 1324, 1270
180	518	7.39	1.75-1.93 (1H, m), 2.10-2.22 (1H, m), 2.38-2.65 (2H, m), 3.75-3.95 (1H, m), 7.37-7.70 (9H, m), 8.05-8.10 (1H, m), 10.19-10.27 (1H, m), 10.82 (1H, s), 12.74 (1H, s)	3183, 1654, 1593, 1541, 1499, 1470, 1434, 1388, 1330, 1203, 1185, 1134, 1049, 1032, 958, 905, 876, 838.
181	526	7.85	1.36 (3H, t), 1.72-1.90 (1H, m), 2.05-2.20 (1H, m), 2.38-2.60 (2H, m), 3.72-3.92 (1H, m), 4.12 (2H, q), 7.16 (1H, d), 7.35-7.68 (8H, m), 7.92-7.96 (1H, m), 10.19-10.28 (1H, m), 10.71 (1H, s), 12.75 (1H, s)	3242, 2919, 1666, 1645, 1597, 1518, 1502, 1491, 1473, 1438, 1390, 1329, 1301, 1281, 1235, 1047, 1030, 911, 823.

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
182	516	7.93	1.75-1.90 (1H, m), 2.05-2.20 (1H, m), 2.38-2.65 (2H, m), 3.85-3.95 (1H, m), 7.35-7.70 (7H, m), 7.95-8.02 (1H, m), 8.05-8.1 (2H, m), 10.2-10.27 (1H, m), 10.8 (1H, br s), 12.8 (1H, s)	1655, 1553, 1473
183	550	8.44	1.75-1.90 (1H, m), 2.05-2.20 (1H, m), 2.38-2.65 (2H, m), 3.9-3.95 (1H, m), 7.35-7.65 (7H, m), 7.80-7.85 (1H, m), 8.00-8.1 (2H, m), 8.30(1H, s), 10.3 (1H, br s), 10.9 (1H, br s), 12.8 (1H, s)	1643, 1536, 1307
184	550	8.46	1.78(1H, m), 2.11 (1H, m), 3.31 (2H, m), 3.90(1H, br m), 7.39 (2H, br m), 7.50(1H, br m), 7.60 (2H, m), 7.92(1H, m), 7.98(1H,m), 8.08(2H, m), 10.85-13.10(1H, br s), 12.79 (1H, br s).	1664, 1643, 1554, 1473
185	496	7.72	1.70(1H, m), 2.05 (1H, m), 2.41 (3H, s), 3.30(2H, m), 3.85(1H, br m), 7.27-7.44 (4H, br m), 7.51(1H, m), 7.60 (2H, m), 7.85(2H, m), 7.93(1H,s), 10.18(1H, m), 10.61(1H, br s), 12.70 (1H, br s).	1641, 1587, 1545, 1470
186	560	8.04	1.78(1H, m), 2.16 (1H, m), 3.30 (2H, br m), 3.88(1H, m), 7.32(2H, m), 7.32(1H, m) 7.41(1H, m), 7.50(2H, m), 7.60 (2H, m), 7.85(1H, m), 7.95(1H,s), 8.05(1H, m), 8,21(1H, m), 10.20(1H, m), 10.59-11.09(1H, br s), 12.37-12.92 (1H, br s).	1644, 1528, 1475
187	510	8.12	1.10(3H, t), 1.70(1H, m), 2.10 (1H, m), 3.32 (2H, br m), 2.70(2H, q), 3.87(1H, m), 7.35(4H, m), 7.32(1H, m) , 7.50(2H, m), 7.60 (2H, m), 7.90(1H, s), 7.95(1H,m), 10.20(1H, s), 10.60(1H, s), 12.57-12.88 (1H, br s).	1653, 1542, 1472
188	524	8.55	0.91(3H, t), 1.62(2H, m), 1.74(1H, m), 2.10 (1H, m), 3.30 (2H, m), 2.60(2H, q), 3.88(1H, m), 7.35(4H, m), 7.41(1H, m) , 7.59(2H, m), 7.93(3H, br m), 10.20(1H, s), 10.59(1H, s), 12.58-12.90 (1H, br s).	1654, 1541, 1491
189	560	8.00	1.70(1H, m), 2.10 (1H, m), 3.29 (2H, m), 3.87(1H, m), 7.32(1H, m), 7.41(1H, m) , 7.58(2H, m), 7.77(2H, m), 7.91(1H, m), 7.80(2H, m), 10.65-11.00(1H, br s), 12.50-12.96 (1H, br s).	1655, 1541, 1472
190	518	7.15	1.82(1H, m), 2.19 (1H, m), 2.58(2H, m), 3.89(1H, m), 7.16(1H, m), 7.29(1H, m) , 7.40(4H, m), 7.65(2H, m), 7.77(2H, m), 7.96(1H, m), 10.19(1H, s), 11.55-12.27(1H, br s).	654, 1541, 1507
191	554	7.46	1.85(1H, m), 2.19 (1H, m), 2.61(2H, m), 3.89(1H, m), 7.06(1H, m), 7.18(1H, m) , 7.30-7.40(3H, m), 7.61(2H, m), 7.78(1H, m), 7.85(1H, m), 9.97(1H, s), 11.02-11.41(1H, br s).	1653, 1558, 1507
192	496	7.49	1.82(1H, m), 2.12 (1H, m), 3.25 (2H, m), 3.75(2H, s), 3.89(1H, m), 7.20(1H, m), 7.34(6H, br m) , 7.51(1H, m), 7.60(2H, m), 7.93(1H, s), 10.20 (1H, br s), 10.51(1H, s), 12.10-13.10(1H, br s).	1655, 1600, 1471

Compd. No	M+1 (obs)	R_t	^1H NMR	IR (cm^{-1})
193	483	6.49	(D_4-MeOH) 2.09 - 2.14 (1H, m), 2.40 - 2.44 (1H, m), 2.85 - 2.90 (1H, m), 2.95 - 3.01 (1H, m), 3.79 (1H, t), 7.38 - 7.40 (1H, m), 7.48 (2H, s), 7.55 - 7.57 (1H, m), 7.60 - 7.65 (1H, m), 8.03 (2H, d), 8.12 (1H, s), 8.83 (2H, s)TFA salt	3242, 3083, 1675, 1557, 1511, 1465, 1184, 1132, 846, 974, 722
194	483	6.54	(D_4-MeOH) 2.02 - 2.05 (1H, m), 2.30 - 2.36 (1H, m), 2.70 - 2.80 (2H, m), 3.76 (1H, t), 7.38 - 7.54 (4H, m), 7.65 (2H, s), 8.10 (1H, d), 8.46 (1H, d), 8.80 (1H, s), 9.20 (1H, s)	3191, 1660, 1542, 1465, 1306, 1117, 1030
195	483	7.27	(D_4-MeOH) 1.99 - 2.06 (1H, m), 2.30 - 2.39 (1H, m), 2.70 - 2.82 (2H, m), 3.78 (1H, t), 7.39 - 7.54 (4H, m), 7.65 - 7.68 (2H, m), 8.07 (1H, t), 8.20 (1H, s), 8.27 (1H, d), 8.77 (1H, d)	3268, 1670, 1542, 1465, 1317, 1122, 799, 738
196	508	7.94	1.80-1.91 (1H, m), 2.10-2.25 (1H, m), 2.50-2.70 (2H, m), 3.85 (1H, m), 5.38 (1H, d, J 11.0 Hz), 5.55 (1H, d J 17.7 Hz), 6.81-6.88 (1H, m), 7.37-7.73 (7H, m), 7.97 (2H, s), 8.20 (1H, s), 10.26 (1H, br), 10.80 (1H, br), 12.78 (1H, br).	2232.0, 1669.1, 1602.3, 1573.0, 1535.7, 1443.5, 1244.62, 1203.3, 1154
197	511	6.75	1.90-2.10 (1H, m), 2.20-2.30 (1H, m), 2.60-2.82 (2H, m), 3.79 (1H, t J 7.3 Hz), 4.15 (2H, s), 7.00-7.45 (4H, m), 7.58-7.80 (6H, s), 8.00-8.30 (6H, m), 10.27 (1H, br), 10.80 (1H, br), 12.83 (1H, br). TFA salt	1669.8, 1547.8, 1200.8, 1134.9
198	511	6.45	1.92-2.04 (1H, m), 2.20-2.31 (1H, m), 2.60-2.82 (2H, m), 3.78 (1H, t J 7.0 Hz), 4.15 (2H, s), 7.36-7.52 (3H, m), 7.61-7.66 (3H, s), 7.74 (3H, br), 7.98 (1H, s), 8.00-8.30 (6H, m), 8.11 (2H, d, J 7.6 Hz), 8.29 (3H, br), 10.25 (1H, br), 10.82 (1H, br), 12.82 (1H, br). TFA salt	1669.6, 1547.8, 1200.8, 1134.6
199	574	8.55	1.95 (1H, m), 2.21 (1H, m), 2.67 (1H, s), 2.73(1H, m), 3.73 (1H, m), 7.07 (2H, d, J=8.6Hz), 7.13 (2H, d, J=8.5Hz), 7.33 (1H, m), 7.32 (1H,m), 7.35-7.52 (4H, br m), 7.55-7.76 (5H, br m), 7.91 (1H, s), 8.05 (2H, d, J=8.6Hz), 10.20 (1H, s), 10.70 (1H, s), 12.73 (1H, s).	1597, 1573, 1533, 1300, 1142
200	550	8.14	1.78 (1H, m), 2.10 (1H, m), 3.85 (1H, m), 7.31 (1H, d, J=9.0Hz), 7.37 (1H, d, J=9.0Hz) 7.49 (1H, m), 7.58 (2H, m), 7.79 (2H, m), 7.95 (2H, m), 8.31 (1H, m), 8.36 (1H, s), 10.18(1H, s), 10.89-11.18 (1H, br s), 12.68-12.89 (1H, br s).	1587, 1555, 1324, 1128
201	518	7.72	1.80 (1H, m), 2.11 (1H, m), 2.55 (2H, m), 3.81 (1H, m), 5.11-5.97 (2H, br s), 7.30 (1H, d, J=8.3Hz), 7.39 (1H, d, J=9.0Hz) 7.50 (1H, m), 7.57 (3H, m), 7.75 (2H, m), 7.91 (1H, s), 10.20 (1H, s), 10.72-10.10 (1H, br s), 12.81 (1H, s).	1598, 1552, 1472, 1330, 1125
202	616	8.93	1.78 (1H, m), 2.10 (1H, m), 3.85 (1H, m), 7.35 (1H, d, J=8.3Hz), 7.41 (1H, d, J=9.0Hz) 7.50 (1H, m), 7.58 (3H, m), 8.01 (1H, s), 8.41 (1H, s), 8.70 (2H, s), 10.25(1H, s), 12.68-13.01	1557, 1473, 1320, 1195

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
203	568	8.37	1.85 (1H, m), 2.07 (1H, m), 2.49-2.71 (2H, br m), 3.81 (1H, m), 6.09-7.89 (2H, br s), 7.35 (1H, d, J=8.3Hz), 7.43 (1H, d, J=9.0Hz), 7.51 (1H, m), 7.60 (2H, m), 7.94 (1H, s), 8.02 (1H, m), 8.21(1H, m), 8.29(1H, s), 10.23 (1H, s), 10.93-11.41 (1H, br s), 12.82 (1H, s).	1551, 1470, 1551, 1328, 1124
204	566	8.29	1.78 (1H, m), 2.08 (1H, m), 3.89 (1H, m), 7.32 (1H, d, J=8.3Hz), 7.42 (1H, d, J=9.0Hz) 7.51 (1H, m), 7.60 (3H, m), 7.70 (1H, s), 7.95(1H, m), 8.01 (1H, m), 8.10(1H, m), 10.23(1H, s), 10.78-11.01 (1H, br s), 12.75 (1H, s).	1586, 1552, 1474, 1260, 1162
205	506	7.63	1.90-2.04 (1H, m), 2.20-2.31 (1H, m), 2.60-2.82 (2H, m), 3.77 (1H, t J 7.4 Hz), 4.35 (1H, s), 7.36-7.74 (9H, m), 7.96 (1H, s), 8.08 (1H, d, J 7.64 Hz), 8.16 (1H, s), 10.23 (1H, br), 10.88 (1H, br), 12.81 (1H, br). TFA salt	1669.1, 1550.1, 1474.0, 1202.4, 1133.3
206	511	7.08	(D_4-MeOH) 2.02 - 2.07 (1H, m), 2.33 - 2.40 (1H, m), 2.72 - 2.87 (2H, m), 2.87 (3H, s), 3.81 (1H, t), 6.67 (2H, d), 7.39 - 7.53 (4H, m), 7.65 (1H, s), 7.87 (2H, d), 8.01 (1H, s)	3247, 2950, 1655, 1598, 1537, 1475, 1322, 1271, 1184, 1132, 825, 753
207	525	7.45	(D_4-MeOH) 1.29 (3H, t), 2.03 - 2.10 (1H, m), 2.37 - 2.43 (1H, m), 2.78 - 2.90 (2H, m), 3.23 (2H, q), 3.79 (1H, t), 6.68 (2H, d), 7.38 - 7.54 (4H, m), 7.64 (1H, s), 7.86 (2H, d), 8.02 (1H, s)	3263, 2966, 1665, 1603, 1527, 1475, 1327, 1265, 1184, 1132, 825, 794, 769
208	528	7.58	1.72 - 1.80 (1H, m), 2.10 - 2.16 (1H, m), 3.90 (1H, t), 7.38 (1H, d), 7.43 (1H, d), 7.51 - 7.62 (4H, m), 7.87 (1H, t), 8.00 (1H, s), 8.49 (1H, t), 8.90 (1H,s), 10.28 (1H, s), 12.94 (1H, s)	3217, 1639, 1521, 1465, 1347, 1322, 1296, 1127, 876, 810
209	511	7.29	1.90-2.03 (1H, m), 2.20-2.31 (1H, m), 2.58-2.80 (2H, m), 2.74 (3H, s), 3.77 (1H, t), 6.70-6.80 (1H, m), 7.15-7.28 (3H, m), 7.35-7.45 (2H, m), 7.50-7.55 (1H, m), 7.60-7.75 (5H, m), 7.93 (1H, s), 10.21 (1H, s), 10.56 (1H, s), 12.74 (1H, s) TFA salt	3252, 3047, 1671, 1604, 1547, 1472, 1431, 1326, 1201, 1135, 1031, 839.
210	525	7.68	1.19 (3H, t), 1.90-2.05 (1H, m), 2.14-2.32 (1H, m), 2.55-2.80 (2H, m), 3.11 (2H, q), 3.76 (1H, t), 6.70-6.85 (1H, m), 7.18-7.28 (3H, m), 7.32-7.45 (2H, m), 7.50-7.53 (1H, m), 7.60-7.73 (5H, m), 7.93 (1H, s), 10.20 (1H, s), 10.55 (1H, s), 12.74 (1H, s) TFA salt	3236, 3035, 1671, 1548, 1472, 1434, 1327, 1201, 1134, 1031, 953, 835.
212	8.57	468	1.80-1.92 (1H, m), 2.16-2.28 (1H, m), 2.26 (3H, s), 2.50-2.67 (2H, m), 3.90 (1H, t J 7.3 Hz), 6.58-6.60 (1H, m), 7.00-7.70 (8H, m), 8.30 (1H, s), 8.76 (1H, s), 10.21 (1H, br), 11.92 (1H, br).	1665.6, 1611.2, 1560.2, 1473.4, 1201.3
213	8.53	472	1.80-1.90 (1H, m), 2.12-2.25 (1H, m), 2.50-2.65 (2H, m), 3.92 (1H, m), 6.56 (1H, m), 7.21-7.42 (5H, m), 7.62-7.68 (3H, m), 8.35 (1H, s), 9.15 (1H, br), 10.25 (1H, br), 12.06 (1H, br).	1664.7, 1616.5, 1554.4, 1533.1, 1492.2, 1143.5
214	7.49	579	1.40 (2H, m), 1.51 (4H, m), 1.80 (1H, m), 2.13 (4H, m), 3.50 (2H, s), 3.88 (1H, t), 7.36-7.42 (2H, m), 7.46- 7.54 (3H, m), 7.58-7.63 (2H, m), 7.94 (1H, s), 7.96 (2H, s), 10.27 (1H, s), 10.72 (1H, s), 12.75 (1H, brs).	1662, 1545, 1470, 1324, 1032

