(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 April 2006 (20.04.2006)

PCT

(10) International Publication Number
WO 2006/040646 A1

(51) International Patent Classification:
C07D 401/12 (2006.01) *C07D 403/14* (2006.01)
C07D 401/14 (2006.01) *C07D 413/06* (2006.01)
C07D 235/16 (2006.01) *C07D 417/06* (2006.01)
C07D 409/12 (2006.01) *A61K 31/415* (2006.01)
C07D 417/14 (2006.01) *A61K 31/40* (2006.01)
C07D 403/06 (2006.01) *A61K 31/35* (2006.01)
C07D 413/12 (2006.01) *A61P 35/00* (2006.01)
C07D 405/12 (2006.01)

(21) International Application Number:
PCT/IB2005/003019

(22) International Filing Date: 3 October 2005 (03.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/619,211 14 October 2004 (14.10.2004) US

(71) Applicant *(for all designated States except US)*: **PFIZER, INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DO, Quyen-Quyen, Thuy** [US/US]; Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive, San Diego, CA 92121 (US). **GUO, Chuangxing** [US/US]; Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive, San Diego, CA 92121 (US). **HUMPHRIES, Paul, Stuart** [GB/US]; Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive, San Diego, CA 92121 (US). **MARAKOVITS, Joseph, Timothy** [US/US]; Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive, San Diego, CA 92121 (US). **DONG, Liming** [CN/US]; Agouron Pharmaceuticals, Inc., A Pfizer Company, 10777 Science Center Drive, San Diego, CA 92121 (US). **HOU, Xinjun** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). **JOHNSON, Mary, Catherine** [US/US]; Agouron Pharmaceuticals, Inc., a Pfizer Company, 10777 Science Center Drive, San Diego, CA 92121 (US).

(74) Agents: **FULLER, Grover, F., Jr.** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

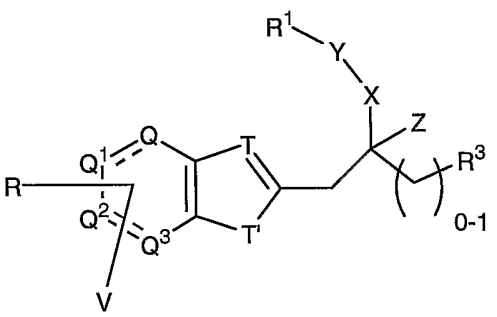
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BENZIMIDAZOLE OR INDOLE AMIDES AS INHIBITORS OF PIN1



(I)

(57) Abstract: The invention relates to compounds of the formula (1) and to pharmaceutically acceptable salts and solvates thereof, wherein the variables are defined herein. The invention also relates to methods of treating abnormal cell growth in mammals by administering the compounds of formula (1) and to pharmaceutical compositions for treating such disorders that contain the compounds of formula (1). The invention also relates to methods of preparing the compounds of formula (1).

WO 2006/040646 A1

Benzimidazole or Indole Amides as Inhibitors of PIN1

Background of the Invention

This invention relates to carboxylic acids and tetrazoles that are useful in the treatment of abnormal cell growth, such as cancer, in mammals. This invention also relates to a method of using such compounds in the treatment of abnormal cell growth in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

The cell cycle represents a series of ordered processes that ultimately results in the duplication of a cell. In general, somatic cell division consists of two sequential processes - DNA replication and chromosome separation. The cell spends most of its time preparing for these events in a growth cycle (interphase), which in turn consists of three subphases: initial gap (G1), synthesis (S), and secondary gap (G2). In G1, the cell undergoes a high rate of biosynthesis. The S phase begins when DNA synthesis starts and ends when the DNA content of the nucleus has doubled. The cell then enters G2, which lasts until the cell enters the final phase of division, mitosis (M). The M phase begins with nuclear envelope breakdown, chromosome condensation, and the formation of two identical sets of chromosomes that are separated into two new nuclei. This is followed by cell division (cytokinesis), which results in two daughter cells, terminates the M phase, and marks the beginning of interphase for the new cells.

Entry into mitosis is a highly regulated event in normal cells. In eukaryotic cells studied to date, Cdc2/cyclin B, a Ser/Thr kinase, regulates entry into mitosis (Nurse, *Nature*, 344, 503-508 (1990)). To prevent inappropriate mitotic activity, the activity of Cdc2/cyclin B is tightly regulated, both positively and negatively, by phosphorylation. Cdc2/cyclin B, when activated by dephosphorylation by Cdc25, drives cells into mitosis.

One regulator of Cdc25 is PIN1, a peptidyl-prolyl isomerase (PPIase). PIN1, a member of the parvulin family of PPIases, is an enzyme that catalyzes the cis/trans isomerization of the peptidyl-prolyl peptide bond which can be the rate-limiting step in protein folding or assembly under some circumstances (Schmid, *Curr. Biol.*, 5, 993-994 (1995)).

PIN1 has been identified in various eukaryotic organisms, including plants, yeasts, insects, and mammals (Hanes et al., *Yeast*, 5, 55-72 (1989); Lu et al., *Nature*, 380, 544-547 (1996); Maleszka et al., *Proc. Natl. Acad. Sci. USA*, 93, 447-451 (1996); and U.S. Patent No. 5,952,467). It was first isolated through its interaction with the Ser/Thr kinase NIMA, a protein essential for cell cycle progression in *Aspergillus nidulans* (Osmani et al., *Cell,* 53, 237 (1988)). NIMA's phosphotransferase activity is regulated by Ser/Thr phosphorylation and thus, it has been surmised that NIMA kinase corresponds to its closest human ortholog nek2 which is activated downstream of Cdc2/cyclin B (Lu et al., *Cell,* 81, 413-424 (1995)).

The full-length PIN1 mRNA and amino acid sequences are disclosed in U.S. Patent Nos. 5,952,467 and 5,972,697 and have been deposited in GenBank under accession numbers U49070 (mRNA) and S68520 (protein). The chromosomal locations of human PIN1 and the closely related PIN gene are 19p13 and 1p31, respectively (Campbell et al., *Genomics*, 44, 157-162 (1997)). Sequencing of the

PIN1 gene revealed a putative nuclear localization signal, an amino-terminal protein binding domain (WW motif), and a carboxy-terminal region with homology to other parvulin PPIases (Lu et al., *Nature,* 380, 544-547 (1996)). Studies have shown that PIN1 can behave either as two independent domains connected by a flexible linker or as a single intact domain with a certain amount of hinge bending motion depending on the sequence of the peptide that binds to PIN1 (Jacobs et al., *J. Bio. Chem.,* 278, 26174-26182 (2003)).

Modulation of human PIN1 activity has been reported to cause dramatic changes in cellular phenotypes. For example, overexpression of PIN1 in HELA cells was reported to cause G2 arrest, whereas its depletion caused mitotic arrest (Lu et al., *Nature*, 380, 544-547 (1996); Crenshaw et al., *EMBO J.*, 17, 1315-1327 (1998); Fujimori et al., *Biochem. Biophys. Res. Commun.*, 265, 658-663 (1999)). Additionally, it has been reported that decreasing PIN1 expression via antisense technology causes cells to progress into mitosis prematurely, results in the presence of aberrant nuclei due to premature chromosome condensation, and induces apoptosis (Lu et al., *Nature*, 380, 544-547 (1996)); thus, confirming that PIN1 is a negative regulator of mitosis through its interaction with Cdc2/cyclin B (Thorpe et al., *J. Histochem. & Cytochem.*, 49, 97-107 (2001); Gozes, *J. Molecular Neuroscience*, 19, 337-338 (2002); and Holzer et al., *Acta Neuropathol.,* 104, 471-481 (2002)).

In addition to its role in mitosis and Cdc2/cyclin B regulation, PIN1 has a putative role in neurodegeneration in Alzheimer's disease (Holzer et al., *Acta Neuropathol.*, 104, 471-481 (2002)). PIN1 levels have been shown to be elevated in patients afflicted with Alzheimer's disease as PIN1 can bind to the tau protein that has been shown to be a major component of the intracellular neurofibrillary tangles found in Alzheimer's disease brain lesions. More specifically, PIN1 binding is elevated in the neurofibrillary tangle-rich cytoplasm of Alzheimer's disease-affected neurons and thus, is thought to be involved in the vulnerability of certain neurons to neurofibrillary degeneration.

PIN1 has been shown to have a variety of other functions and interactions. For example, PIN1 can interact with other cell cycle regulators (Messenger et al., *J. Bio. Chem.*, 277, 23054-23064 (2002)) and affect the proliferation of mammalian primordial germ cells and embryonic development (Atchison et al., *Development,* 130, 3579-3586 (2003)). Moreover, PIN1 knockout mice display developmental defects during pregnancy particularly with respect to mammary epithelial duct development and gland development (Wulf et al., *Breast Cancer Research*, 5, 76-82 (2003)). The possible role of PIN1 in mammary gland physiology is underscored by the observation that PIN1 is overexpressed in human breast cancer cells (Wulf et al., *Breast Cancer Research*, 5, 76-82 (2003)).

Cancer and other neoplastic cells, due to their inherent genetic instability, have lost many of the control mechanisms regulating cell division and therefore, are more susceptible to cell-cycle modulation or intervention as a means of inducing cell death. Further, because alterations in cell-cycle control are one of the differences between normal cells and cancer cells, proteins involved in cell-cycle control are attractive targets for developing agents effective for use in diagnosing and treating cancer and other cell proliferative disorders. One such target in PIN1. Thus, there is a need

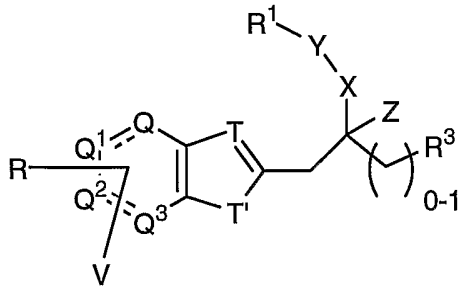
in the art for tools useful in studying the role of PIN1 and PIN1 pathways involved in normal and abnormal cell growth.

Inhibitors of PIN1 have been described in the literature. For example, Hennig et al. (*Biochemistry*, 37, 5953-5960 (1998)) report that juglone (5-hydroxy-1,4-naphthoquinone) selectively inhibits several parvulins, including human PIN1. Noel et al. in U.S. Patent Application no. 20030096387, using data based on the crystal structure derived from full-length human PIN1, suggest compounds postulated to be inhibitors of PIN1. Lu et al. in International Publication No. WO 99/12962 report inhibitors that mimic the phospho-Ser/Thr moiety of the phosphoserine or phosphothreonine-proline peptidyl prolyl isomerase substrate.

Given the important role that PIN1 plays in the regulation of the cell cycle, additional compounds that inhibit PIN1 are needed. These compounds, along with pharmaceutical compositions thereof, can serve as effective chemotherapeutic agents for the treatment of a variety of disorders characterized by inappropriate cell proliferation, including cancer, infectious diseases, and neurodegenerative brain disorders.

Summary of the Invention

The present invention relates to compounds of the formula **1**



1

and to pharmaceutically acceptable salts and solvates thereof, wherein:

Q, Q^1, Q^2, Q^3 is independently selected from N, CH_2 or CH and wherein not more than two of Q are N;

T is CH, or N;

T' is O, NH, or NCH_3;

X is NH, O, -CH=, or NR' wherein R' can be alkyl or alkyl substituted with halogen, hydroxyl, amine, or carboxyl;

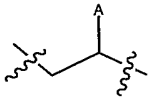
Y is -C(O)-, $-CH_2-$ or $-C(O)NR^2-$, or N wherein R^2 is H or C_1 to C_3 alkyl;

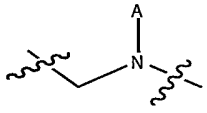
Z is H, alkyl, alkyl substituted with halogen, hydroxyl, amine, or carboxyl; or

X Y and Z can form a heterocyclic ring or

X and Y can form a heterocyclic ring;