Compd. No	M+1 (obs)	R_t	^1H NMR	IR (cm^{-1})
215	7.22	581	1.78 (1H, m), 2.11 (1H, m), 2.39 (4H, m), 3.55 (2H, s), 3.59 (4H, m), 7.36-7.42 (2H, m), 7.47-7.62 (5H, m), 7.95-7.99 (3H, m), 10.20 (0.5H, brs), 10.29 (0.5H, brs), 10.73 (1H, brs), 12.75 (1H, brs).	3227, 1661, 1545, 1437, 1113
216	567	7.07	0.99 (6H, t), 1.73 (1H, m), 2.09 (1H, m), 3.30 (2H, s), 3.76 (0.5H, t), 3.69 (0.5H, t), 7.25-7.61 (7H, m), 7.92-7.99 (3H, m), 10.20 (1H, brs), 10.71 (1H, brs), 12.75 (1H, brs).	2967, 1655, 1557, 1472, 1323, 1055, 1013, 811
217	562	6.85	1.78 (1H, m), 2.11 (1H, m), 2.88 (1H, m), 3.76 (0.5H, t), 3.86 (0.5H, t), 5.30 (2H, s), 6.92 (1H, s), 7.25 (1H, s), 7.35-7.43 (2H, m), 7.49-7.61 (5H, m), 7.81 (1H, s), 7.92-8.02 (3H, m), 10.19 (1H, brs), 10.79 (1H, brs), 12.75 (1H, brs).	2981, 1668, 1540, 1473, 1323, 1054, 1013, 815, 722
218	580	6.37	1.80 (1H, m), 2.12 (1H, m), 2.32 (4H, m), 2.71 (4H, m), 2.87 (1H, m), 3.51 (2H, s), 3.75 (0.5H, t), 3,90 (o.5H, m), 7.36-7.43 (2H, m), 7.46-7.52 (5H, m), 7.94-7.97 (3H, m), 10.20 (0.5H, brs), 10.29 (0.5H, brs), 10.71 (1H, brs), 12.75 (1H, brs).	1662, 1550, 1469, 1324, 1134, 1031.
219	564	8.20	1.75 (1H, m), 2.08 (1H, m), 2.85(1H, m), 3.90 (1H, m), 7.33 (2H, m), 7.51 (1H, m), 7.53-7.60 (4H, br m), 7.82 (1H, d), 7.95(1H, m), 8.15 (1H, d), 8.26(1H, s), 10.27(1H, s), 10.90 (1H, br s), 12.74 (1H, br s).	1657, 1546, 1469, 1324
220	524	7.09	1.75 (1H, m), 2.09 (1H, m), 2.78(3H, s), 2.83(1H, m), 3.89 (1H, m), 7.35 (1H, d), 7.40(1H, d), 7.50 (1H, m), 7.59 (2H, m), 7.68(1H, t), 7.95(1H, m), 8.15 (1H, d), 8.30(1H, d), 8.61(1H, s), 10.28(1H, s), 10.95 (1H, br s), 12.73 (1H, br s).	1660, 1545, 1491, 1324
221	560	6.93	1.75 (1H, m), 2.10 (1H, m), 2.48(2H, m), 2.81(1H, m), 3.84 (1H, m), 7.31 (1H, d), 7.41(1H, d), 7.50 (1H, m), 7.59 (2H, m), 7.80(1H, t), 7.98(1H, m), 8.15 (1H, d), 8.35(1H, d), 8.66(1H, s), 10.25(1H, s), 11.05 (1H, br s), 12.78 (1H, br s).	-
222	479	9.28	(D_4-MeOH) 1.35 (6H, d), 1.99 - 2.04 (1H, m), 2.30 - 2.39 (1H, m), 2.67 - 2.80 (2H, m), 3.00 - 3.07 (1H, m), 3.79 (1H, t), 7.31 (1H, d), 7.41 - 7.54 (5H, m), 7.67 - 7.73 (2H, m), 7.79 (1H, s), 8.36 (1H, s)	1675, 1557, 1496, 1470, 1189, 1132, 794
223	515	9.55	(D_4-MeOH) 2.00 - 2.05 (1H, m), 2.35 - 2.40 (1H, m), 2.72 - 2.82 (2H, m), 3.78 (1H, t), 7.38 - 7.49 (2H, m), 7.50 - 7.57 (5H, m), 7.60 - 7.71 (3H, m), 7.75 - 7.77 (2H, m), 7.91 (1H, d), 8.17 (1H, s), 8.44 (1H, s)	3226, 1670, 1562, 1495, 1470, 1321, 1137, 1029, 810
224	507	9.11	(D_4-MeOH) 2.10 - 2.18 (1H, m), 2.42 - 2.51 (1H, m), 2.86 - 3.03 (2H, m), 3.82 (1H, t), 7.42 (1H, d), 7.51 - 7.58 (3H, m), 7.68 (1H, s), 7.73 - 7.74 (2H, m), 8.22 (2H, s), 8.41 (1H, s) TFA salt	3206, 3068, 1665, 1557, 1501, 1475, 1327, 1301, 1184, 1122, 794

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
225	365	13.7	1.7-1.8(1H, m), 2.1-2.2(1H, m), 2.8-3.4(2H, m), 3.9-4.0(1H, m), 7.3-7.7(5H, m), 7.9-8.2(2H, m), 10.1-10.4(1H, br s), 12.7-13.3(1H, br s)	1644.2
226	391	7.54	2.06-2.12 (1H, m), 2.35-2.50 (1H, m), 2.79 (6H, s), 2.92-3.06 (2H, m), 3.76 (1H, t J7.5 Hz), 7.36-7.49 (3H, m), 7.66-7.70 (2H, m), 8.01 (1H, s), 8.11 (1H, s), 9.52 (1H, br), 10.26 (1H, br), 13.02 (1H, br).	1670.8, 1199.7, 1132.7
227	377	8.75	3.47-3.51 (1H, m), 3.85-3.93 (1H, m), 4.29 (1H, t J 7.2 Hz), 7.36-7.51 (3H, m), 7.67-7.77 (2H, m), 8.03 (1H, s), 8.09 (1H, s), 9.39 (1H, br), 10.43 (1H, br), 13.04 (1H, br). TFA salt	1671.4, 1200.1, 1132.3
228	447	8.48	2.01 - 2.10 (1H, m), 2.32 - 2.41 (1H, m), 2.66 - 2.81 (2H, m), 3.78 (1H, t), 7.27 - 7.31 (1H, d), 7.35 - 7.42 (3H, m), 7.48 - 7.56 (6H, m), 7.60 - 7.64 (1H, m), 7.70 (1H, d), 7.75 (2H, d), 7.90 (1H, d), 8.16 (1H, s), 8.42 (1H, s) D_4-MeOH	3211, 1665, 1598, 1562, 1496, 1312, 805, 764
229	413	8.10	2.04 - 2.13 (1H, m), 2.34 - 2.43 (1H, m), 2.71 - 2.86 (2H, m), 3.02 - 3.07 (1H, m), 3.79 (1H, t), 7.28 - 7.53 (9H, m), 7.71 (1H, d), 7.79 (1H, s), 8.36 (1H, s) D_4-MeOH	3227, 2966, 1660, 1598, 1557, 1491, 1312, 1199, 1184, 1132, 794
230	439	8.12	2.14 - 2.22 (1H, m), 2.41 - 2.51 (1H, m), 2.85 - 3.02 (2H, m), 3.82 (1H, t), 7.31 - 7.35 (1H, m), 7.41 (2H, t), 7.47 - 7.57 (4H, m), 7.72 - 7.74 (2H, m), 8.22 (2H, s), 8.40 (1H, s) D_4-MeOH	-
231	425	8.90	-	-
232	465	8.93	2.91 (1H, dd), 3.24 (1H, dd), 3.78 (1H, t), 7.21 (1H, d), 7.29 (1H, d), 7.37 (2H, t), 7.44 (1H, t), 7.60-7.65 (2H, m), 7.84 (1H, d), 8.17 (1H, s), 8.40 (1H, s), 9.36 (1H, s), 10.24 (1H, s), 12.14 (1H, s).	3267, 1649, 1613, 1564, 1538, 1493, 1474, 1405, 1330, 1265, 1241, 1204, 1134, 1031, 877, 859
233	363	7.50	2.43 (3H, s), 2.86 (1H, dd), 3.21 (1H, dd), 3.74 (1H, t), 7.30-7.38 (3H, m), 7.59-7.62 (2H, m), 8.08 (1H, s), 10.21 (1H, s), 12.54 (1H, s).	3242, 2918, 1655, 1596, 1560, 1510, 1473, 1375, 1308, 1261, 1181, 1133, 1064, 1031, 989, 949, 870, 844.
234	457	8.59	1.81 (1H, m), 2.15 (1H, m), 2.52 (1H, m), 2.99 (1H, m), 3.91 (1H, m), 7.45 (3H, m), 7.60(2H, s), 7.69 (1H, m), 7.75 (1H, s), 7.91(2H, m), 8.43 (1H, s), 10.35 (1H, s), 12.77-13.56 (1H, br s).	1662, 1609, 1560, 1494, 1282

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
235	429	7.32	1.79 (1H, m), 2.18 (1H, m), 2.50 (1H, m), 2.89(1H, m), 3.72 (1H, m), 3.89 (3H, s), 7.18 (1H, m), 7.28(2H, m), 7.40 (2H, m), 7.55(2H, m), 8.01(2H, d, J=8.0Hz), 8.08(2H, d, J=8.2Hz), 8.45 (1H, s), 10.24 (1H, s), 12.92-13.45 (1H, br s).	1654, 1610, 1493, 1281
236	447	8.57	1.79 (1H, m), 2.18 (1H, m), 2.51 (1H, m), 2.92(1H, m), 3.88 (1H, m), 7.20 (1H, m), 7.30(2H, m), 7.40 (3H, m), 7.50(4H, m), 7.74 (2H, d, J= 7.9Hz), 7.81(2H, d, J= 8.1Hz), 7.99(2H, d, J= 7.4Hz), 8.53(1H, s), 10.24(1H, s), 12.70-13.48 (1H, br s).	1660, 1557, 1492, 1320
237	415	5.21	1.99 (1H, m), 2.26 (1H, m), 2.63 (1H, m), 2.78(1H, m), 3.73 (1H, m), 7.22 (1H, m), 7.36(4H, m), 7.57 (2H, s), 7.55(2H, m), 7.66(3H, br s), 7.99(2H, d, J=8.1Hz), 8.08(2H, d, J=8.2Hz), 8.45 (1H, s), 10.20 (1H, s), 13.33 (1H, s). TFA salt	1667, 1591, 1493, 1325
238	385	7.46	2.05 - 2.11 (1H, m), 2.32 - 2.42 (1H, m), 2.47 (3H, s), 2.68 - 2.80 (2H, m), 3.78 (1H, t), 7.24 - 7.31 (2H, m), 7.36 - 7.42 (3H, m), 7.47 - 7.53 (4H, m), 7.69 (1H, d), 7.73 (1H, s), 8.35 (1H, s) D_4-MeOH	3267, 1665, 1588, 1562, 1491, 1312, 1173, 789
239	455	8.26	2.02 - 2.11 (1H, m), 2.35 - 2.41 (1H, m), 2.67 - 2.82 (2H, m), 3.79 (1H, t), 7.27- 7.39 (4H, m), 7.48 - 7.55 (4H, m), 7.83 (1H, s), 7.96 (1H, d), 8.38 (1H, s) D_4-MeOH	3227, 1665, 1547, 1501, 1265, 1219, 1163, 805
240	389	7.27	2.03 - 2.11 (1H, m), 2.33 - 2.42 (1H, m), 2.69 - 2.84 (2H, m), 3.79 (1H, t), 7.14- 7.18 (1H, m), 7.28 - 7.31 (1H, m), 7.38 (2H, t), 7.47 - 7.57 (5H, m), 7.66 (1H, d), 7.77 (1H, d), 8.40 (1H, s) D_4-MeOH	3237, 1660, 1588, 1552, 1491, 1465, 1306, 1194, 861
241	405	7.76	2.15 - 2.22 (1H, m), 2.42 - 2.51 (1H, m), 2.85 - 3.01 (2H, m), 3.82 (1H, t), 7.31- 7.35 (1H, m), 7.39 - 7.55 (8H, m), 7.87 (1H, d), 7.93 (1H, s), 8.37 (1H, s) D_4-MeOH, TFA salt	3048, 1655, 1486, 1214, 1143, 799
242	315	6.30	2.84 (1H, dd), 3.22 (1H, dd), 3.75 (1H, t), 7.37-7.47 (6H, m), 7.99 (1H, s), 8.13 (1H, s), 10.19 (1H, s), 12.97 (1H, s).	3281, 1644, 1597, 1547, 1492, 1442, 1341, 1309, 1234, 1093, 1048, 1014, 944, 896, 880, 860, 823.
243	349	7.15	2.93 (1H, dd), 3.27 (1H, dd), 3.81 (1H, t), 7.35-7.40 (2H, m), 7.47 (1H, d), 7.61-7.64 (2H, m), 8.00 (1H, s), 8.12 (1H, s), 10.24 (1H, s), 12.99 (1H, s).	3280, 2926, 1670, 1597, 1560, 1507, 1473, 1369, 1310, 1290, 1236, 1202, 1133, 1079, 1031, 945, 878, 855, 838, 819.

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
244	429	7.32	2.02 - 2.12 (1H, m), 2.33 - 2.43 (1H, m), 2.70 - 2.85 (2H, m), 3.79 (1H, t), 3.98 (3H, s), 7.28- 7.32 (1H, m), 7.38 (2H, t), 7.48 - 7.56 (4H, m), 7.66 (1H, t), 8.07 (1H, d), 8.18 (1H, d), 8.36 (1H, s), 8.59 (1H, s) D_4-MeOH	3232, 1711, 1650, 1547, 1486, 1424, 1271, 1250, 1184, 805
245	335	6.76	2.44 (3H, s), 2.86-2.90 (1H, m), 3.12-3.17 (1H, m), 3.97 (1H, t J 6.5 Hz), 6.88 (1H, m), 6.98 (1H, m), 7.34-7.41 (2H, m), 8.09 (1H, s), 10.29 (1H, br), 12.57 (1H, br).	1654.4, 1566.6, 1510.9, 1307.4
246	415	5.49	2.14 - 2.22 (1H, m), 2.41 - 2.49 (1H, m), 2.87 - 3.01 (2H, m), 3.83 (1H, t), 7.31- 7.35 (1H, m), 7.41 (2H, t), 7.47 - 7.56 (4H, m), 7.65 (1H, t), 8.09 (1H, d), 8.16 (1H, d), 8.34 (1H, s), 8.59 (1H, s) D_4-MeOH, TFA salt	3063, 1680, 1557, 1491, 1189, 1143
247	349	7.17	2.89 (1H, dd), 3.22 (1H, dd), 3.77 (1H, t), 7.35-7.40 (2H, m), 7.46 (1H, d), 7.60-7.63 (2H, m), 8.00 (1H, s), 8.12 (1H, s), 10.23 (1H, s), 12.98 (1H, s).	3278, 2928, 1650, 1597, 1558, 1507, 1473, 1338, 1311, 1236, 1200, 1133, 1077, 1031, 945, 877.
248	414	5.90	2.08 - 2.15 (1H, m), 2.37 - 2.42 (1H, m), 2.74 - 2.90 (2H, m), 3.80 (1H, t), 7.29- 7.32 (1H, m), 7.39 (2H, t), 7.47 - 7.54 (4H, m), 7.63 (1H, t), 7.92 (1H, d), 8.17 (1H, d), 8.34 (1H, s), 8.45 (1H, s) D_4-MeOH	3263, 1644, 1547, 1486, 1383, 1317, 1204, 1137, 799
249	385	7.49	1.99 (1H, m), 2.29 (1H, m), 2.65 (3H, s), 2.69(1H, m), 2.80 (1H, m), 3.60 (1H, m), 7.29(1H, m), 7.21-7.43(4H, br m), 7.55(2H, m), 7.69(2H, br s), 8.05(2H, m),8.11(2H, m), 8.53(1H, s), 10.28 (1H, s), 13.41(1H, br s).	1671, 1606, 1202
250	413	6.87	-	-
251	453	8.64	1.98 - 2.06 (1H, m), 2.31 - 2.39 (1H, m), 2.47 (3H, s), 2.67 - 2.83 (2H, m), 3.78 (1H, t), 7.25 (1H, d), 7.39 - 7.42 (2H, m), 7.49 - 7.54 (3H, m), 7.67 - 7.73 (3H, m), 8.35 (1H, s) D_4-MeOH	3217, 1644, 1568, 1496, 1465, 1312, 1199, 1178, 1127, 974
252	457	8.55	2.01 - 2.15 (1H, m), 2.31 - 2.40 (1H, m), 2.59 - 2.83 (2H, m), 3.78 (1H, t), 7.16 (1H, d), 7.41 (1H, d), 7.48 - 7.57 (4H, m), 7.65 - 7.67 (2H, m), 7.77 (1H, d), 8.41 (1H,s) D_4-MeOH	3227, 1650, 1588, 1557, 1485, 1470, 1312, 1137, 1040, 876
253	475	9.04	2.11 - 2.18 (1H, m), 2.45 - 2.51 (1H, m), 2.82 - 3.03 (2H, m), 3.81 (1H, t), 7.41 - 7.45 (2H, m), 7.50 - 7.58 (4H, m), 7.67 (1H, s), 7.87 (1H, d), 7.94 (1H, s), 8.39 (1H,s) D_4-MeOH	3227, 1680, 1491, 1465, 1194, 1137, 846, 805

Compd. No	M+1 (obs)	R_t	^1H NMR	IR (cm^{-1})
254	371	6.55	1.95-2.01 (1H, m), 2.28-2.33 (1H, m), 2.70-2.83 (2H, m), 4.13 (1H, t), 4.52 (1H, s), 7.27 (1H, t), 7.40-7.45 (2H, m), 7.53-7.58 (2H, m), 7.72 (3H, br s), 8.22 (1H, s), 10.30 (1H, s), 13.40 (1H, s). TFA salt	3291, 3068, 2924, 1670, 1554, 1498, 1459, 1306, 1201, 1137, 1063, 959, 840, 801.
255	391	7.56	2.67 (3H, s), 3.15-3.27 (1H, m), 3.45-3.53 (1H, m), 4.07 (1H, t), 7.37-7.43 (2H, m), 7.60-7.71 (4H, m), 7.87 (3H, br s), 8.54 (1H, s), 10.45 (1H, s), 13.84 (1H, s). TFA salt	3016, 1669, 1564, 1497, 1467, 1408, 1364, 1324, 1201, 1135, 1033, 951, 881, 838, 828.
256	523	9.11	2.00 - 2.05 (1H, m), 2.32 - 2.42 (1H, m), 2.70 - 2.85 (2H, m), 3.79 (1H, t), 7.34 (1H, d), 7.42 (1H, d), 7.49 - 7.57 (3H, m), 7.61 - 7.68 (2H, m), 7.83 (1H, s), 7.96 (1H, d), 8.40 (1H,s) D_4-MeOH	2.00 - 2.05 (1H, m), 2.32 - 2.42 (1H, m), 2.70 - 2.85 (2H, m), 3.79 (1H, t), 7.34 (1H, d), 7.42 (1H, d), 7.49 - 7.57 (3H, m), 7.61 - 7.68 (2H, m), 7.83 (1H, s), 7.96 (1H, d), 8.40 (1H,s)
257	333	6.13	2.87-2.91 (1H, m), 3.17-3.22 (1H, m), 4.06-4.10 (1H, m), 7.19-7.23 (1H, m), 7.39-7.52 (4H, s), 8.01 (1H, s), 8.14 (1H, s), 10.35 (1H, br), 12.98 (1H, br).	1664.0, 1507.9, 1457.7
258	333	6.24	2.83-2.88 (1H, m), 3.13-3.19 (1H, m), 4.00-4.03 (1H, m), 7.27-7.29 (1H, m), 7.39-7.52 (4H, s), 8.00 (1H, s), 8.14 (1H, s), 10.34 (1H, br), 12.98 (1H, br).	1738.7, 1365.7, 1216.9
259	396	6.67	2.03 - 2.11 (1H, m), 2.32 - 2.41 (1H, m), 2.67 - 2.81 (2H, m), 3.78 (1H, t), 7.28 - 7.31 (1H, m), 7.38 (2H, t), 7.46 - 7.49 (3H, m), 7.55 (1H, d), 7.87 (2H, d), 8.15 (2H, d), 8.40 (1H,s) D_4-MeOH	3283, 2930, 2228, 1655, 1609, 1557, 1496, 1317, 1194, 989, 846
260	400	5.26	2.16 - 2.25 (1H, m), 2.42 - 2.51 (1H, m), 2.80 - 2.03 (2H, m), 3.84 (1H, t), 4.25 (2H, s), 7.30 - 7.56 (8H, m), 7.38 (1H, t), 7.99 - 8.02 (2H, m), 8.45 (1H, s) D_4-MeOH, TFA salt	3042, 2945, 1670, 1496, 1199, 1132, 820, 794
261	439	5.33	2.16 - 2.24 (1H, m), 2.42 - 2.52 (1H, m), 2.83 - 2.91 (1H, m), 2.96 - 3.02 (1H, m), 3.83 (1H, t), 7.32 - 7.35 (1H, m), 7.41 (2H, t), 7.47 - 7.50 (3H, m), 7.56 (1H, d), 8.17 - 8.21 (4H, m), 8.49 (1H, s) D_4-MeOH, TFA salt	3211, 3063, 1665, 1491, 1194, 1132, 835, 789
262	414	5.45	-	-
263	415	4.96	2.12 - 2.22 (1H, m), 2.42 - 2.51 (1H, m), 2.84 - 2.92 (1H, m), 2.95 - 3.03 (1H, m), 3.84 (1H, t), 7.30 - 7.34 (1H, m), 7.40 (2H, t), 7.47 - 7.54 (4H, m), 7.98 (2H, d), 8.14 (2H, d), 8.40 (1H, s) D_4-MeOH	3033, 1657, 1609, 1541, 1495, 1380, 1315, 1262, 1175, 1099, 1016, 995, 955, 865, 842.
264	443	5.37	1.88-1.90 (1H, m), 2.32-2.35 (1H, m), 2.62-2.64 (1H, m), 2.70-2.72 (1H, m), 2.90-2.94 (2H, m), 4.13-4.17 (1H, m), 7.23-7.27 (1H, m), 7.32-7.51 (8H, m), 7.78-7.83 (3H, m), 8.33 (1H, s), 11.01 (1H, brs), 13.10 (1H, vbrs).	3036, 1655, 1553, 1495, 1400, 1319, 699