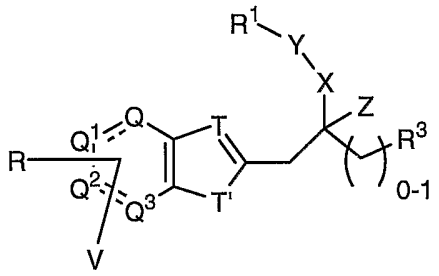
R and V are independently H, halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile;

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, ,

, $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

The present invention includes the compounds of formula 1 wherein:



1

and to pharmaceutically acceptable salts and solvates thereof, wherein:

Q, Q^1, Q^2, Q^3 is independently selected from N, CH_2 or CH and wherein not more than two of Q are N;

T is CH, or N;

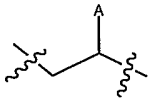
T' is O, NH, or NCH_3;

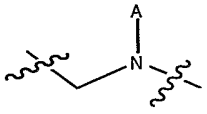
X is NH, O, or NR' wherein R' can be alkyl or alkyl substituted with halogen, hydroxyl, amine, or carboxyl;

Y is -C(O)-, $-CH_2-$ or $-C(O)NR^2-$, or N wherein R^2 is H or C_1 to C_3 alkyl;

Z is H, alkyl, alkyl substituted with halogen, hydroxyl, amine, or carboxyl;

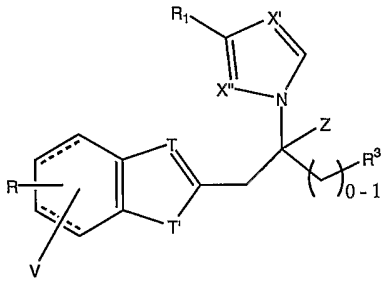
R and V are independently H, halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile;

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, ,

, $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, -$CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $–SO_2$-alkyl or $–SO_2H$.

The present invention also includes the compounds of formula 2



2

and to pharmaceutically acceptable salts and solvates thereof, wherein:

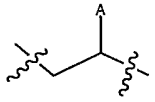
X' and X" are independently selected from CR^2 or N wherein R^2 is H or C_{1-3} alkyl;

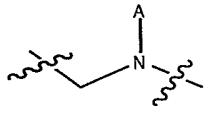
T is CH, or N;

T' is O, NH or NCH_3;

Z is H, alkyl or alkyl substituted with halogen, hydroxyl, amine or carboxy;

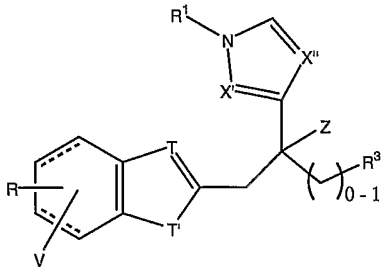
R and V are independently H, halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, ,

, $-CH_2S-$ or $–CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, -$CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $–SO_2$-alkyl or $–SO_2H$.

The present invention also includes the compounds of formula 3



3

and to pharmaceutically acceptable salts and solvates thereof, wherein:

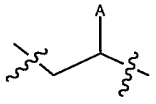
X' and X" are independently selected from CR^2 or N wherein R^2 is H or C_{1-3} alkyl;

T' is O, NCH_3 or N;

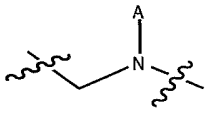
T is CH or N;

Z is H, alkyl, alkyl substituted with halogen, hydroxyl, amine, or carboxyl;

R and V are independently H, halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, 

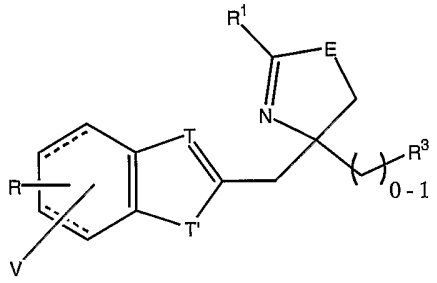
,



, $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

The compounds of the invention further include compounds of formula 4 having the following structure



4

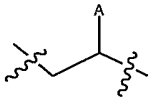
and the pharmaceutically active salts and solvates thereof wherein:

T' is O, NH or NCH_3;

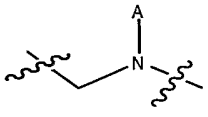
T is CH, or N;

E is selected from CH_2, O, S, and NR' wherein R' can be H, alkyl or alkyl substituted with halogen, hydroxyl or nitrile;

R and V are independently H, halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, 

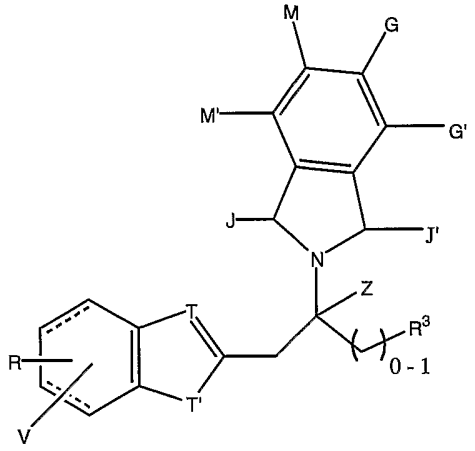
,



, $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

The compounds of the invention further include compounds of formula **5** having the following structure



5

and the pharmaceutically active salts and solvates thereof wherein

T is CH, or N;

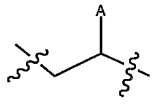
T' is O, NH or NCH_3;

Z is H, alkyl, substituted alkyl;

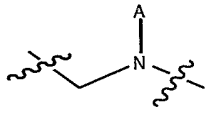
M, M', G and G' are independently H, halogen or M and N together form a cycloalkyl or an aromatic ring or M and M" and G and G' form a cycloalkyl or aromatic ring;

J and J' are independently H or =O;

R and V are independently H, halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, 

,



, $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

The present invention also relates to the inhibition of PIN1 and the treatment of abnormal cell growth by the inhibition of PIN1.

In another embodiment, the invention provides a method of treating abnormal cell growth in a mammal, including a human, the method comprising administering to the mammal any of the pharmaceutical compositions of the invention.

In a specific embodiment of any of the inventive methods described herein, the abnormal cell growth is cancer, including, but not limited to, lung cancer, bone cancer, pancreatic cancer, skin cancer,

cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

In further specific embodiments of any of the inventive methods described herein, the method further comprises administering to the mammal an amount of one or more substances selected from anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth with the compounds of the invention exemplified by formula 1 above.. Such substances include those disclosed in PCT Publication Nos. WO 00/38715, WO 00/38716, WO 00/38717, WO 00/38718, WO 00/38719, WO 00/38730, WO 00/38665, WO 00/37107 and WO 00/38786, the disclosures of which are incorporated herein by reference in their entireties.

Examples of anti-tumor agents include mitotic inhibitors, for example vinca alkaloid derivatives such as vinblastine vinorelbine, vindescine and vincristine; colchines allochochine, halichondrine, N-benzoyltrimethyl-methyl ether colchicinic acid, dolastatin 10, maystansine, rhizoxine, taxanes such as taxol (paclitaxel), docetaxel (Taxotere), 2'-N-[3-(dimethylamino)propyl]glutaramate (taxol derivative), thiocholchicine, trityl cysteine, teniposide, methotrexate, azathioprine, fluorouricil, cytocine arabinoside, 2'2'-difluorodeoxycytidine (gemcitabine), adriamycin and mitamycin. Alkylating agents, for example cis-platin, carboplatin oxiplatin, iproplatin, Ethyl ester of N-acetyl-DL-sarcosyl-L-leucine (Asaley or Asalex), 1,4-cyclohexadiene-1,4-dicarbamic acid, 2,5 –bis(1-azirdinyl)-3,6-dioxo-, diethyl ester (diaziquone), 1,4-bis(methanesulfonyloxy)butane (bisulfan or leucosulfan) chlorozotocin, clomesone, cyanomorpholinodoxorubicin, cyclodisone, dianhydroglactitol, fluorodopan, hepsulfam, mitomycin C, hycantheonemitomycin C, mitozolamide, 1-(2-chloroethyl)-4-(3-chloropropyl)-piperazine dihydrochloride, piperazinedione, pipobroman, porfiromycin, spirohydantoin mustard, teroxirone, tetraplatin, thiotepa, triethylenemelamine, uracil nitrogen mustard, bis(3-mesyloxypropyl)amine hydrochloride, mitomycin, nitrosoureas agents such as cyclohexyl-chloroethylnitrosourea, methylcyclohexyl-chloroethylnitrosourea 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitroso-urea, bis(2-chloroethyl)nitrosourea, procarbazine, dacarbazine, nitrogen mustard-related compounds such as mechloroethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, estramustine sodium phosphate, strptozoin, and temozolamide.

DNA anti-metabolites, for example 5-fluorouracil, cytosine arabinoside, hydroxyurea, 2-[(3hydroxy-2-pyrinodinyl)methylene]-hydrazinecarbothioamide, deoxyfluorouridine, 5-hydroxy-2-formylpyridine thiosemicarbazone, alpha-2'-deoxy-6-thioguanosine, aphidicolin glycinate, 5-azadeoxycytidine, beta-thioguanine deoxyriboside, cyclocytidine, guanazole, inosine glycodialdehyde, macbecin II, pyrazolimidazole, cladribine, pentostatin, thioguanine, mercaptopurine, bleomycin, 2-chlorodeoxyadenosine, inhibitors of thymidylate synthase such as raltitrexed and pemetrexed disodium, clofarabine, floxuridine and fludarabine. DNA/RNA antimetabolites, for example, L-alanosine, 5-azacytidine, acivicin, aminopterin and derivatives thereof such as N-[2-chloro-5-[[(2, 4-diamino-5-methyl-6-quinazolinyl)methyl]amino]benzoyl]-L-aspartic acid, N-[4-[[(2, 4-diamino-5-ethyl-6-quinazolinyl)methyl]amino]benzoyl]-L-aspartic acid, N -[2-chloro-4-[[(2, 4-diaminopteridinyl)methyl]amino]benzoyl]-L-aspartic acid, soluble Baker's antifol, dichloroallyl lawsone, brequinar, ftoraf, dihydro-5-azacytidine, methotrexate, N-(phosphonoacetyl)-L-aspartic acid tetrasodium salt, pyrazofuran, trimetrexate, plicamycin, actinomycin D, cryptophycin, and analogs such as cryptophycin-52 or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; proteins, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex□ (tamoxifen) or, for example anti-androgens such as Casodex™ (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

Anti-angiogenesis agents include MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25,

1997), all of which are herein incorporated by reference in their entirety. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Examples of MMP inhibitors include AG-3340, RO 32-3555, RS 13-0830, and the following compounds: 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide; and pharmaceutically acceptable salts, solvates and hydrates thereof.

Examples of signal transduction inhibitors include agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA).

EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998). EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusettes).

VEGF inhibitors, for example SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined or co-administered with the composition. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422

(published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are herein incorporated by reference in their entirety. Other examples of some specific VEGF inhibitors are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody bevacizumab (Genentech, Inc. of South San Francisco, California); and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California).

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), may be administered in combination with the composition. Such erbB2 inhibitors include those described in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), each of which is herein incorporated by reference in its entirety. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are herein incorporated by reference in their entirety.

Other antiproliferative agents that may be used include inhibitors of the enzyme farnesyl protein transferase and inhibitors of the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following United States patent applications: 09/221946 (filed December 28, 1998); 09/454058 (filed December 2, 1999); 09/501163 (filed February 9, 2000); 09/539930 (filed March 31, 2000); 09/202796 (filed May 22, 1997); 09/384339 (filed August 26, 1999); and 09/383755 (filed August 26, 1999); and the compounds disclosed and claimed in the following United States provisional patent applications: 60/168207 (filed November 30, 1999); 60/170119 (filed December 10, 1999); 60/177718 (filed January 21, 2000); 60/168217 (filed November 30, 1999), and 60/200834 (filed May 1, 2000). Each of the foregoing patent applications and provisional patent applications is herein incorporated by reference in their entirety.