Compd. No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
265	463	8.19	1.88 (1H, m), 2.15 (1H, m), 2.50 (2H, m), 3.87 (1H, m), 7.06 (2H, m), 7.18(4H, m), 7.29 (2H, m), 7.40(4H, m), 7.50(2H, s), 7.90(2H, m), 8.56 (1H, s), 10.20 (1H, s), 12.75-13.35(1H, br s).	1661, 1589, 1521, 1490, 1236
272	421	4.68	1.95 - 2.04 (1H, m), 2.32 - 2.41 (1H, m), 2.66 - 2.76 (2H, m), 3.83 (1H, dd), 7.24 (1H, t), 7.44 - 7.53 (3H, m), 7.79 (1H, d), 7.98 - 8.00 (2H, m), 8.04 (1H, s), 8.47 (1H, dd), 8.62 (1H, d) D_4-MeOH	3237, 3083, 1665, 1537, 1204, 1137, 840, 810, 728

Example 42

[00170] We have prepared other compounds of formula **I** by methods substantially similar to those described in Examples 1 through 39 and by the general synthetic Schemes I-VII. The characterization data for these compounds is summarized in Table 7 below and includes HPLC, LC/MS (observed), IR, and ^{1}H NMR data.

[00171] ^{1}H NMR data is summarized in Table 7 below wherein ^{1}H NMR data was obtained at 400 MHz in deuterated DMSO, unless otherwise indicated, and was found to be consistent with structure. Compound numbers correspond to the compound numbers listed in Table 1.

Table 7. Characterization data for Selected Compounds of Formula I

Compd No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
1000	489	7.68	1.79-1.83 (1H, m), 2.12-2.24 (1H, m), 2.95-3.08 (2H, m), 3.64 (1H, t, J = 7.4Hz), 3.71 (3H, s), 3.76 (3H, s), 5.00 (2H, s), 6.80-7.49 (9H, m), 7.99 (1H, s), 8.10 (1H, s), 9.98 (1H, s), 12.90 (1H, s).	IR (Solid): 2967, 2865, 1715, 1513, 1459, 1262, 1151, 1081, 1012.
1001	395	6.93	0.72-0.89 (3H, m), 1.30-1.50 (2H, m), 1.82-2.30 (3H, m), 2.90-3.09 (2H, m), 3.32-3.65 2H, m), 3.74 (3H, s), 6.85-6.95 (2H, m), 7.20-7.50 (4H, m), 7.58-8.12 (3H, m), 10.00 (1H, s), 12.90 (1H, s).	-
1002	355	4.80	1.69-1.81 (1H, m), 2.07-2.19 (1H, m), 2.45-2.59 (2H, m), 3.67-3.80 (7H, m), 6.82-6.96 (2H, m), 7.01-7.05 (1H, m), 7.46-7.49 (2H, m), 7.99 (1H, s), 8.10 (1H, s), 10.00 (1H, s), 12.90 (1H, brs).	IR (Solid): 1665, 1593, 1551, 1508, 1455, 1269, 1231, 1141, 1026.
1003	443	7.55	1.90-2.30 (4H, m), 3.50-3.70 (1H, m), 3.71-3.75 (3H, m), 4.18-4.32 (2H, m), 6.86-6.93 (2H, m), 7.10-7.49 (8H, m), 7.95-8.02 (1H, m), 8.08-8.14 (1H, m), 8.23-8.50 (1H, m), 9.78-10.05 (1H, m), 12.92 (1H, brs).	IR (Solid): 1651, 1546, 1508, 1455, 1246, 1174, 1026.

Compd No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
1004	423	6.49	1.85-1.97 (1H, m), 2.16-2.33 (3H, m), 3.25-3.58 (8H, m), 3.63-3.69 (1H, m), 3.72 (3H, s), 6.90 (2H, d, J = 11.58Hz), 7.31 (2H, d, J = 11.4Hz), 7.36-7.49 (2H, m), 7.99 (1H, s), 8.11 (1H, s), 10.00 (1H, s), 12.90 (1H, s).	IR (Solid): 1655, 1627, 1503, 1465, 1431, 1246, 1112.
1005	311	4.85	1.92-2.05 (1H, m), 2.20-2.32 (1H, m), 2.78-2.88 (2H, m), 4.07-4.13 (1H, m), 6.81 (1H, t), 6.89 (1H, d), 7.11 (1H, t), 7.29 (1H, d), 7.38-7.50 (2H, m), 8.00 (1H, s), 8.12 (1H, s), 9.82 (1H, s), 9.95 (1H, s), 13.00 (1H, br s)	1672, 1511, 1457, 1193, 1137, 838, 816, 800, 756, 723
1006	309	5.26	1.90-2.08 (1H, m), 2.27-2.38 (1H, m), 2.43 (3H, s), 2.65-2.75 (1H, m), 2.75-2.85 (1H, m), 3.75-3.82 (1H, m), 7.20-7.50 (8H, m, + 2H br hump), 8.04 (1H, s), 10.10 (1H, s), 12.57 (1H, br s)	1672, 1199, 1135, 838, 799, 722, 701
1007	339	5.54	1.68-1.80 (1H, m), 2.04-2.16 (1H, m), 2.45 (3H, s), 2.55-2.62 (2H, m), 3.85 (3H, s), 4.15-4.20 (1H, m), 6.95 (1H, t), 7.00 (1H, d), 7.20-7.25 (1H, m), 7.35-7.48 (3H, m), 8.08 (1H, s), 9.91 (1H, s), 12.48 (1H,br s)	1674, 1492, 1247, 1201, 1135, 752, 672
1008	351	6.40	1.78 (3H, s), 1.80-1.90 (1H, m), 2.18-2.29 (1H, m), 2.40 (3H, s), 2.97-3.05 (2H,m), 3.69-3.77 (1H, m), 7.29 (1H, t), 7.34-7.40 (4H, m), 7.40-7.45 (2H, m), 7.86 (1H, br t), 8.05 (1H, s), 10.01 (1H, s), 12.51 (1H, br s)	3279, 1648, 1553, 1513, 1490, 1449, 1367, 1310, 995, 803, 773, 741, 696
1009	338	7.29	1.90-2.12 (1H, m), 2.21-2.41 (3H, m), 3.51 (3H, s), 3.69-3.76 (1H, m), 7.22-7.50 (6H, m), 8.00 (1H, s), 8.09 (1H, s), 9.81 (1H, s), 12.90 (1H, brs).	IR (Solid): 1722, 1651, 1598, 1555, 1508, 1450, 1255, 1155, 945.
1010	414	8.65	1.96-2.12 (1H, m), 2.24-2.41 (3H, m), 3.69-3.83 (1H, m), 5.05-5.13 (2H, m), 7.21-7.48 (6H, m), 7.90 (1H, s), 8.11 (1H, s), 10.09 (1h, s), 12.91 (1H, s).	-
1011	324	4.95	-	3280, 1703, 1655, 1593, 1551, 1503, 1236.
1012	338	7.29	1.90-2.12 (1H, m), 2.21-2.41 (3H, m), 3.51 (3H, s), 3.69-3.76 (1H, m), 7.22-7.50 (6H, m), 8.00 (1H, s), 8.09 (1H, s), 9.81 (1H, s), 12.90 (1H, brs).	IR (Solid): 1722, 1651, 1598, 1555, 1508, 1450, 1255, 1155, 945.
1013	473	8.22	($CDCl_3$) 1.95-2.08 (1H, m), 2.45-2.61 (4H, m), 3.23-3.46 (2H, m), 3.58-3.65 (1H, m), 3.84 (3H, s), 4.99-5.19 (3H, m), 6.81-7.02 (3H, m), 7.21-7.42 (7H, m), 7.92 (1H, s), 8.08 (1H, s), 9.78 (1H, brs)	-
1014	325	5.34	1.69-1.84 (1H, m), 2.06-2.21 (1H, m), 2.44-2.58 (2H, m), 3.75 (3H, s), 3.78-3.83 (1H, m), 6.78-6.84 (1H, m), 6.95-7.01 (2H, m), 7.21-7.27 (1H, m), 7.35-7.41 (1H, m), 7.41-7.47 (1H, m), 7.99 (1H, brs), 8.11 (1H, brs), 10.08 (1H, s), 12.96 (1H, brs).	-

Compd No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
1015	339	5.56	1.68-1.80 (1H, m), 2.06-2.20 (1H, m), 2.41 (3H, s), 2.42-2.59 (2H, m), 3.75 (3H, s), 3.78-3.83 (1H, m), 6.75-6.83 (1H, m), 6.91-7.02 (2H, m), 7.19-7.28 (1H, m) 7.31-7.43 (2H, m), 8.09 (1H, m), 10.10 (1H, s), 12.53 (1H, s).	1651, 1593, 1555, 1508, 1484, 1303, 1260, 1146, 1045.
1016	-	5.15	1.70-1.82 (1H, m), 2.05-2.15 (1H, m), 2.55-2.65(2H, m), 2.82 (3H, d), 3.83 (3H, s), 4.13-4.28 (1H, m), 5.85 (1H, d), 6.92 (1H, t), 7.00 (1H, d), 7.11 (1H,d), 7.18-7.28 (2H, m), 7.38 (1H, t), 8.00 (1H, s), 9.84 (1H, s), 11.24 (1H, s)	1657, 1599, 1491, 1415, 1303, 1244, 1026, 810, 756, 735, 667
1017	325	5.34	1.69-1.84 (1H, m), 2.06-2.21 (1H, m), 2.44-2.58 (2H, m), 3.75 (3H, s), 3.78-3.83 (1H, m), 6.78-6.84 (1H, m), 6.95-7.01 (2H, m), 7.21-7.27 (1H, m), 7.35-7.41 (1H, m), 7.41-7.47 (1H, m), 7.99 (1H, brs), 8.11 (1H, brs), 10.08 (1H, s), 12.96 (1H, brs).	-
1018	339	5.56	1.68-1.80 (1H, m), 2.06-2.20 (1H, m), 2.41 (3H, s), 2.42-2.59 (2H, m), 3.75 (3H, s), 3.78-3.83 (1H, m), 6.75-6.83 (1H, m), 6.91-7.02 (2H, m), 7.19-7.28 (1H, m)7.31-7.43 (2H, m), 8.09 (1H, m), 10.10 (1H, s), 12.53 (1H, s).	IR (Solid): 1651, 1593, 1555, 1508, 1484, 1303, 1260, 1146, 1045.
1019	487	8.69	1.36 (3H, t), 1.78-1.92 (1H, m), 2.08-2.20 (1H, m), 2.43 (3H, s), 2.91-3.11 (2H,m), 4.06 (2H, q), 5.00 (2H, s), 6.85-7.02 (2H, m), 7.20 (1H, t), 7.25-7.45 (9H, m), 8.09 (1H, s), 9.85 (1H, s)	3280, 1686, 1648, 1601, 1494, 1474, 1453, 1296, 1267, 1248, 1079, 1051, 1009, 771, 750, 694
1020	461	8.22	1.89-2.08 (2H, m), 2.25-2.46 (5H, m), 4.86-5.03 (3H, m), 7.10-7.51 (11H, m), 7.96-8	-
1021	461	8.32	1.78-1.93 (1H, m), 2.11-2.25 (1H, m), 2.42 (3H, s), 2.92-3.12 (2H, m), 4.05 (1H, brt, J = 6.3Hz), 4.99 (2H, s), 7.11-7.59 (12H, m), 8.09 (1H, s), 10.13 (1H, s), 12.55 (1H, s).	-
1022	327	5.54	1.70-1.86 (1H, m), 2.06-2.20 (1H, m), 2.42 (3H, s), 2.42-2.65 (2H, m), 4.01-4.18 (1H, m), 7.10-7.61 (5H, m), 8.09 (1H, s), 10.18 (1H, s), 12.51 (1H, brs).	-
1023	401	6.79	2.06 (1H, m), 2.35 (1H, m), 2.67 (1H, m), 2.77 (1H, m), 3.82 (3H, s), 3.98 (1H, t), 7.10 (2H, d), 7.25-7.57 (7H, m), 7.81 (2H, d), 8.13 (3H, s), 8.50 (1H, s), 10.60 (1H, s) HCl salt	-
1024	461	8.22	1.89-2.08 (2H, m), 2.25-2.46 (5H, m), 4.86-5.03 (3H, m), 7.10-7.51 (11H, m), 7.96-8	-
1025	369	5.65	1.75-1.87 (1H, m), 2.10-2.25 (1H, m), 2.44 (3H, s), 2.57-2.70 (2H, m), 3.79 (3H, s), 3.81 (3H, s), 4.10-4.19 (1H, m), 5.20 (2H, br hump), 6.92-7.02 (1H, m), 7.00-7.09 (2H, m), 7.30-7.40 (2H, m), 8.08 (1H,s), 10.00 (1H, s), 12.50 (1H, br s)	1658, 1586, 1550, 1510, 1478, 1431, 1307, 1278, 1234, 1202, 1172, 1086, 1001, 801, 769, 751

Compd No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
1026	315	5.26	1.80-1.95 (1H, m), 2.10-2.22 (1H, m), 2.45 (3H, s), 2.55-2.65 (1H, m), 4.15-4.25 (1H, m), 6.93-7.00 (1H, m), 7.00-7.05 (1H, m), 7.30-7.42 (3H, m), 8.07 (1H, s), 10.27 (1H, s), 12.58 1H, br s)	1658, 1564, 1511, 1484, 1309, 991, 806, 771, 700
1027	389	7.10	2.03 (1H, m), 2.34 (1H, m), 2.67 (1H, m), 2.78 (1H, m), 3.90 (1H, t), 7.28 (1H, m), 7.35-7.45 (6H, m), 7.51-7.57 (2H, m), 7.92 (2H, m), 7.97 (3H, s), 8.49 (1H, s), 10.48 (1H, s) HCl salt	-
1028	371	6.86	2.03 (1H, m), 2.35 (1H, m), 2.67 (1H, m), 2.78 (1H, m), 3.93 (1H, t), 7.26-7.58 (11H, m), 7.90 (2H, d), 8.01 (3H, s), 8.52 (1H, s), 10.51 (1H, s) HCl salt	-
1029	-	7.72	2.44-2.75 (2H, m), 3.09-3.20 (2H, m), 4.12-4.20 (4H, m), 7.21-7.30 (2H, m), 7.41-7.51(2H, m), 7.64-7.75 (4H, m), 7.88 (1H, m), 8.13 (1H, m), 8.27 (1H, m), 8.73 (1H, s), 9.55 (1H, s), 10.50 (1H, s), 12.50 (1H, s) TFA salt	-
1030	-	5.82	1.99-2.09 (2H, m), 2.62-2.67 (2H, m), 3.71-3.78 (4H, m), 6.95-6.99 (2H, m), 7.26-7.31 (4H, m), 7.68-7.83 (3H, m), 8.28-8.33 (2H, m), 9.01 (1H, s), 10.05 (1H, s), 12.02 (1H, s) TFA salt	-
1031	-	7.19	2.26-2.32 (2H, m), 2.67-2.78 (2H, m), 3.69-3.78 (4H, m), 6.87-6.99 (3H, m), 7.20-7.46 (4H, m), 7.70 (1H, m), 7.83 (1H, d), 8.14 (1H, m), 8.33 (1H, m), 9.35 (1H, s), 10.09 (1H, s), 12.15 (1H, s) TFA salt	-
1032	313	5.23	1.69-1.82 (1H, m), 2.05-2.20 (1H, m), 2.45-2.61 (2H, m), 4.05-4.19 (1H, m), 7.10-7.61 (6H, m), 7.99 (1H, s), 8.13 (1H, s), 10.18 (1H, s), 12.99 (1H, brs).	1660, 1589, 1555, 1498, 1479, 1227.
1033	309	5.46	1.70-1.88 (1H, m), 2.10-2.23 (1H, m), 2.42 (3H, s), 2.45-2.62 (2H, m), 3.69-3.89 (1H, m), 7.20-7.48 (7H, m), 8.08 (1H, s), 10.15 (1H, brs), 12.50 (1H, brs).	1651, 1593, 1560, 1503, 1479, 1446, 1308.
1034	309	5.45	1.70-1.88 (1H, m), 2.10-2.23 (1H, m), 2.42 (3H, s), 2.45-2.62 (2H, m), 3.69-3.89 (1H, m), 7.20-7.48 (7H, m), 8.08 (1H, s), 10.15 (1H, brs), 12.50 (1H, brs).	1651, 1593, 1560, 1503, 1479, 1446, 1308.
1035	315	5.25	1.75-1.90 (1H, m), 2.08-2.24 (1H, m), 2.2 (3H, s), 2,53-2.65 (2H, m), 3.96-4.02 (1H, m), 7.15-7.20 (1H, m), 7.30-7.45 (3H, m), 7.45-7.53 (1H, m), 8.10 (1H, s), 10.18 (1H, s), 12.61 (1H, br s)	3273, 1656, 1663, 1551, 1511, 1483, 1450, 1309, 1237, 992, 866, 805, 786, 752, 701, 669
1036	428	7.07	1.70-1.83 (1H, m), 2.09-2.23 (1H, m), 3.15-3.52 (2H, m), 3.79-3.90 (1H, m), 4.42-4.53 (2H, m), 7.15-7.61 (11H, m), 8.49 (1H, s), 8.84-8.95 (1H, m), 10.23 (1H, brs).	-
1037	299	4.85	1.83-1.97 (1H, m), 2.02-2.14 (1H, m), 2.43 (3H, s), 2.54-2.66 (2H, m), 3.93-4.02 (1H, m), 6.27 (1H, s), 6.41 (1H, s), 7.25-7.42 (2H,m), 7.56 (1H,s), 8.08 (1H, s), 10.19 (1H, s), 12.57 (1H, br s)	1659, 1566, 1511, 1484, 1449, 1308, 1011, 993, 936, 876, 807, 791, 770, 740

Compd No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
1038	400	7.43	1.90 (1H, m), 2.07-2.25 (1H, m), 2.26 (3H, s), 2.56-2.67 (2H, m), 3.81 (1H, m), 6.59 (1H, m), 7.09 (1H, m), 7.24-7.48 (9H, m), 8.29 (1H, s), 8.75 (1H, s), 10.10 (1H, s), 11.92 (1H, s)	-
1039	404	7.41	2.27 (1H, m), 2.64-2.72 (2H, m), 3.81 (1H, m), 4.02 (1H, m), 6.56 (1H, m), 7.22-7.44 (9 H, m), 7.62 (1H, d), 8.34 (1H, s), 9.15 (1H, br s), 10.15 (1H, br s), 12.07 (1H, br s)	-
1040	414	7.24	1.71-1.82 (1H, m), 2.12-2.25 (1H, m), 2.46-2.61 (2H, m), 3.86 (1H, brt, J = 6.6Hz), 7.05-7.12 (1H, m), 7.20-7.28 (1H, m), 7.29-7.48 (6H, m), 7.52-7.65 (2H, m), 7.89 (1H, d, J = 8.0Hz), 8.56 (1H, s), 10.25 (2H, brs).	1651, 1593, 1527, 1489, 1455, 1308, 1231, 1146.
1041	404	5.44	1.67-1.75 (1H, m), 2.06-2.22 (1H, m), 2.42-2.60 (2H, m), 3.78-3.88 (1H, m), 6.69-6.75 (1H, m), 7.19-7.59 (8H, m), 7.90-8.00 (2H, m), 10.18 (1H, s), 10.60 (1H, brs), 12.70 (1H, brs).	-
1042	428	6.03	1.65-1.83 (1H, m), 2.10-2.22 (1H, m), 2.5 (2H obscured), 3.80-3.88 (1H, m), 4.75 (2H,d), 7.20-7.57 (10H, m), 7.82-7.95 (2H, m), 8.08 (1H, s), 9.01 (1H, s), 10.13 (1H, s), 12.77 (1H, br s)	3277, 1650,1630, 1602, 1543, 1507, 1489, 1313, 1232, 1202, 1180, 1135, 799, 715, 695, 668
1043	420	5.86	1.61-1.80 (1H, m), 2.08-2.11 (1H, m), 3.10-3.60 (2H, m), 3.79-3.88 (1H, m), 7.10-7.60 (8H, m), 7.81-8.08 (3H, m), 10.18 (1H, s), 10.80 (1H, brs), 12.76 (1H, brs).	-
1044	420	5.95	1.61-1.80 (1H, m), 2.08-2.11 (1H, m), 3.10-3.60 (2H, m), 3.79-3.88 (1H, m), 7.10-7.60 (8H, m), 7.81-8.08 (3H, m), 10.18 (1H, s), 10.80 (1H, brs), 12.76 (1H, brs).	1651, 1536, 1498, 1412, 1322, 1284.
1045	490	6.42	1.78-1.90 (1H, m), 2.20-2.36 (1H, m), 3.23-3.50 (2H, m), 4.17-4.24 (1H, m), 7.09-7.28 (2H, m), 7.32-7.62 (3H, m), 7.80-7.91 (2H, m), 8.10 (1H, s), 10.20 (1H, brs), 10.80 (1H, brs), 12.75 (1H, brs).	1647, 1546, 1468, 1439, 1422, 1318, 1282
1046	490	6.44	1.78-1.90 (1H, m), 2.20-2.36 (1H, m), 3.23-3.50 (2H, m), 4.17-4.24 (1H, m), 7.09-7.28 (2H, m), 7.32-7.62 (3H, m), 7.80-7.91 (2H, m), 8.10 (1H, s), 10.20 (1H, brs), 10.80 (1H, brs), 12.75 (1H, brs).	1647, 1546, 1468, 1439, 1422, 1318, 1282
1047	481	7.50	1.82-1.96 (1H, m), 2.24-2.39 (1H, m), 2.52-2.65 (2H, m), 4.20-4.29 (1H, m), 7.15-7.26 (2H, m), 7.28-7.40 (2H, m), 7.45 (1H, t), 7.56-7.67 (1H, m), 7.80-7.90 (1H, m), 8.20 (1H, s), 8.36 (1H, s), 9.36 (1H, s), 10.20 (1H, br s), 12.13 (1H, s).	3308, 1669, 1603, 1559, 1535, 1473, 1443, 1328, 1270, 1237, 1218, 1188, 1127, 994, 876, 806, 784, 666

Compd No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
1048	481	4.48	1.82-1.96 (1H, m), 2.24-2.39 (1H, m), 2.52-2.65 (2H, m), 4.20-4.29 (1H, m), 7.15-7.26 (2H, m), 7.28-7.40 (2H, m), 7.45 (1H, t), 7.56-7.67 (1H, m), 7.80-7.90 (1H, m), 8.20 (1H, s), 8.36 (1H, s), 9.36 (1H, s), 10.20 (1H, br s), 12.13 (1H, s).	3308, 1669, 1603, 1559, 1535, 1473, 1443, 1328, 1270, 1237, 1218, 1188, 1127, 994, 876, 806, 784, 666
1049	420	6.00	1.61-1.80 (1H, m), 2.08-2.11 (1H, m), 3.10-3.60 (2H, m), 3.79-3.88 (1H, m), 7.10-7.60 (8H, m), 7.81-8.08 (3H, m), 10.18 (1H, s), 10.80 (1H, brs), 12.76 (1H, brs).	-
1050	420	6.59	1.13-1.95 (11H, m), 2.12-2.25 (1H, m), 2.39-2.62 (2H, m), 2.84-2.96 (1H, m), 3.67-3.88 (1H, m), 7.15-7.61 (7H, m), 7.89 (1H, s), 10.03-10.15 (2H, m), 12.52 (1h, brs).	1651, 1551, 1484, 1441, 1327
1051	444	6.60	1.69-1.83 (1H, m), 2.07-2.23 (1H, m), 3.19-3.50 (2H, m), 3.78-3.89 (1H, m), 4.80 (2H, s), 6.90-7.59 (12H, m), 8.01 (1H, s), 10.15 (1H, brs), 10.48 (1H, brs), 12.68 (1H, brs).	1670, 1646, 1598, 1536, 1489, 1303, 1231.
1052	369	6.91	1.70-1.82 (1H, m), 2.11-2.24 (1H, m), 2.44-2.59 (2H, m), 3.82-3.91 (1H, m), 7.18-7.60 (10H, m), 7.83-7.95 (1H, m), 8.50 (1H, s), 10.22 (1H, s),	2975, 2885, 1660, 1555, 1489, 1384, 1317, 1255, 1146
1053	369	6.94	1.70-1.82 (1H, m), 2.11-2.24 (1H, m), 2.44-2.59 (2H, m), 3.82-3.91 (1H, m), 7.18-7.60 (10H, m), 7.83-7.95 (1H, m), 8.50 (1H, s), 10.22 (1H, s), 13.20 (1H, brs).	-
1054	411	7.25	1.77-1.87 (1H, m), 2.16-2.27 (1H, m), 2.55-2.66 (2H, m), 3.82-3.90 (1H, m), 7.12-7.50 (8H, m), 7.81-7.88 (1H, m), 8.20 (1H, s), 8.43 (1H, s), 9.34 (1H, s), 10.16 (1H, s), 12.15 (1H, s).	1658, 1628, 1602, 1589, 1560, 1533, 1479, 1330, 1307, 1265, 1238, 1202, 1180, 1134, 799, 786, 729, 699, 682.
1055	411	7.26	1.77-1.87 (1H, m), 2.16-2.27 (1H, m), 2.55-2.66 (2H, m), 3.82-3.90 (1H, m), 7.12-7.50 (8H, m), 7.81-7.88 (1H, m), 8.20 (1H, s), 8.43 (1H, s), 9.34 (1H, s), 10.16 (1H, s), 12.15 (1H, s).	1670, 1603, 1559, 1479, 1329, 1203, 1181, 1137, 799, 723, 700, 675
1056	441	7.40	1.84-1.93 (1H, m), 2,27-2.38 (1H, m), 2.55-2.65 (2H, m), 4.20-4.30 (1H, m), 7.15-7.25 (1H, m), 7.36-7.44 (1H, m), 7.50-7.66 (5H, m), 7.87-7.95 (2H, m), 8.39 (1H, s), 10.30 (1H, br s), 13.20 (1H, br s).	1668, 1560, 1496, 1473, 1443, 1321, 1269, 1218, 993, 957, 825, 807, 777, 749, 720, 698.

Compd No	M+1 (obs)	R_t	^{1}H NMR	IR (cm^{-1})
1057	441	7.38	1.84-1.93 (1H, m), 2,27-2.38 (1H, m), 2.55-2.65 (2H, m), 4.20-4.30 (1H, m), 7.15-7.25 (1H, m), 7.36-7.44 (1H, m), 7.50-7.66 (5H, m), 7.87-7.95 (2H, m), 8.39 (1H, s), 10.30 (1H, br s), 13.20 (1H, br s).	1669, 1559, 1496, 1473, 1443, 1320, 1269, 1218, 1202, 993, 807, 776, 749, 720, 699, 675.

Example 43

AKT-3 Inhibition Assay

[00172] Compounds were screened for their ability to inhibit AKT using a standard coupled enzyme assay (Fox et al., Protein Sci., (1998) **7**, 2249). Assays were carried out in a mixture of 100 mM HEPES 7.5, 10 mM MgCl2, 25 mM NaCl , 1 mM DTT and 3% DMSO. Final substrate concentrations in the assay were 170 μM ATP (Sigma Chemicals) and 200 μM peptide (RPRAATF, American Peptide, Sunnyvale, CA). Assays were carried out at 30 °C and 45 nM AKT. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μM NADH, 30 μg/ML pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[00173] An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of AKT, DTT, and the test compound of interest. 55 μl of the stock solution was placed in a 96 well plate followed by addition of 2 μl of 1 mM DMSO stock containing the test compound (final compound concentration 30 μM). The plate was pre-incubated for about 10 minutes at 30°C and the reaction initiated by addition of 10 μl of enzyme (final concentration 45 nM) and 1 mM DTT. Rates of reaction were obtained using a Molecular Devices SpectraMax Plus plate reader over a 15 minute read time at 30°C. Compounds showing greater than 50% inhibition versus standard wells containing the assay mixture and DMSO without test compound were titrated to determine IC_{50} values.

[00174] The following compounds were shown to have K_i values less than 1 μM for Akt-3 (Compound numbers correspond to the compound numbers listed in Table 1.): I-59, I-60, I-61, I-62, I-64, I-67, I-70, I-73, I-74, I-97 through I-106, I-108 through I-110, I-112, I-115 through I-122, I-124 through I-127, I-129 through I-136, I-138 through I-141, I-141 through I-145, I-147, I-149, I-153, I-155, I-160 through I-175, I-177 though I-189, I-193 through I-210, I-212 through I-227, I-231 through I-234, I-242, I-243, I-245, I-247,

I-251 through I-254, I-256 through I-258, I-1005, I-1006, I-1014, I-1022, I-1043 through I-1047,I-1049 and I-1054.

[00175] The following compounds were shown to have K_i values between 1.0 and 10.0 μM for AKT-3 (Compound numbers correspond to the compound numbers listed in Table 1.): I-5, I-16, I-35, I-40, I-43, I-48 through I-51, I-53 through I-56, I-58, I-63, I-68, I-71, I-72, I-76, I-77, I-78, I-83, and I-85, I-107, I-111, I-113, I-114, I-123, I-128, I-137, I-142, I-150 through I-152, I-154, I-156 through I-159, I-176, I-191, I-192, I-235, I-236, I-241, I-250, I-255, I-259, I-1017, I-1018, I-1023, I-1028, I-1038, I-1039, I-1041, I-1048, I-1050 through I-1052, I-1055 and I-1056.

[00176] The following compounds were shown to have K_i values between 10.0 and 20.0 μM for AKT-3 (Compound numbers correspond to the compound numbers listed in Table 1.): I-2, I-37, I-52, I-65, I-66, I-79, I-82, I-94, and I-95, I-146, I-190, I-1040, I-1053 and I-1057.

Example 44

PDK-1 Inhibition Assay

[00177] Compounds were screened for their ability to inhibit PDK-1 using a radioactive-phosphate incorporation assay (Pitt and Lee, J. Biomol. Screen., (1996) **1**, 47). Assays were carried out in a mixture of 100 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 25 mM NaCl , 2 mM DTT. Final substrate concentrations in the assay were 40 μM ATP (Sigma Chemicals) and 65 μM peptide (PDKtide, Upstate, Lake Placid, NY). Assays were carried out at 30 °C and 25 nM PDK-1 in the presence of ~27.5 nCi/μL of [γ-^{32}P]ATP (Amersham Pharmacia Biotech, Amersham, UK). An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP, and the test compound of interest. 15 μl of the stock solution was placed in a 96 well plate followed by addition of 1 μl of 0.5 mM DMSO stock containing the test compound (final compound concentration 25 μM, final DMSO concentration 5%). The plate was preincubated for about 10 minutes at 30°C and the reaction initiated by addition of 4 μl ATP (final concentration 40 μM).

[00178] The reaction was stopped after 10 minutes by the addition of 100μL 100mM phosphoric acid, 0.01% Tween-20. A phosphocellulose 96 well plate (Millipore, Cat no. MAPHNOB50) was pretreated with 100μL 100mM phosphoric acid, 0.01% Tween-20

prior to the addition of the reaction mixture (100μL). The spots were left to soak for at least 5 minutes, prior to wash steps (4 × 200μL 100mM phosphoric acid, 0.01% Tween-20). After drying, 20μL Optiphase 'SuperMix' liquid scintillation cocktail (Perkin Elmer) was added to the well prior to scintillation counting (1450 Microbeta Liquid Scintillation Counter, Wallac).

[00179] Compounds showing greater than 50% inhibition versus standard wells containing the assay mixture and DMSO without test compound were titrated to determine IC_{50} values.

[00180] The following compounds were shown to have a K_i of less than 1 μM for PDK-1 (Compound numbers correspond to the compound numbers listed in Table 1.): I-100, I-106, I-109, I-110, I-117, I-119, I-120, I-121, I-123, I-125, I-126, I-127, I-130, I-132, I-136, I-138, I-139, I-141, I-162, I-165, I-167, I-168, I-169, I-171, I-172, I-173, I-174, I-179, I-181, I-182, I-189, I-193, I-194, I-195, I-197, I-198, I-206, I-207, I-230, I-231, I-234 through I-238, I-240, I-241, I-242, I-248 through I-251, I-253, I-259 through I-265, I-272, I-1006, I-1022, I-1023, I-1026, I-1027, I-1028, I-1032, I-1034, I-1035, I-1041, I-1043 through I-1046, I-1048, I-1049, I-1052, I-1053, I-1056 and I-1057.

[00181] The following compounds were shown to have a K_i of between 1 μM and 3μM for PDK-1 (Compound numbers correspond to the compound numbers listed in Table 1.): I-98, I-101, I-107, I-112, I-115, I-118, I-122, I-124, I-129, I-137, I-140, I-147, I-158, I-160, I-164, I-166, I-170, I-175, I-176, I-177, I-180, I-185, I-186, I-187, I-188, I-199, I-108, I-212, I-213, I-225, I-228, I-233, I-239, I-1000, I-1005, I-1007, I-1018, I-1036, I-1038, I-1040, I-1054 and I-1055.

[00182] The following compounds were shown to have a K_i of greater than 3μM for PDK-1 (Compound numbers correspond to the compound numbers listed in Table 1.): I-16, I-33, I-54, I-99, I-102, I-105, I-111, I-113, I-114, I128, I-131, I-133, I-134, I-135, I-142, I-145, I-148, I-150, I-153, -154, I-155, I-156, I-159, I-161, I-163, I-178, I-183, I-184, I-190, I-191, I-196, I-200, I-201 through I-204, I-222, I-226, I-227, I-229, I-232, I-233, I-247, I-254, I-257, I-258, I-1000, I-1014 through I-1021, I-1024, I-1025, I-1029, I-1030, I-1031, I-1033, I-1037, I-1039, I-1042, I-1047, I-1050, I-1051 and I-1054.

Example 45

ROCK Inhibition Assay

[00183] Compounds were screened for their ability to inhibit ROCK using a standard coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249). Reactions were carried out in 100 mM HEPES pH 7.5, 10 mM MgCl2, 25 mM NaCl , 1 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay were 13 μM ATP (Sigma chemicals) and 200 μM peptide (KKRNRTLSV, American Peptide, Sunnyvale, CA). Assays were carried out at 30 °C and 200 nM ROCK. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 400 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[00184] An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ROCK, DTT and the test compound of interest. 56 μl of the test reaction was placed in a 384 well plate followed by addition of 1 μl of 2 mM DMSO stock containing the test compound (final compound concentration 30 μM). The plate was preincubated for about 10 minutes at 30 °C and the reaction initiated by addition of 10 μl of enzyme (final concentration 100 nM). Rates of reaction were obtained using a BioRad Ultramark plate reader (Hercules, CA) over a 5 minute read time at 30°C. Compounds showing >50 % inhibition versus standard wells containing DMSO, but no compound, were titrated and IC50's determined using a similar protocol.

[00185] The following compounds were shown to have a K_i of less than 1 μM for ROCK (Compound numbers correspond to the compound numbers listed in Table 1.): I-5, I-6, I-8, I-20, I-25, I-35, I-54, I-69, I-98, I-99, I-100, I-103 through I-107, I-109, I-110, I-120, I-123, I-125, I-126, I-129, I-132, I-137, I-136, I-141, I-142, I-144, I-145, I-153, I-1002, I-1005, I-1006, I-1007, I-1008, and I-1018.