Compositions of the invention can also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors. Specific CTLA4 antibodies that can be used in the present invention include those described in

United States Provisional Application 60/113,647 (filed December 23, 1998) which is herein incorporated by reference in its entirety.

For purposes of the present invention, as described and claimed herein, the following terms are defined as follows:

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated and unsaturated monovalent hydrocarbon radicals having straight or branched moieties.

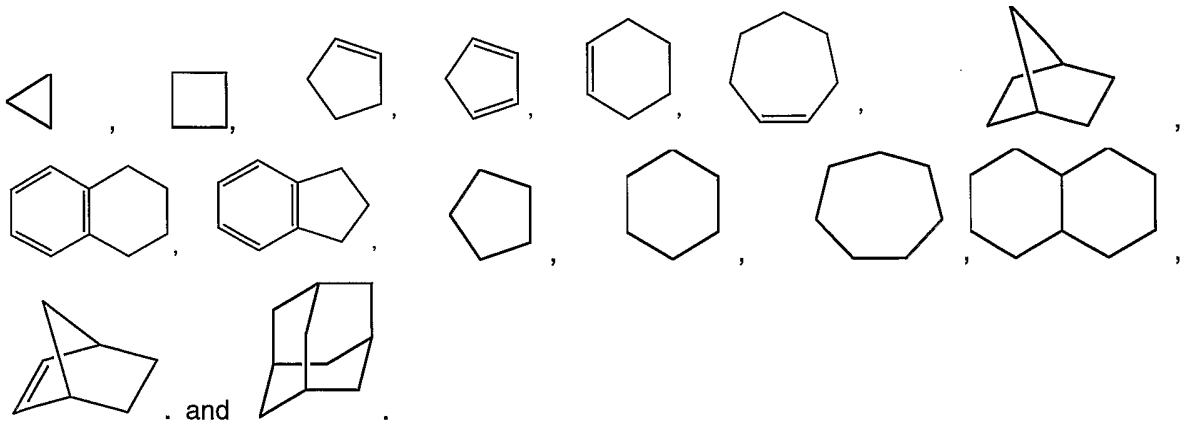
The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above and including E and Z isomers of said alkenyl moiety.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "Me" means methyl, "Et" means ethyl, and "Ac" means acetyl.

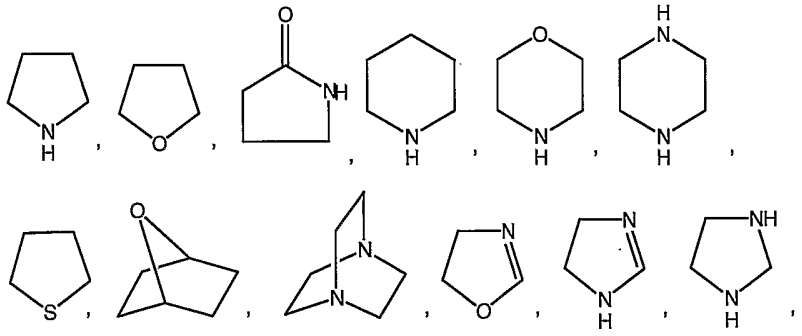
The term "cycloalkyl", as used herein, unless otherwise indicated refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Illustrative examples of cycloalkyl are derived from, but not limited to, the following:

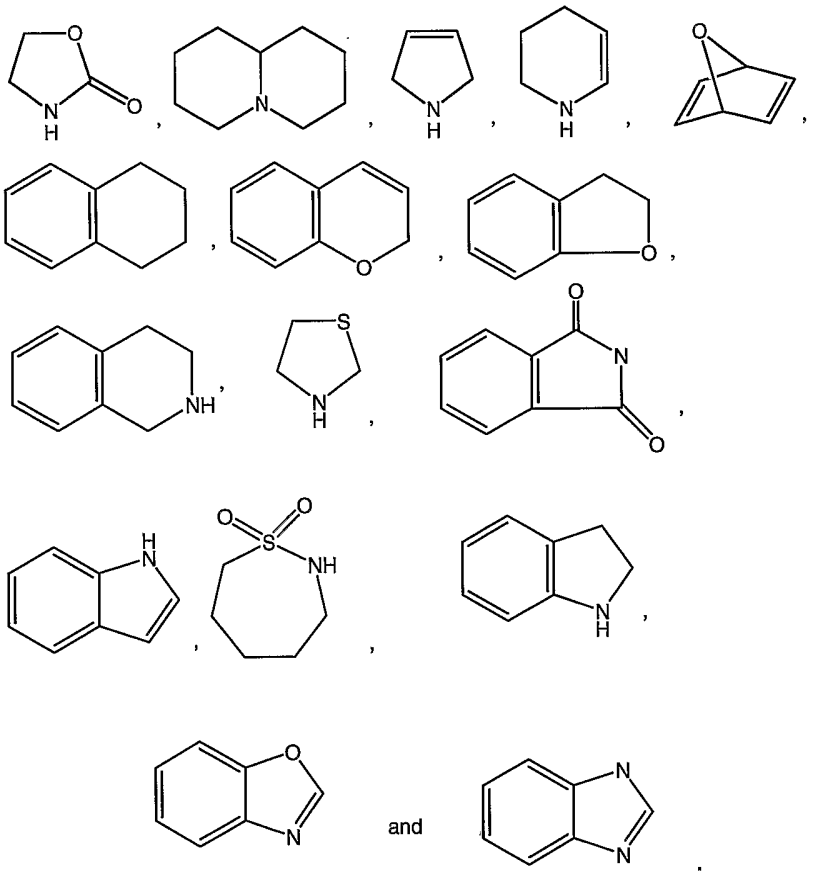


. and .