[00186] The following compounds were shown to have a K_i of between 1 μM and 3μM for ROCK (Compound numbers correspond to the compound numbers listed in Table 1.): I-4, I-7, I-9, I-24, I-26, I-27, I-31 through I-34, I-38, and I-41.

[00187] The following compounds were shown to have a K_i of greater than 3μM for ROCK (Compound numbers correspond to the compound numbers listed in Table 1.): I-12, I-13, I-15, I-16, I-23, I-28, I-29, I-30, O-102, I-118, I-139, I-140, I-1003, I-1014, and I-1019.

EXAMPLE 46

PKA Inhibition Assay

[00188] Compounds were screened for their ability to inhibit PKA using a standard coupled enzyme assay (Fox et al., Protein Sci., (1998) **7**, 2249). Assays were carried out in a mixture of 100 mM HEPES 7.5, 10 mM MgCl2, 25 mM NaCl , 1 mM DTT and 3% DMSO. Final substrate concentrations in the assay were 50 μM ATP (Sigma Chemicals) and 80 μM peptide (Kemptide, American Peptide, Sunnyvale, CA). Assays were carried out at 30 °C and 18 nM PKA. Final concentrations of the components of the coupled enzyme system were 2.5 mM phosphoenolpyruvate, 300 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[00189] An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP, and the test compound of interest. 55 μl of the stock solution was placed in a 96 well plate followed by addition of 2 μl of DMSO stock containing serial dilutions of the test compound (typically starting from a final concentration of 5μM). The plate was preincubated for 10 minutes at 30°C and the reaction initiated by addition of 5 μl of ATP (final concentration 50 μM). Initial reaction rates were determined with a Molecular Devices SpectraMax Plus plate reader over a 15 minute time course. IC50 and Ki data were calculated from non-linear regression analysis using the Prism software package (GraphPad Prism version 3.0a for Macintosh, GraphPad Software, San Diego California, USA).

[00190] The following compounds were shown to have a K_i of less than 1 μM for PKA (Compound numbers correspond to the compound numbers listed in Table 1.): I-2, I-35, I-40, I-43, I-48, I-51, I-52, I-54, I-55, I-56, I-59, I60, I-67, I-69, I-73, I-76 through I-78, I-85, I-93, I-97, I-98 through I-110, I-113, I-116 through I-136, I-138 through I-141, I-143 through I-145, I-147, I-149, I-153, I-155 through I-169, I-172, I-174, I-175, I-177 through I-189, I-193 through I-201, I-203 through I-210, I-226, I-227, I-230 through I-237, I-240, I-242 through I-247, I-249, I-252, I-254, I-260, I-261, I-263, I-1006, I-1022, I-1023, I-1026, I-1028, I-1033, I-1034, I-1039, I-1041, I-1043 and I-1044.

[00191] The following compounds were shown to have a K_i between 1μM and 5μM on PKA (Compound numbers correspond to the compound numbers listed in Table 1.): I-6, I-24, I-84, I-92, I-202 and I-1053.

EXAMPLE 47

p70S6K Inhibition Assay

[00192] Compounds were screened for their ability to inhibit p70S6K using a radioactive-phosphate incorporation assay at Upstate Biotechnology (Pitt and Lee, J. Biomol. Screen., (1996) **1**, 47). Assays were carried out in a mixture of 8mM MOPS (pH 7.0), 10mM MgAcetate, 0.2mM EDTA. Final substrate concentrations in the assay were 15μM ATP (Sigma Chemicals) and 100μM peptide (KKRNRTLTV, Upstate Ltd., Dundee, UK). Assays were carried out at 30°C and in the presence of p70S6K (5-10mU, Upstate Ltd., Dundee, UK) and [γ-^{33}P]ATP (Specific activity approx. 500 cpm/pmol, Amersham Pharmacia Biotech, Amersham, UK). An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP, and the test compound of interest. 15 μL of the stock solution was placed in a 96 well plate followed by addition of 1μL of 40μM or 8μM DMSO stock containing the test compound, in duplicate (final compound concentration 2μM or 0.4μM, respectively, final DMSO concentration 5%). The plate was preincubated for about 10 minutes at 30°C and the reaction initiated by addition of 4μL ATP (final concentration 15μM).

[00193] The reaction was stopped after 10 minutes by the addition of 5μL 3% phosphoric acid solution. A phosphocellulose 96 well plate (Millipore, Cat no. MAPHNOB50) was pretreated with 100μL 100mM phosphoric acid, 0.01% Tween-20 prior to the addition of the reaction mixture (20μL). The spots were left to soak for at least 5 minutes, prior to wash steps (4 × 200μL 100mM phosphoric acid, 0.01% Tween-20). After drying, 20μL Optiphase 'SuperMix' liquid scintillation cocktail (Perkin Elmer) was added to the well prior to scintillation counting (1450 Microbeta Liquid Scintillation Counter, Wallac).

[00194] Percentage inhibition of compounds at 2μM and 0.4μM was calculated by comparing p70S6K activity with standard wells containing the assay mixture and DMSO without test compound.

[00195] Compounds showing high inhibition versus standard wells were titrated to determine IC_{50} values.

[00196] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments which utilize the compounds and methods of this invention. Therefore, it will be appreciated

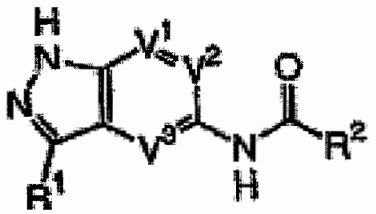
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that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments which have been represented by way of example.

Claims

1. Use of

a compound of formula I':



I'

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting AKT, PKA, PDK1, p70S6K, or ROCK kinase, wherein:

R^1 is selected from T-Ar, chloro, bromo, fluro, NH_2, NHMe, NHEt, NH-(optionally substituted phenyl), NH-cyclohexyl, $NHCH_2$(optionally substituted phenyl), NHC(O)(optionally substituted phenyl), NHC(O)NH(optionally substituted phenyl), $NHC(O)CH_2$(optionally substituted phenyl), $NHC(O)CH_2CH_2$(optionally substituted phenyl), N(R)C(O)(optionally substituted phenyl), NHC(O)naphthyl, NHC(O)thienyl, NRC(O)thienyl, SC(O)thienyl, $CH_2C(O)$thienyl, NHC(O)pyridyl, NHC(O)furanyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, acetylenyl, or t-butyl;

T is selected from a valence bond or a C_{1-6}alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

T' is a C_{1-6}alkylidene chain, wherein up to two methylene units of T' are optionally, and independently, replaced by –O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

each R is independently selected from hydrogen or an optionally substituted C_{1-6}aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from Q-Ar, $Q\text{-}N(R^5)_2$, or $Q\text{-}C(R)(Q\text{-}Ar)R^3$, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4}alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0 - 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-$OC(O)R^5$, Q-$CONHR^5$, Q-$OC(O)NHR^5$, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), $N(R)C(O)Q\text{-}N(R^4)_2$, or N(R) Q-$N(R^4)_2$;

R' is an optionally substituted C_{1-6}aliphatic group;

each R^4 is independently selected from R, COR^5, CO_2R^5, $CON(R^5)_2$, SO_2R^5, $SO_2N(R^5)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, N(R)COR, $N(R)CON(R^4)_2$, $N(R)C(O)OR$, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, OC(O)R, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

when V^1, V^2, and V^3 are each CH and R^1 is hydrogen, then R^2 is Q-$C(R)(Q\text{-}Ar)R^3$, wherein R^3 is other than R', Q-$OC(O)R^5$, or OCH_2phenyl.

2. The use according to claim 1, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, or optionally substituted C_{1-6}aliphatic; and

R^2 is selected from Q-Ar or Q-$N(R^5)_2$; wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar is an optionally substituted ring selected from a 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

3. The use according to claim 1, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, or T-R; and

R^2 is selected from Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^3 is selected from Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$.

4. The use according to claim 1, wherein:

R^1 is T'-Ar, wherein:

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

T' is selected from -NHC(O)-, -NH-, -$NHCH_2$-, -$NHSO_2$-, -CH_2NH-, -C≡C-, -CH_2- or -CH_2CH_2-;

5. The use according to claim 4, wherein:

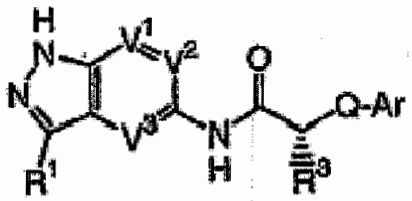
R^2 is Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

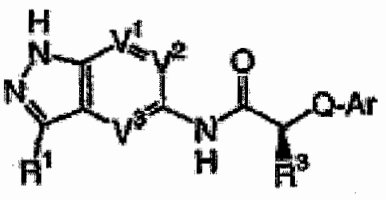
Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^3 is R', Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$.

6. The use according to either of claims 3 or 5, wherein said compound has the formula III or IV:



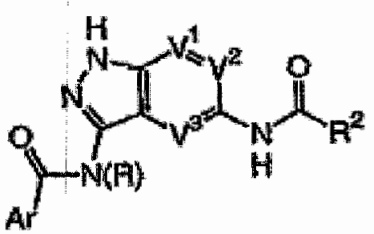
III



IV

or a pharmaceutically acceptable salt thereof.

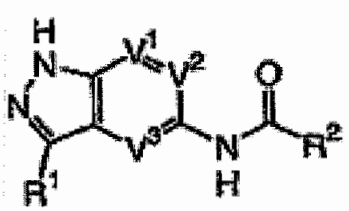
7. The use according to claim 1, wherein said compound has the formula V:



V

or a pharmaceutically acceptable salt thereof.

8. A compound of formula **IIa**:



IIa

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, or T-R;

T is selected from a valence bond or a C_{1-6}alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by-O-, -N(R)-, -S-, - N(R)C(O)-, -C(O)N(R)-,-C(O)-, or -SO2-;

each R is independently selected from hydrogen or an optionally substituted C_{1-6}aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4} alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-$OC(O)R^5$, Q-$CONHR^5$, Q-$OC(O)NHR^5$, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$;

R' is an optionally substituted C_{1-6}aliphatic group;

each R^4 is independently selected from R, COR, CO_2R, $CON(R)_2$, SO_2R, $SO_2N(R)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, N(R)COR, $N(R)CON(R^4)_2$, N(R)C(O)OR, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, OC(O)R, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that when V^1, V^2, and V^3 are each CH and R^1 is hydrogen then R^3 is other than R', Q-$OC(O)R^5$, or OCH_2phenyl.

9. The compound according to claim 8, wherein:

R^1 is selected from halogen, $N(R^4)_2$, or optionally substituted C_{1-6}aliphatic; and

R^2 is Q-$C(R)(Q-Ar)R^3$, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$; and

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

10. The compound according to claim 9, wherein:

R^1 is selected from chloro, bromo, fluoro, NH_2, NHMe, NHEt, NH-cyclohexyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, acetylenyl, or d t-butyl; and

R^3 is selected from CH_2OH, OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2CH_2NH_2$, $NHCO_2t$-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, or $NHCH_2$-imidazol-4-yl.

11. The compound according to claim 8, wherein:

R^1 is hydrogen; and

R^2 is $Q\text{-}C(R)(Q\text{-}Ar)R^3$, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

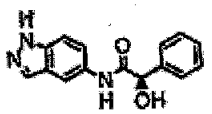
R^3 is selected from $Q\text{-}OR^5$, $Q\text{-}N(R^4)_2$, Ar^1, $N(R)C(O)Q\text{-}N(R^4)_2$, or $N(R)Q\text{-}N(R^4)_2$; and

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

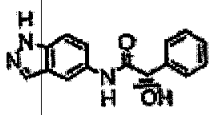
12. The compound according to claim 11, wherein:

R^3 is selected from OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $NHCO_2t$-butyl, phenyl, $NH(CH_2)_3NH_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, or $NHCH_2$-imidazol-4-yl.

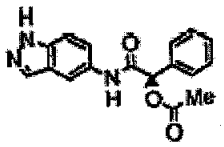
13. The compound according to claim 8, wherein said compound is selected from the group consisting of:



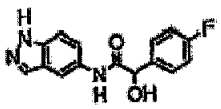
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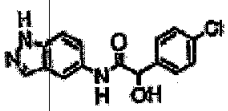
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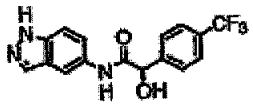
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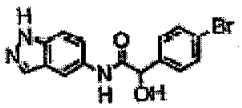
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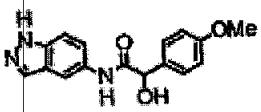
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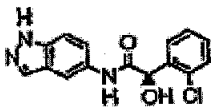
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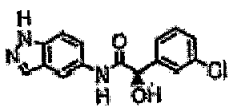
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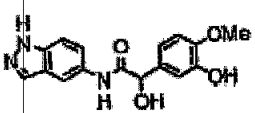
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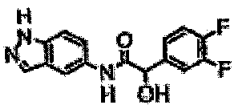
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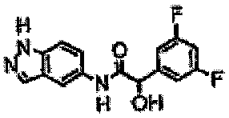
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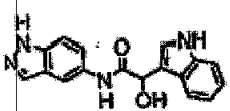
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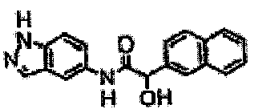
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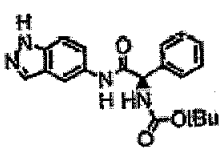
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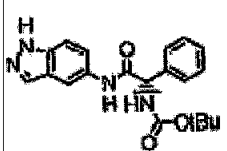
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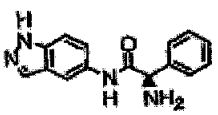
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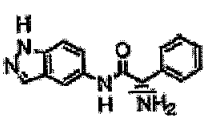
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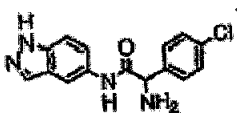
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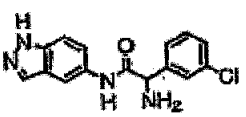
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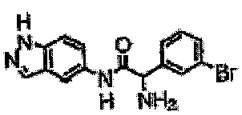
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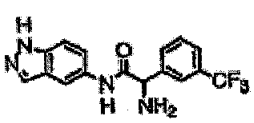
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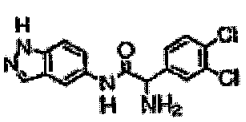
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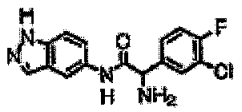
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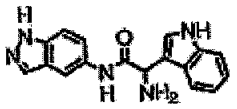
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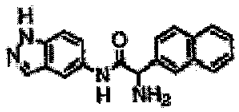
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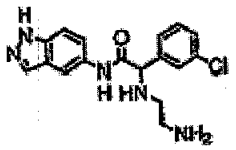
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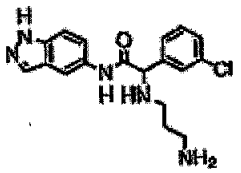
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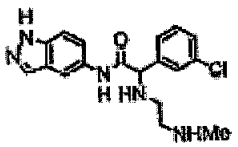
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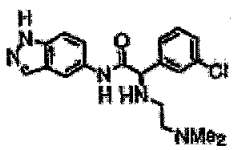
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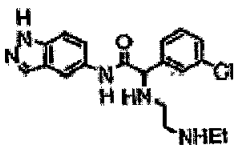
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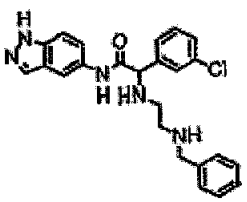
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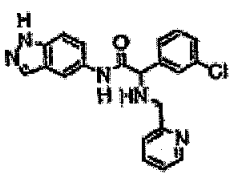
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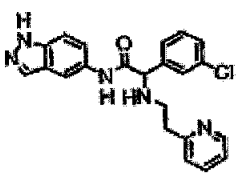
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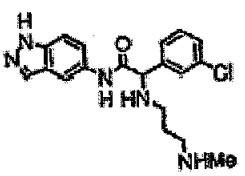
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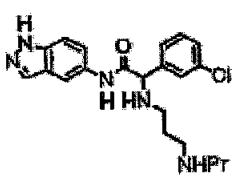
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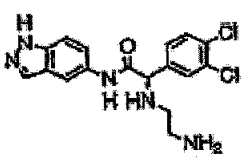
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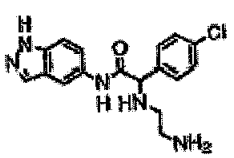
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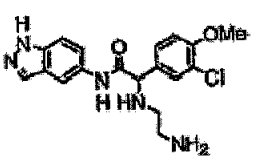
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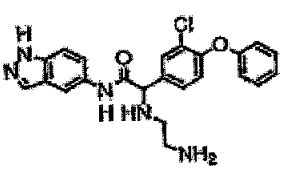
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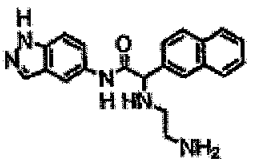
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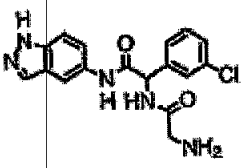
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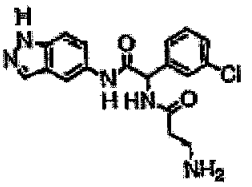
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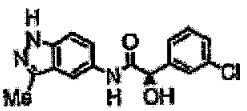
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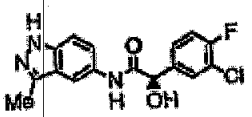
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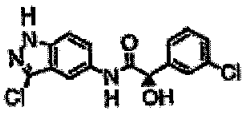
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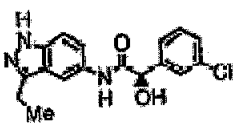
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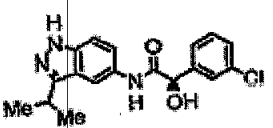
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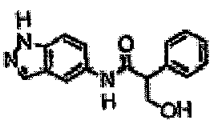
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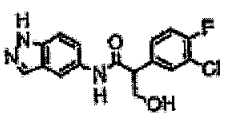
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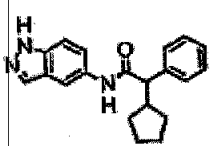
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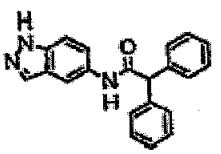
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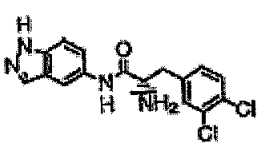
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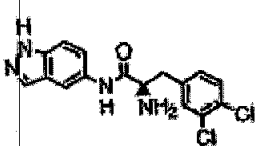
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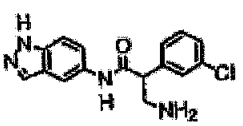
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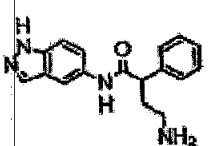
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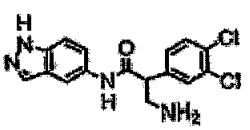
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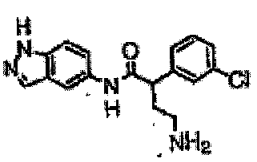
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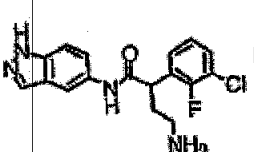
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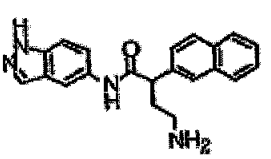
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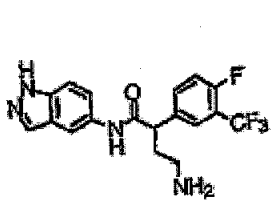
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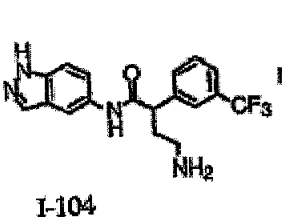
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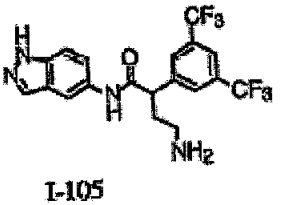
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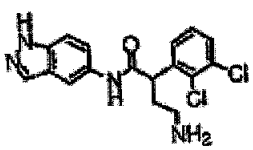
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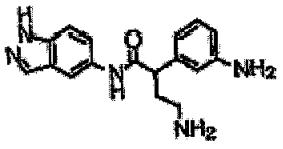
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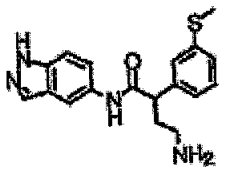
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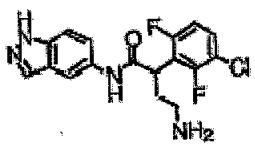
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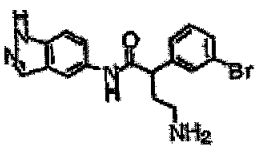
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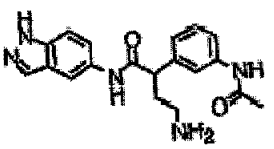
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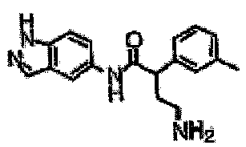
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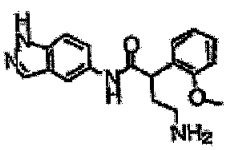
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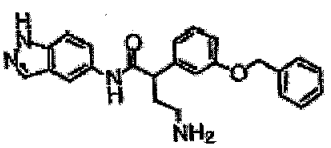
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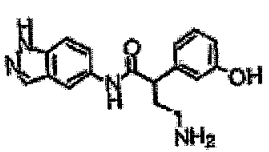
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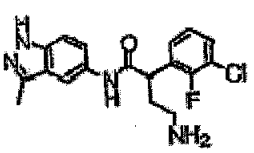
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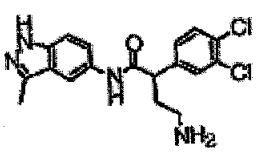
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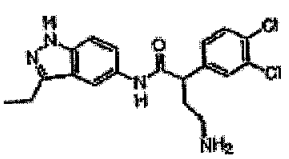
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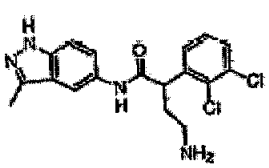
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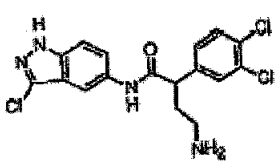
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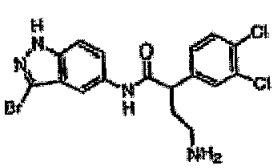
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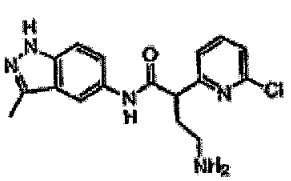
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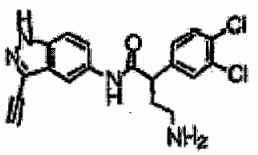
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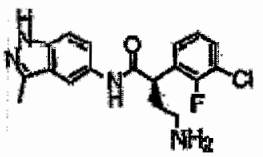
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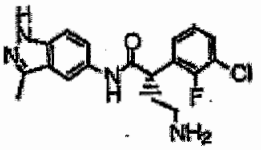
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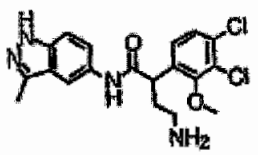
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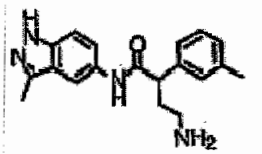
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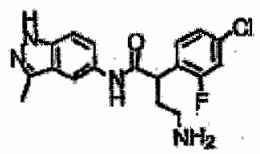
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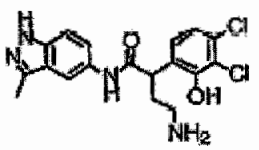
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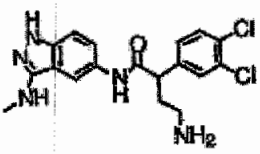
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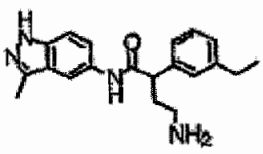
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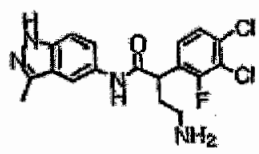
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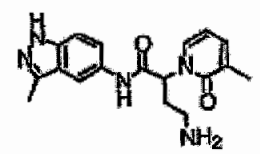
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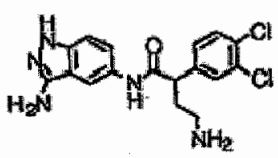
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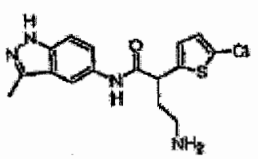
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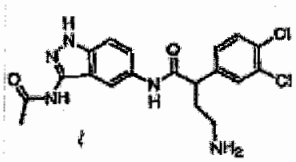
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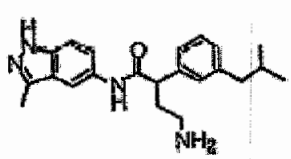
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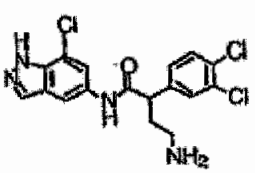
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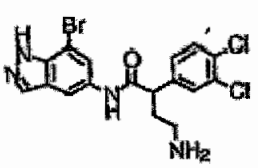
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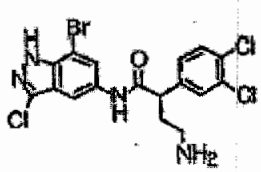
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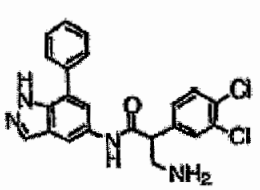
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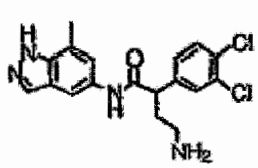
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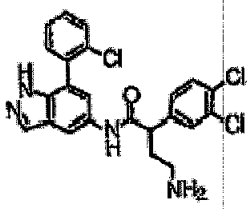
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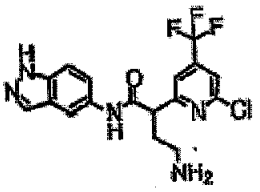
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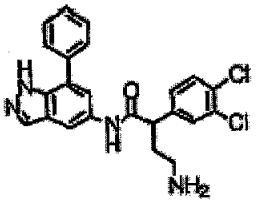
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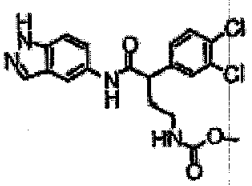
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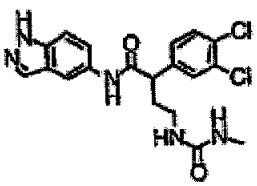
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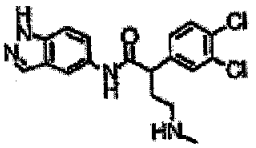
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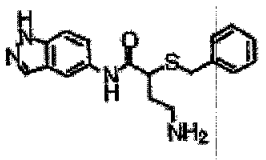
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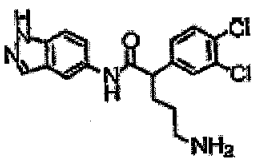
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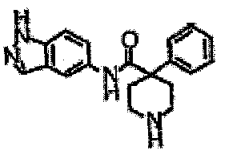
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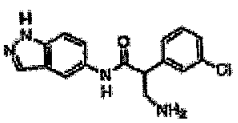
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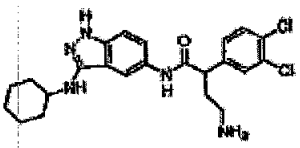
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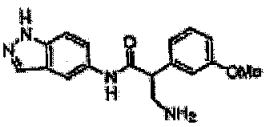
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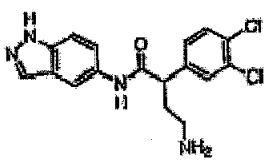
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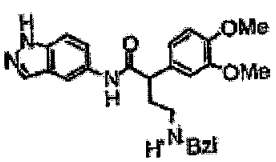
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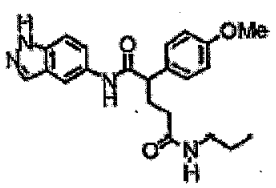
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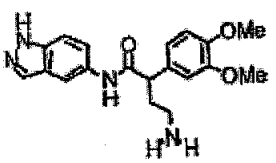
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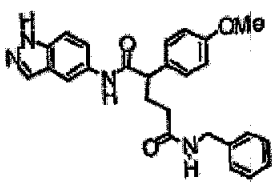
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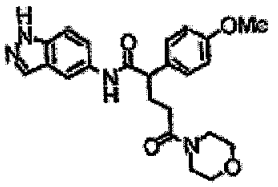
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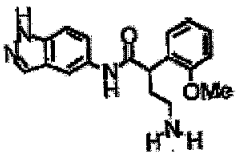
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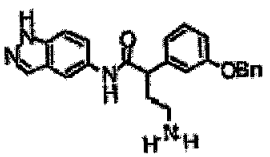
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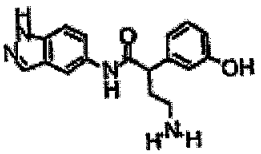
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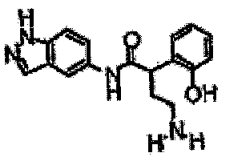
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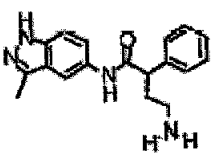
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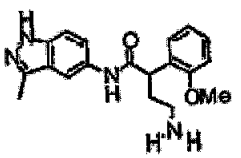
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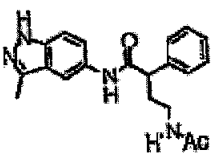
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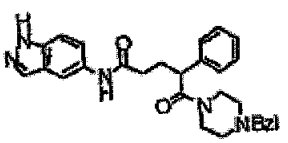
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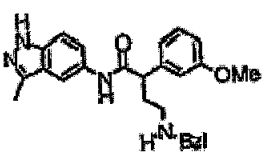
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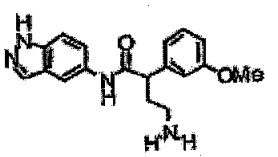
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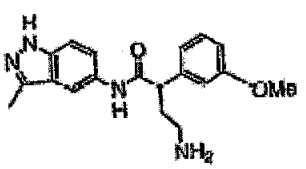
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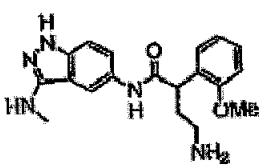
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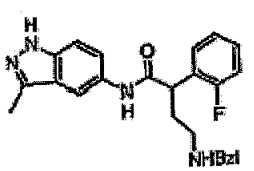
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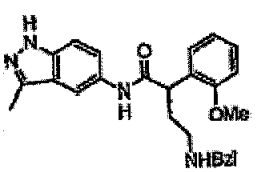
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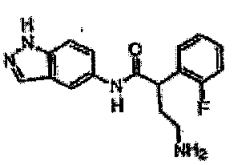
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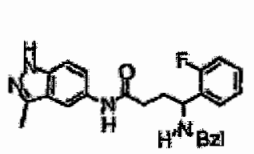
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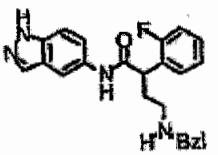
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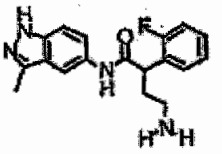
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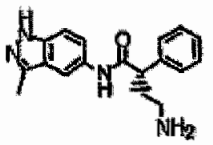
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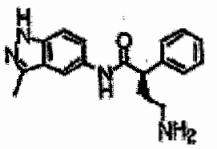
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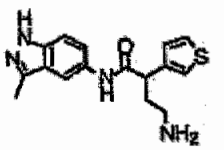
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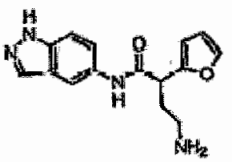
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I-1034

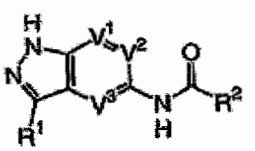


I-1035



and I-1037.

14. A compound of formula **IIb**:



IIb

or a pharmaceutically acceptable salt thereof, wherein :

R^1 is T-Ar;

T is selected from a valence bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or -SO2-;

each R is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4}alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-$OC(O)R^5$, Q-$CONHR^5$, Q-$OC(O)NHR^5$, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), $N(R)C(O)Q\text{-}N(R^4)_2$, or $N(R)Q\text{-}N(R^4)_2$;

R' is an optionally substituted C_{1-6} aliphatic group;

each R^4 is independently selected from R, COR^5, CO_2R^5, $CON(R^5)_2$, SO_2R^5, $SO_2N(R^5)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, N(R)COR, $N(R)CON(R^4)_2$, $N(R)C(O)OR$, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, OC(O)R, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that when V^1, V^2, and V^3 are each CH, T is a valence bond, and R^2 is Q-$C(R)(Q\text{-}Ar)R^3$, wherein Ar is an optionally substituted phenyl ring, then R^3 is other than Q-OR^5 or $C(O)NH_2$.

15. The compound according to claim 14, wherein:

R^1 is T-Ar, wherein:

T is selected from -NHC(O)-, -NH-, $-NHCH_2$-, $-NHSO_2$-, $-CH_2NH$-, -C≡-, $-CH_2$- or $-CH_2CH_2$-; and

Ar is an optionally substituted 5-6 membered aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^2 is $Q\text{-}C(R)(Q\text{-}Ar)R^3$, wherein:

R^3 is R', Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$;

each Q is independently selected from a valence bond, -CH_2-, or -CH_2CH_2-; and

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

16. The compound according to claim 15, wherein:

R^3 is CH_2OH, OH, NH_2, CH_2NH_2, CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2CH_2NH_2$, $NHCO_2t$-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

17. The compound according to claim 14, wherein:

T is a valence bond; and

R^2 is Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

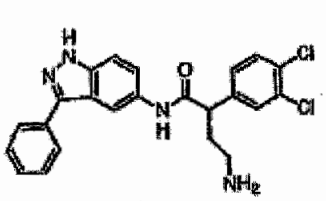
R^3 is Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$; and

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

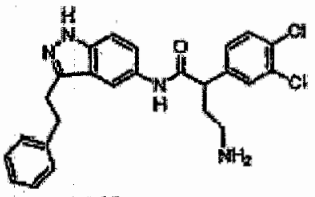
18. The compound according to claim 17, wherein:

R^3 is CH_2NHMe, $CH_2N(Me)_2$, $CH_2CH_2NH_2$, CH_2CH_2NHMe, $CH_2CH_2N(Me)_2$, $CH_2C(Me)_2NH_2$, $CH_2C(Me)_2CHMe$, $NHCO_2$(*t*-butyl), phenyl, $NH(CH_2)_3NH_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_2NHEt$, $NHCH_2$pyridyl, $NHSO_2$phenyl, $NHC(O)CH_2C(O)Ot$-butyl, $NHC(O)CH_2NH_3$, and $NHCH_2$-imidazol-4-yl.