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "4 to 10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). The 4 to 10 membered heterocyclic may be optionally substituted on any ring carbon, sulfur, or nitrogen atom(s) by one to two oxo, per ring. An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo moieties is 1,1-dioxo-thiomorpholinyl. Other illustrative examples of 4 to 10 membered heterocyclic are derived from, but not limited to, the following:





Unless otherwise indicated, the term "oxo" refers to =O.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula I. The compounds of formula I that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formula I are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edislyate, estolate, esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phospate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

Certain compounds of formula I may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula I, and mixtures

thereof, are considered to be within the scope of the invention. With respect to the compounds of formula I, the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini et al., Chem. Rev, 1996, 96, 3147-3176 and references cited therein.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

This invention also encompasses pharmaceutical compositions containing and methods of treating abnormal cell growth through administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula I. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance,

free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews*, **1996**, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* **1996**, *39*, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products, or mixtures thereof. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

The compounds can be administered alone or in combination with one or more other compounds of the invention, or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation can be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995), the disclosure of which is incorporated herein by reference in its entirety.

Oral Administration

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be used as fillers in soft or hard capsules and typically include a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001), the disclosure of which is incorporated herein by reference in its entirety.

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are typically in amounts of from 0.2 wt% to 5 wt% of the tablet, and glidants typically from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally are present in amounts from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other conventional ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80 wt% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded

before tabletting. The final formulation may include one or more layers and may be coated or uncoated; or encapsulated.

The formulation of tablets is discussed in detail in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X), the disclosure of which is incorporated herein by reference in its entirety.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles can be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298. The disclosures of these references are incorporated herein by reference in their entireties.

Parenteral Administration

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

Topical Administration

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection. The disclosures of these references are incorporated herein by reference in their entireties.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Inhaled/Intranasal Administration

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may include a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µL to 100µL. A typical formulation includes a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing a desired mount of the compound of the invention. The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

Rectal/Intravaginal Administration

Compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Ocular Administration

Compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

Other Technologies

Compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in PCT Publication Nos. WO 91/11172, WO 94/02518 and WO 98/55148, the disclosures of which are incorporated herein by reference in their entireties.

Kit-of-Parts

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention includes two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically includes directions for administration and may be provided with a memory aid.

Detailed Description of the Invention

The compounds of the invention can be synthesized by the following reaction schemes. Starting materials, the synthesis of which is not specifically described above, are either commercially available or can be prepared using methods well known to those of skill in the art.

In each of the reactions illustrated or described herein, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable and ambient pressure, i.e. about 1 atmosphere, is preferred as a matter od convienence.

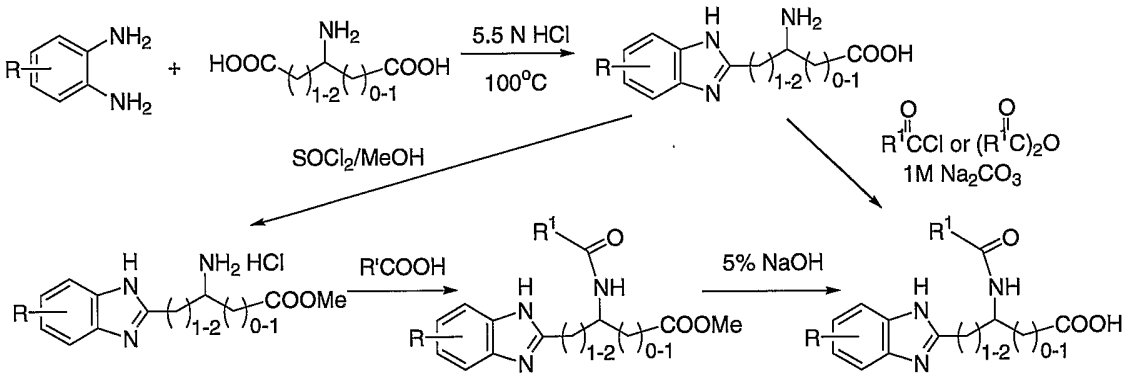
The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted,

exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

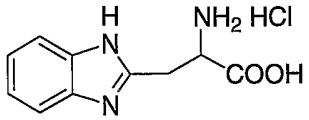
Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is a ZORBAX RXC18 column (manufactured by Hewlett Packard) of 150 mm distance and 4.6 mm interior diameter. The samples are run on a Hewlett Packard- 1100 systemA gradient solvent method is used running 100 percent ammonium acetate / acetic acid buffer (0.2 M) to 100 percent acetonitrile over 10 minutes. The system then proceeds on a wash cycle with 100 percent acetonitrile for 1.5 minutes and then 100 percent buffer solution for 3 minutes. The flow rate over this period is a constant 3 ml / minute.

In the following examples and preparations, "Et" means ethyl, "AC" means acetyl, "Me" means methyl, "ETOAC" or "ETOAc" means ethyl acetate, "THF" means tetrahydrofuran, and "Bu" means butyl. Unless otherwise indicated, X, Y, R^1, R^2, and R^3 in the reaction schemes and experimental procedures that follow are as defined above.

Synthesis of Benzimidazoles:

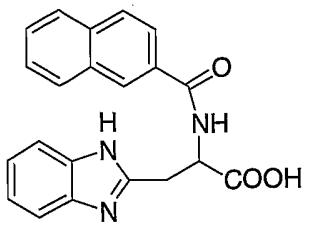


Compound 1a:



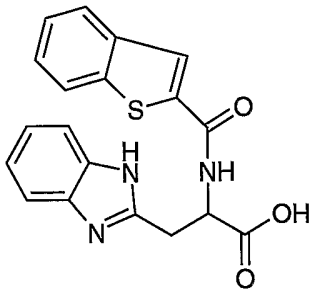
To an aqueous HCl solution (5.5 N, 50mL) was added O-Phenylenediamine dihydrochloride (9.05g, 0.05mol) and DL-aspartic acid (10g, 0.075mol). The mixture was heated at reflux for 70h. After being cooled down to 25°C, the suspension was filtered. The pH of filtrate was adjusted to pH~2 by slow addition of Na_2CO_3 solid. The precipitate was collected by filtration, washed with water and dried in vacuum oven (60°C). A pale green powder (5g, 41.5%yield) was obtained. ^{1}H NMR (CD_3OD): δ 7.75-7.65 (2H, m), 7.55-7.45 (2H, m), 4.64-4.58 (1H, m), 3.8-3.72 (2H, m). LCMS (APCI): 206($M+H^+$) (positive); 204 (M-H) (negative).