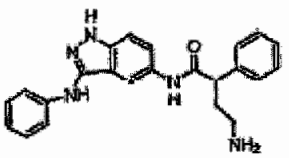
19. The compound according to claim 14, wherein said compound is selected from the group consisting of:



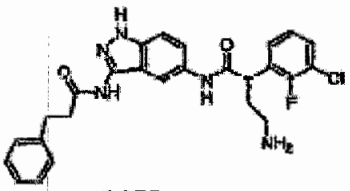
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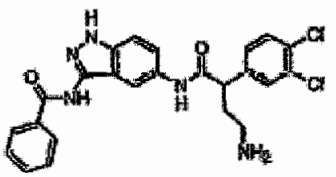
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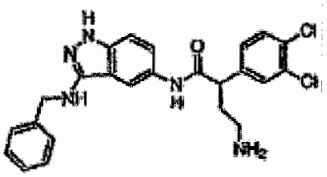
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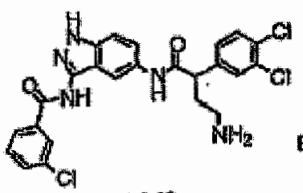
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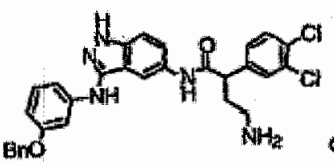
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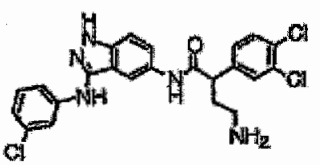
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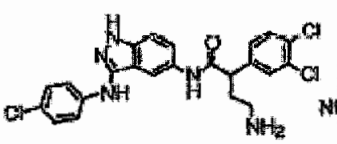
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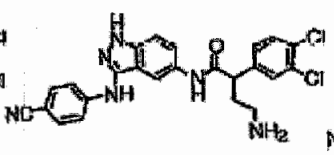
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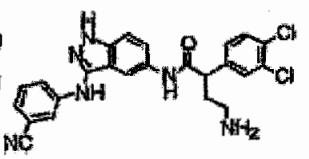
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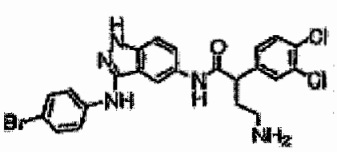
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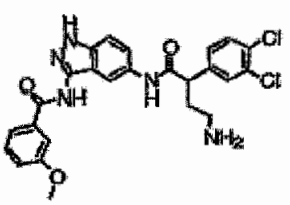
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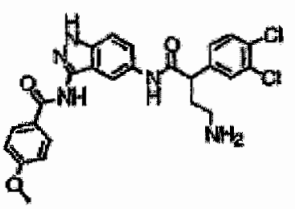
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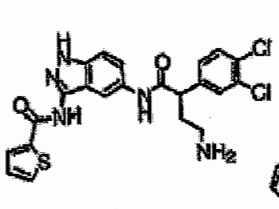
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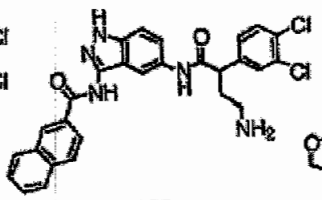
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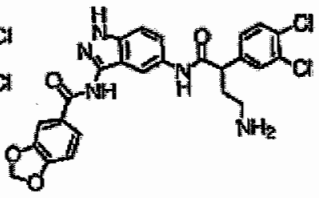
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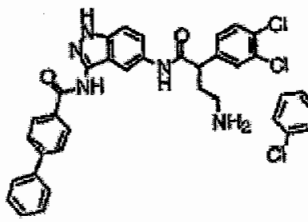
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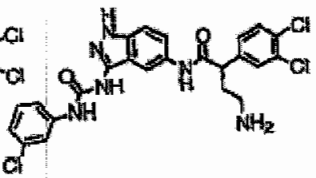
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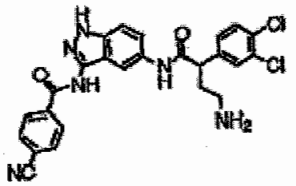
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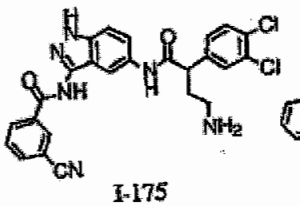
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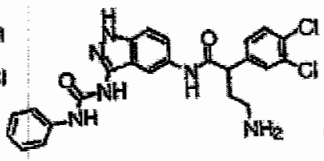
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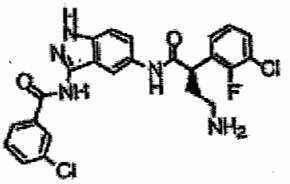
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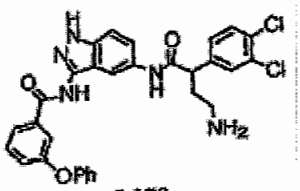
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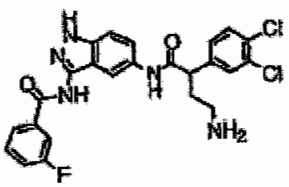
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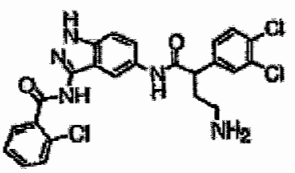
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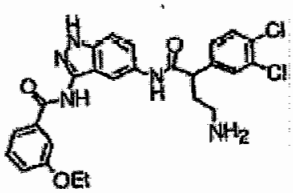
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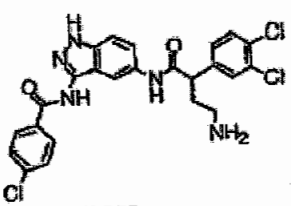
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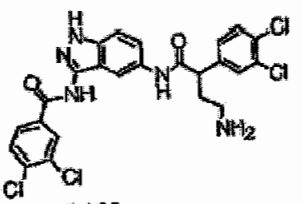
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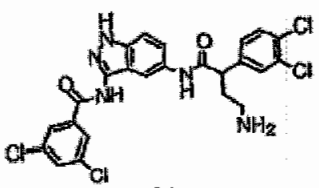
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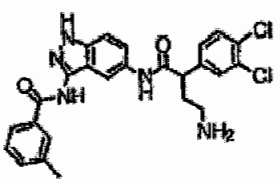
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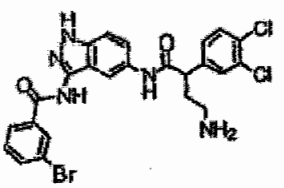
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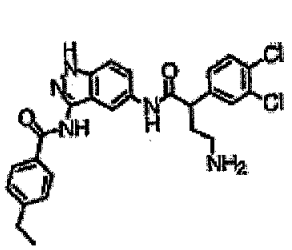
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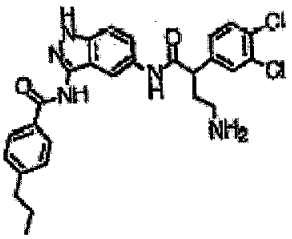
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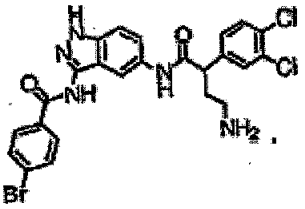
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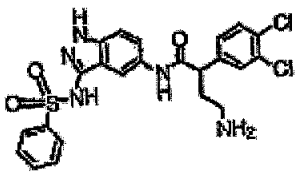
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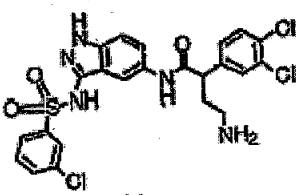
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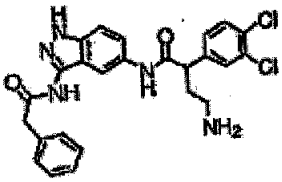
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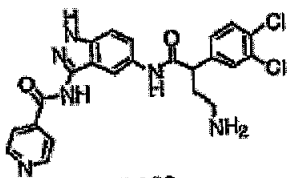
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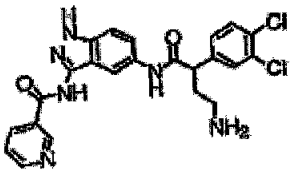
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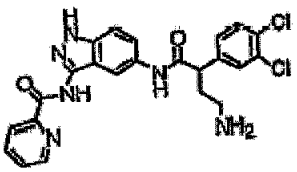
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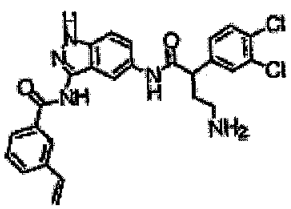
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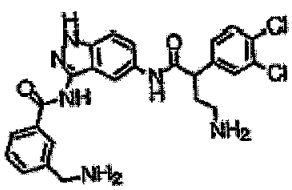
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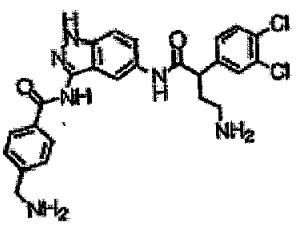
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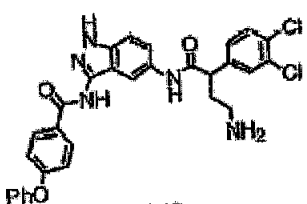
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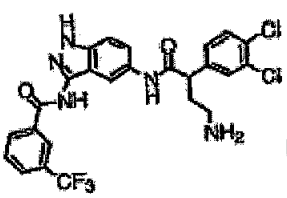
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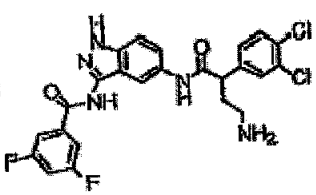
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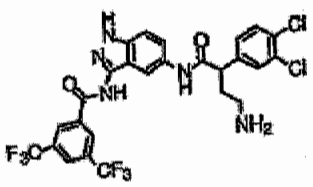
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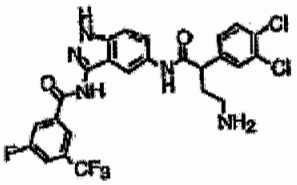
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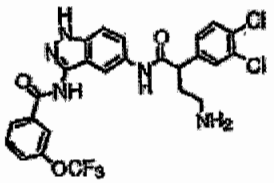
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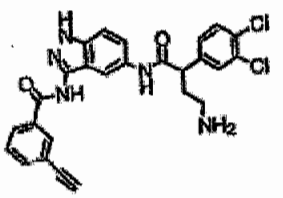
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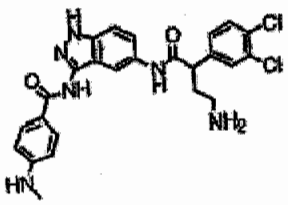
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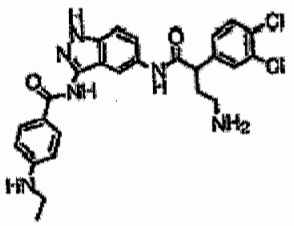
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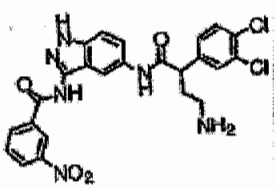
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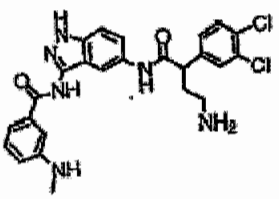
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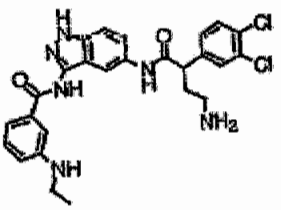
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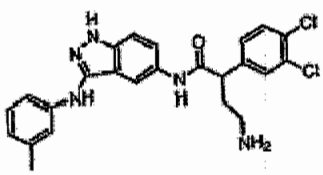
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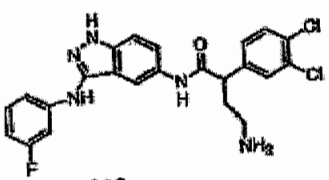
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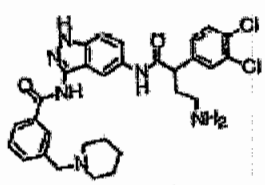
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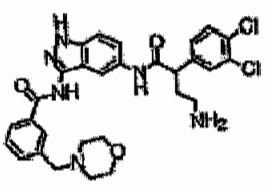
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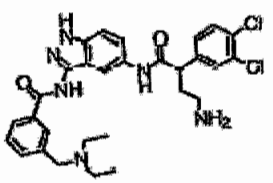
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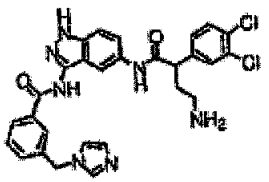
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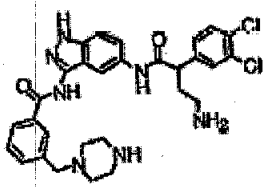
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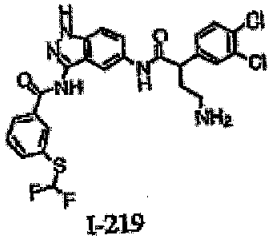
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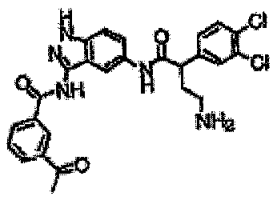
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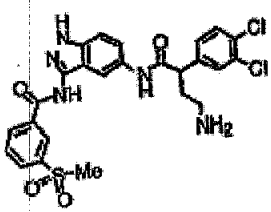
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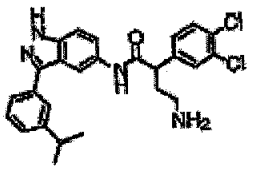
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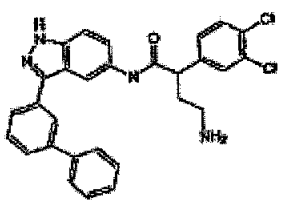
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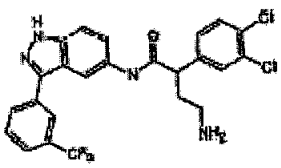
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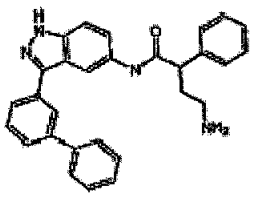
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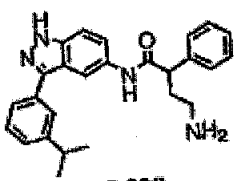
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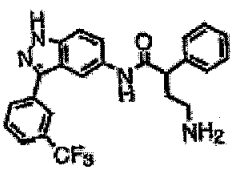
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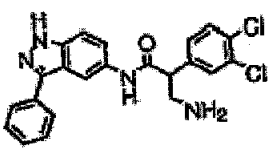
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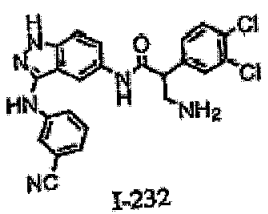
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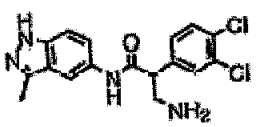
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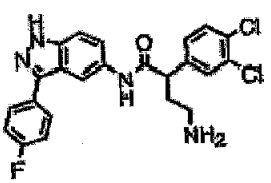
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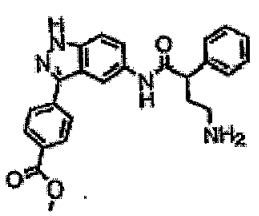
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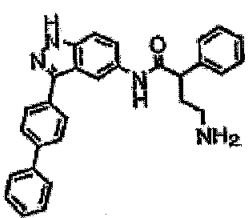
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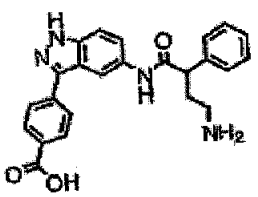
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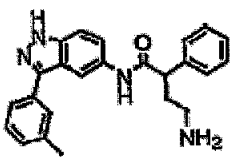
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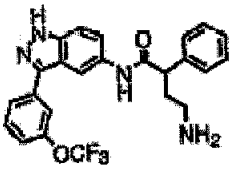
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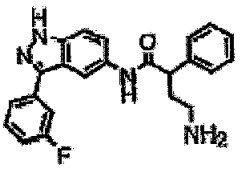
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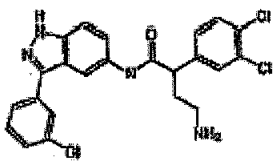
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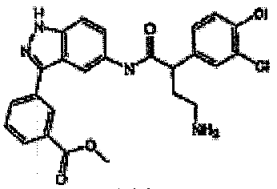
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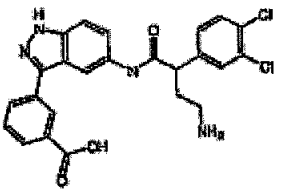
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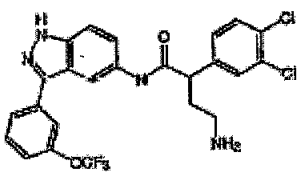
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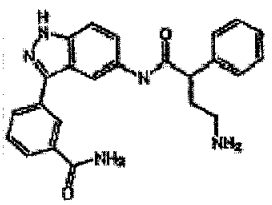
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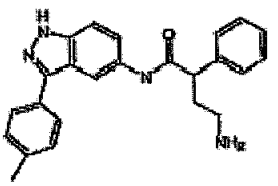
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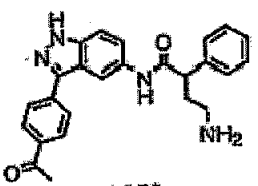
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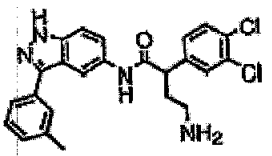
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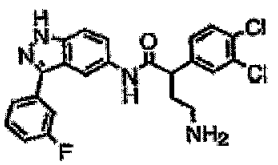
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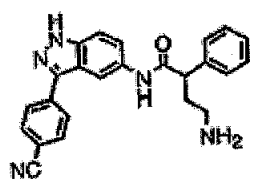
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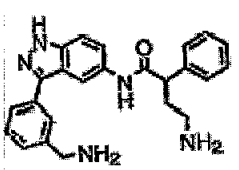
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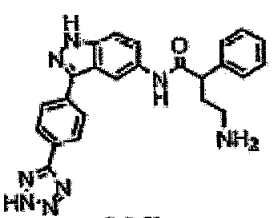
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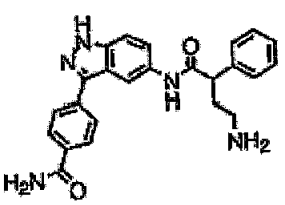
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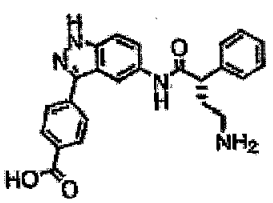
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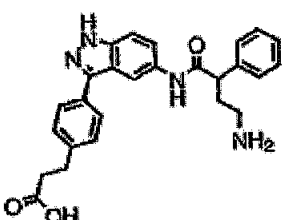
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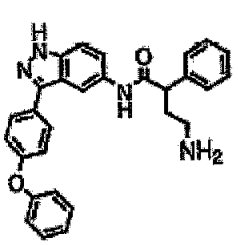
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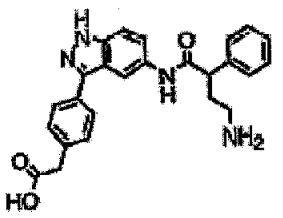
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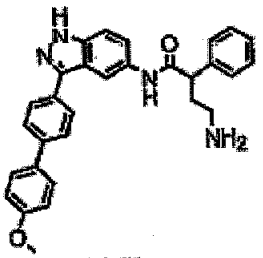
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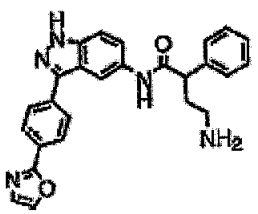
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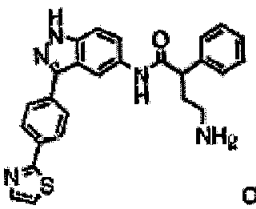
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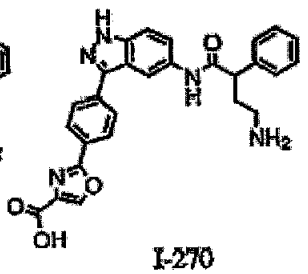
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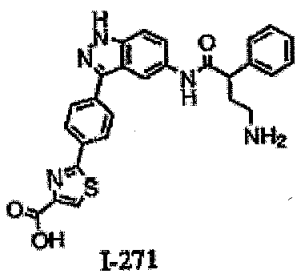
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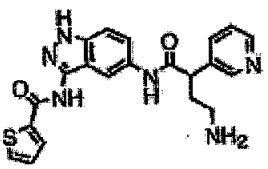
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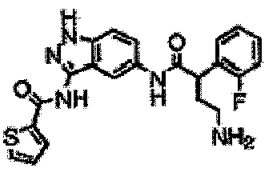
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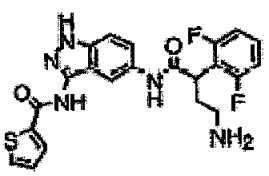
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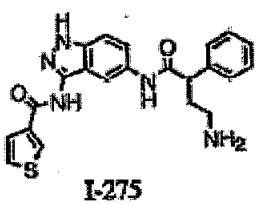
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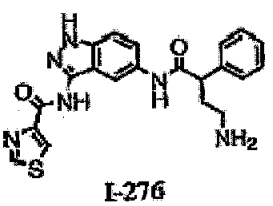
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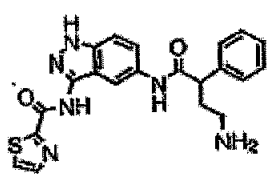
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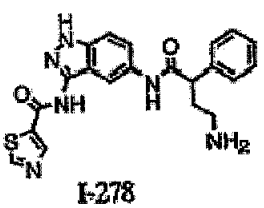
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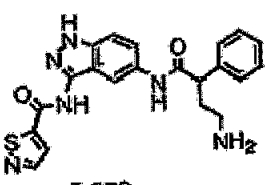
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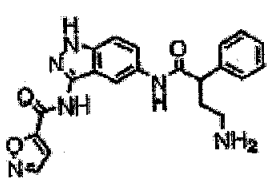
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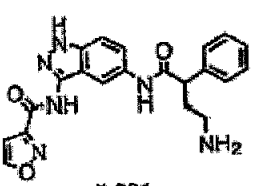
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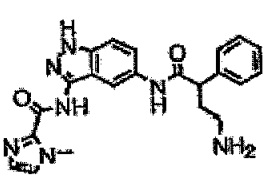
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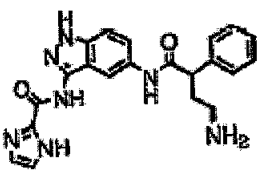
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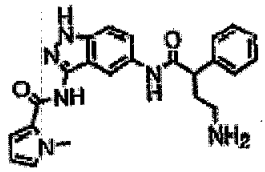
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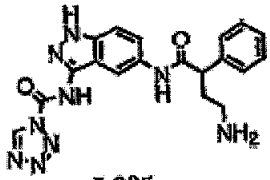
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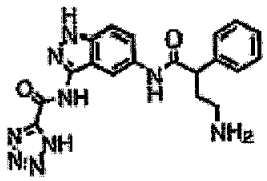
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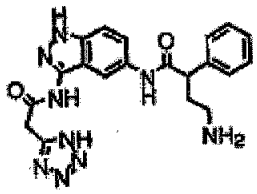
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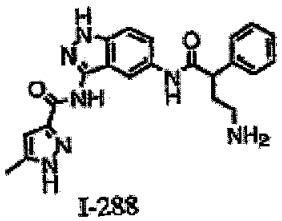
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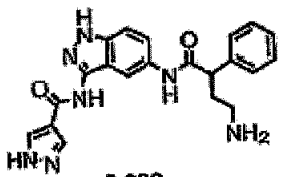
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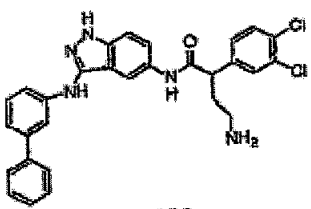
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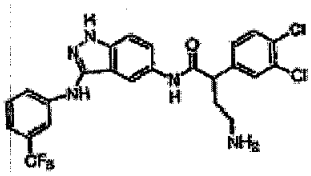
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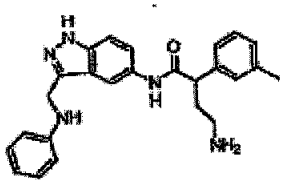
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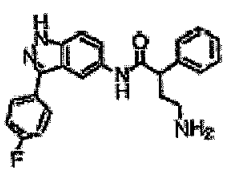
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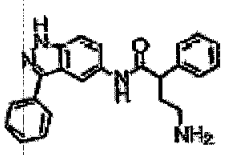
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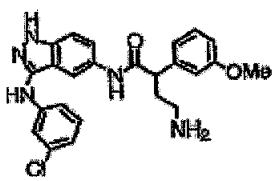
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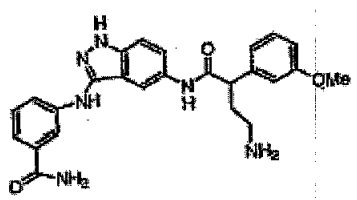
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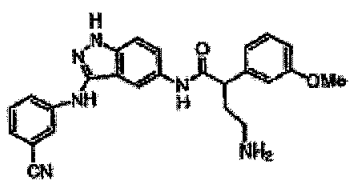
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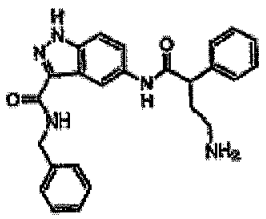
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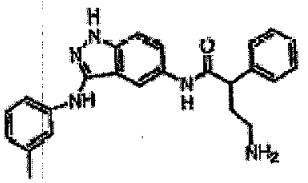
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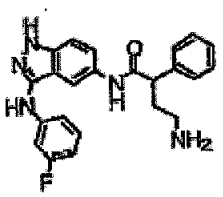
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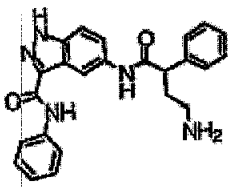
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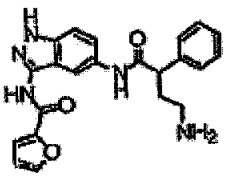
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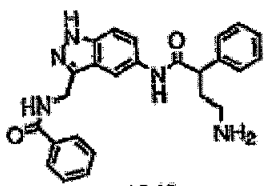
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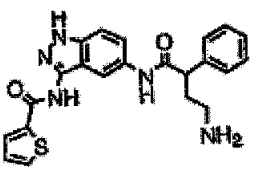
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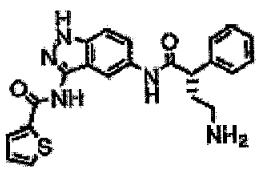
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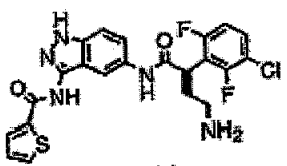
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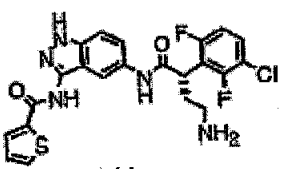
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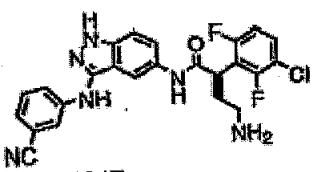
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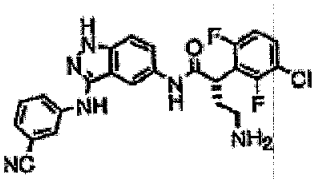
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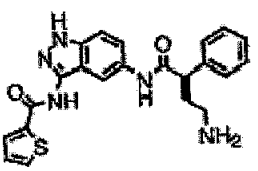
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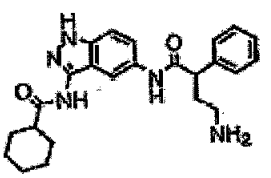
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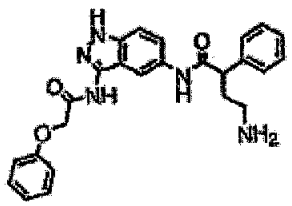
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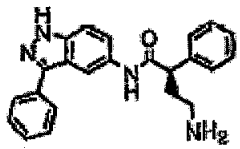
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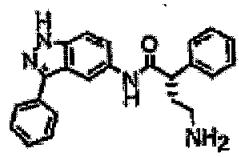
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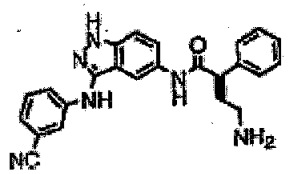
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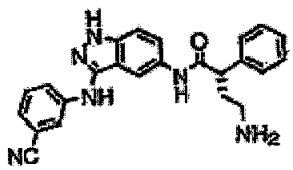
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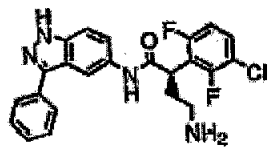
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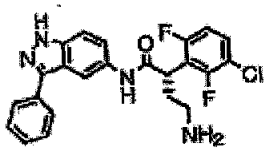
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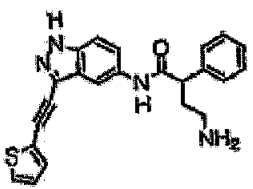
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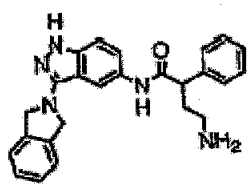
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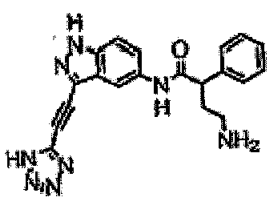
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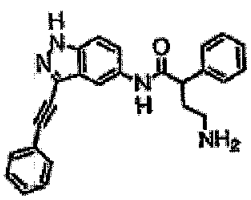
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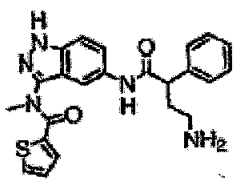
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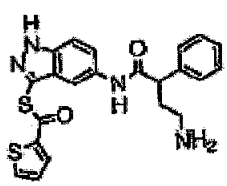
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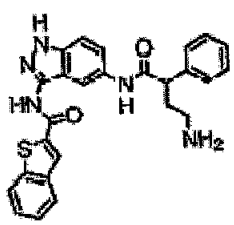
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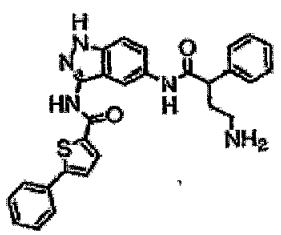
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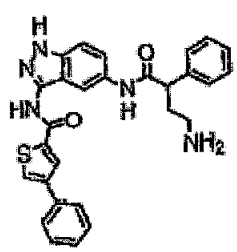
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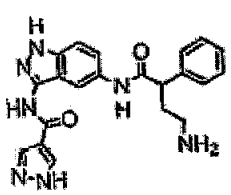