Example 1:



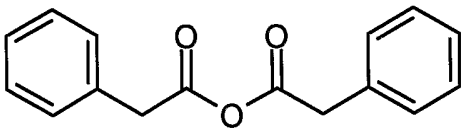
To a sodium carbonate solution (1M, 5mL) was added the amino acid **1a** (150mg, 0.621mmol), 2-Naphthoyl chloride (142mg, 0.745mmol) and acetonitrile (5mL). The mixture was stirred at 25°C for 15h. Iced-cooled 5% HCl solution was added to acidify the reaction solution (pH~1). The precipitate was collected by filtration, washed with water and dried in vacuum oven (60°C). A white solid (140mg, 63%yield) was obtained. ^{1}H NMR (DMSO-d_6): δ 12.58 (1H, br s), 9.07 (1H, d, J=7.9Hz), 8.38 (1H, s), 8.0-7.8 (4H, m), 7.54 (2H, m), 7.45-7.4 (2H, m), 7.1-7.0 (2H, m), 5.00 (1H, q, J=7.9Hz), 3.44 (1H, dd, J=15.1, 5.8Hz), 3.33 (1H, dd, J=15.1, 7.8Hz); LCMS (APCI): 358 (M-H) (negative); Elemental Analysis for ($C_{21}H_{17}N_3O_3$•0.1CF_3COOH) calc: C 68.67, H 4.65, N 11.33; found: C 68.65, H 4.67, N 11.34.

Example 2:



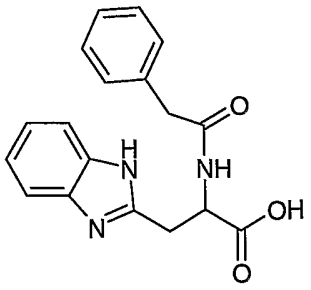
To an acetonitrile/water solution (4 mL/5 mL) of aminoacid **1a** (296 mg, 1.23 mmol) was added benzo[B]thiophene-2-carbonyl chloride (241 mg, 1.23 mmol) and sodium carbonate (456 mg, 4.31 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solids were filtered and washed with water (2x) and ethyl acetate (2x) to give the title compound in 76% yield. ^{1}H NMR (DMSO-D6): δ 9.17 (1H, d, J=7.72 Hz), 8.06 (1H, s), 7.99-7.85 (2H, m), 7.47-7.32 (4H, m), 7.10-7.00 (2H, m), 4.94 (1H, dd, J=13.94, 8.10 Hz), 3.46-3.23 (2H, m). LCMS (AP-ESI): 366.2 ($M+H^+$). Elemental Analysis for ($C_{19}H_{15}N_3O_3S$•0.3H_2O) calc: C 61.54, H 4.24, N 11.33; found: C 61.57, H 4.23, N 11.21.

Compound 3a:



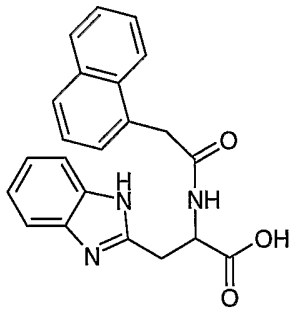
To an ether solution (8 mL) of the phenylacetic acid (349 mg, 2.57 mmol) and pyridine (0.7 mL) was slowly added phenylacetyl chloride (397 mg, 2.57 mmol) at 0°C. The mixture was stirred at room temperature for overnight. It was then diluted with ether (20 mL), washed with cold 1M HCl (10 mL) and saturated sodium bicarbonate (10 mL). Evaporation of ether gave the title compound in 48% yield. ^{1}H NMR (DMSO-d_6): δ 7.35 (5H, m), 3.89 (2H, s).

Example 3:



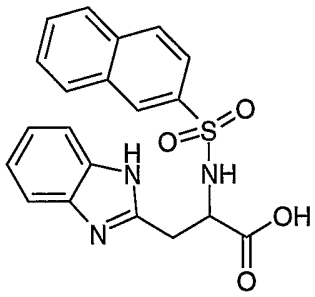
To an acetonitrile/water solution (4 mL/5 mL) of **1a** (289 mg, 1.20 mmol) was added the **3a** (304 mg, 1.20 mmol) and sodium carbonate (445 mg, 4.20 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 25% yield. ^{1}H NMR (DMSO-D6): δ 8.47 (1H, d, J=7.83 Hz), 7.44-7.37 (2H, m), 7.11-7.69 (7H, m), 4.72 (1H, dd, J=13.90, 8.09 Hz), 3.36 (2H, dd, J=18.69, 14.14 Hz), 3.24 (1H, dd, J=15.16, 5.81 Hz), 3.11 (1H, dd, J=14.91, 8.08 Hz). LCMS (APCI): 324.1 ($M+H^+$). Elemental Analysis for ($C_{18}H_{17}N_3O_3 \bullet 0.15H_2O$) calc: C 66.30, H 5.35, N 12.89; found: C 66.20, H 5.29, N 12.85.

Example 4:



To an acetonitrile/water solution (4 mL/5 mL) of **1a** (313 mg, 1.30 mmol) was added 1-naphthyacetic anhydride (459 mg, 1.30 mmol) and sodium carbonate (482 mg, 4.55 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2x) and ethyl acetate (2x) to give the title compound in 78% yield. ^{1}H NMR (DMSO-D6): δ 8.62 (1H, d, J=8.08 Hz), 7.80 (2H, t, J=8.08 Hz), 7.69 (1H, t, J=5.31 Hz), 7.44-7.39 (2H, m), 7.35 (1H, t, J=7.07 Hz), 7.24-7.20 (2H, m), 7.19-7.13 (1H, m), 7.11-7.06 (2H, m), 4.76 (1H, dd, J=16.17, 8.34 Hz), 3.84 (2H, s), 3.27 (1H, dd, J=17.03, 7.95 Hz), 3.14 (1H, dd, J=15.15, 8.33 Hz). LCMS (APCI): 374.1 ($M+H^+$). Elemental Analysis for ($C_{22}H_{19}N_3O_3 \bullet 0.2H_2O$) calc: C 70.09, H 5.19, N 11.15; found: C 70.11, H 5.15, N 10.95.