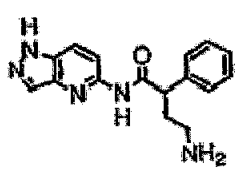
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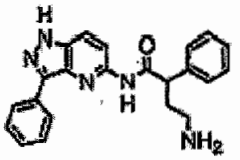
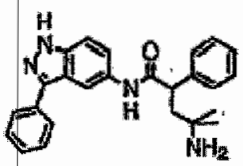
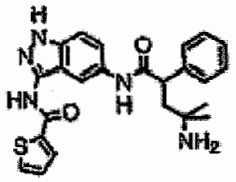


I-1065







I-1066  I-1067  I-1068 

I-1069 I-1070 and I-1071.

20. A composition comprising a compound according to either of claims 8 or 14, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

21. The composition according to claim 20, additionally comprising a therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

22. A method of inhibiting AKT, PKA, PDK1, p70S6K, or ROCK kinase activity in a biological sample comprising the step of contacting said biological sample with:

a) a compound according to claim 8;
b) a compound according to claim 14; or
c) a composition according to claim 20.

23. Use of a composition according to claim 20 for the manufacture of a medicament for treating or lessening the severity of a disease or condition selected from a proliferative disorder, a cardiac disorder, an inflammatory disorder, an autoimmune disorder, a neurodegenerative disorder, a viral disease, or a bone disorder

24. The use according to claim 23, wherein said disease or condition is selected from cancer, rheumatoid arthritis, asthma, HIV, angina pectoris, peripheral circulation disorder, hypertension, arteriosclerosis, tuberous sclerosis, or osteoporosis.

25. The use according to claim 24, wherein said disease or condition is selected from cancer.

26. The use according to claim 25, wherein said cancer is selected from brain (gliomas), breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, or thyroid.

27. The use according to claim 26, wherein said cancer is selected from pancreatic, prostate, or ovarian.

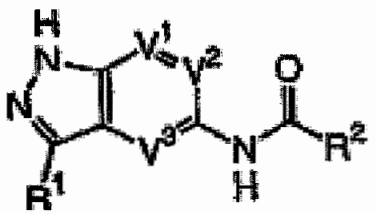
28. The use according to claim 23, comprising the additional step of administering to said patient an additional therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

29. A method of inhibiting AKT, PKA, PDK1, p70S6K, or ROCK kinase in a biological sample;

which method comprises contacting said biological sample with, a compound of formula I':



I'

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from T-Ar, chloro, bromo, fluro, NH_2, NHMe, NHEt, NH-(optionally substituted phenyl), NH-cyclohexyl, $NHCH_2$(optionally substituted phenyl), NHC(O)(optionally substituted phenyl), NHC(O)NH(optionally substituted phenyl), $NHC(O)CH_2$(optionally substituted phenyl), $NHC(O)CH_2CH_2$(optionally substituted phenyl), N(R)C(O)(optionally substituted phenyl), NHC(O)naphthyl, NHC(O)thienyl, NRC(O)thienyl, SC(O)thienyl, $CH_2C(O)$thienyl, NHC(O)pyridyl, NHC(O)furanyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, acetylenyl, or t-butyl;

T is selected from a valence bond or a C_{1-6}alkylidene chain, wherein up to two methylene units of T are optionally, and independently, replaced by -O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

T' is a C_{1-6}alkylidene chain, wherein up to two methylene units of T' are optionally, and independently, replaced by –O-, -N(R)-, -S-, -N(R)C(O)-, -C(O)N(R)-, -C(O)-, or $-SO_2-$;

each R is independently selected from hydrogen or an optionally substituted C_{1-6}aliphatic group, or:

two R groups on the same nitrogen, taken together with the nitrogen atom attached thereto, form a 5-7 membered saturated, partially unsaturated, or aromatic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from Q-Ar, $Q\text{-}N(R^5)_2$, or $Q\text{-}C(R)(Q\text{-}Ar)R^3$, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Q is independently selected from a valence bond or a C_{1-4}alkylidene chain;

each Ar is independently an optionally substituted ring selected from a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0 - 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is selected from R', Ar^1, Q-OR^5, Q-$OC(O)R^5$, Q-$CONHR^5$, Q-$OC(O)NHR^5$, Q-SR^5, Q-$N(R^4)_2$, N(R)(Q-Ar), N(R)C(O)Q-$N(R^4)_2$, or N(R) Q-$N(R^4)_2$;

R' is an optionally substituted C_{1-6}aliphatic group;

each R^4 is independently selected from R, COR^5, CO_2R^5, $CON(R^5)_2$, SO_2R^5, $SO_2N(R^5)_2$, or Ar^1;

each R^5 is independently selected from R or Ar;

V^1, V^2 and V^3 are each independently selected from nitrogen or $C(R^6)$;

each R^6 is independently selected from R, Ar^1, halogen, CN, NO_2, OR, SR, $N(R^4)_2$, N(R)COR, $N(R)CON(R^4)_2$, N(R)C(O)OR, $CON(R^4)_2$, $OC(O)N(R^4)_2$, CO_2R, OC(O)R, $N(R)SO_2R$, $N(R)SO_2N(R^4)_2$, SO_2R, or $SO_2N(R^4)_2$; and

each Ar^1 is independently selected from an optionally substituted 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

when V^1, V^2, and V^3 are each CH and R^1 is hydrogen, then R^2 is Q-C(R)(Q-Ar)R^3, wherein R^3 is other than R', Q-$OC(O)R^5$, or OCH_2phenyl.

30. The method according to claim 29, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, or optionally substituted C_{1-6}aliphatic; and

R^2 is selected from Q-Ar or Q-$N(R^5)_2$; wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar is an optionally substituted ring selected from a 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

31. The method according to claim 29, wherein:

R^1 is selected from halogen, CN, $N(R^4)_2$, or T-R; and

R^2 is selected from Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^3 is selected from Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$.

32. The method according to claim 29, wherein:

R^1 is T'-Ar, wherein:

Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

T' is selected from -NHC(O)-, -NH-, -$NHCH_2$-, -$NHSO_2$-, -CH_2NH-, -C≡C-, -CH_2- or -CH_2CH_2-;

33. The method according to claim 32, wherein:

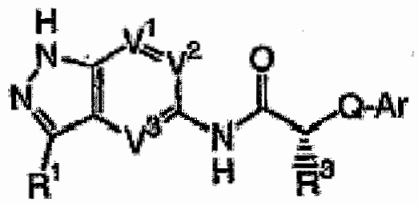
R^2 is Q-C(R)(Q-Ar)R^3, wherein:

R and R^3 optionally form a 5-7 membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

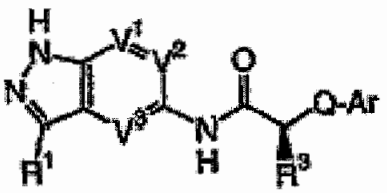
Ar is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 9-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^3 is R', Q-OR^5, Q-$N(R^4)_2$, Ar^1, N(R)C(O)Q-$N(R^4)_2$, or N(R)Q-$N(R^4)_2$.

34. The method according to either of claims 31 or 33, wherein said compound has the formula III or IV:



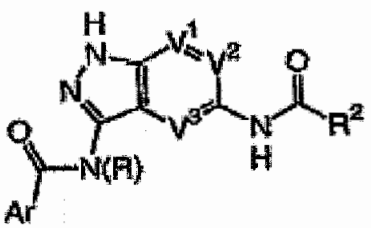
III



IV

or a pharmaceutically acceptable salt thereof.

35. The method according to claim 29, wherein said compound has the formula V:



V

or a pharmaceutically acceptable salt thereof.