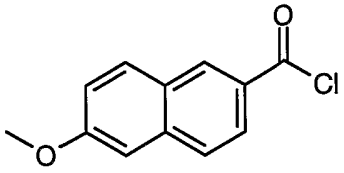
Example 5:



To an acetonitrile/water solution (4 mL/5 mL) of **1a** (245 mg, 1.01 mmol) was added naphthalene-2-sulfonyl chloride (230 mg, 1.01 mmol) and sodium carbonate (375 mg, 3.54 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Acetonitrile was evaporated. The residue was extracted with ethyl acetate (3X). The combined ethyl acetate was concentrated and purified by prep. HPLC to give the title compound in 22% yield. ^{1}H NMR (CD_3OD): δ 8.22 (1H, s), 7.85 (1H, d, J=8.85 Hz), 7.73 (2H, dd, J=18.19, 7.58 Hz), 7.61-7.44 (5H, m), 7.40-7.33 (2H, m), 4.43 (1H, dd, J=9.60, 4.54 Hz), 3.63 (1H, dd, J=15.16, 4.80 Hz), 3.32 (1H, dd, J=14.90, 9.85

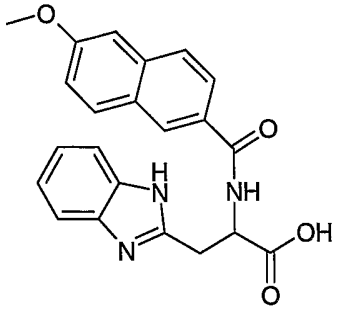
Hz). LCMS (API-ES): 396.0 ($M+H^+$). Elemental Analysis for ($C_{20}H_{17}N_3O_4S1 \bullet CF_3COOH \bullet 0.3H_2O$) calc: C 51.32, H 3.64, N 8.16; found: C 51.45, H 3.86, N 7.94.

Compound 6a:



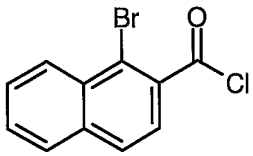
To a dichloromethane solution (15 mL) of 6-methoxy-naphthalene-2-carboxylic acid (497 mg, 2.46 mmol) was added oxalyl chloride (937 mg, 7.38 mmol) and 2 drops of N,N-dimethyl-formamide. The mixture was stirred at room temperature for 2 hours. Solvent was evaporated and dried under high vacuum to give the crude title compound in 100% yield.

Example 6:



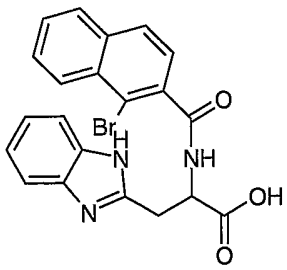
To an acetonitrile/water solution (4 mL/5 mL) of **1a** (241.5 mg, 1.00 mmol) was added **6a** (221 mg, 1.00 mmol) and sodium carbonate (371 mg, 3.50 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2x) and ethyl acetate (2x) to give the title compound in 36% yield. ^{1}H NMR (DMSO-*d6*): δ 9.08 (1H, d, J=7.84 Hz), 8.43 (1H, s), 7.98 (1H, d, J=9.10 Hz), 7.93 (2H, s), 7.54 (2H, dd, J=5.81, 3.04 Hz), 7.43 (1H, d, J=2.02 Hz), 7.29 (1H, dd, J=8.85, 2.28 Hz), 7.18 (2H, dd, J=5.81, 3.04 Hz), 5.10 (1H, dd, J=13.64, 7.58 Hz), 3.85 (3H, s), 3.54 (1H, dd, J=14.90, 5.81 Hz), 3.43 (1H, dd, J=15.16, 8.09 Hz). LCMS (APCI): 390.1 ($M+H^+$). Elemental Analysis for ($C_{22}H_{19}N_3O_4 \bullet 0.22H_2O$) calc: C 67.17, H 4.98, N 10.68; found: C 67.13, H 4.95, N 10.71.

Compound 7a:



To a dichloromethane solution (15 mL) of 1-bromo-2-naphthoic acid (650 mg, 2.59 mmol) was added oxalyl chloride (986 mg, 7.77 mmol) and 2 drops of N,N-dimethyl-formamide. The mixture was stirred at room temperature for 3 hours. Solvent was evaporated and dried under high vacuum to give the crude title compound in 100% yield.

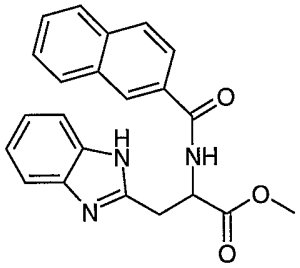
Example 7:



To an acetonitrile/water solution (5 mL/6 mL) of **1a** (314 mg, 1.30 mmol) was added **7a** (326 mg, 1.30 mmol) and sodium carbonate (482 mg, 4.55 mmol). The mixture was stirred at room temperature for

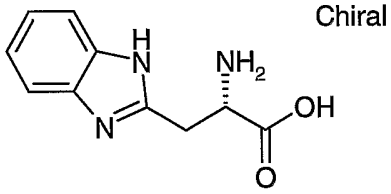
overnight. It was then acidified with 1M HCl. Solids was collected by filtration and washed with water (2x) and ethyl acetate (2x). Purification by preparative HPLC gave the title compound in 14% yield. ^{1}H NMR (DMSO-D6): δ 9.05 (1H, d, J=7.83 Hz), 8.14 (1H, d, J=8.34 Hz), 7.99 (2H, d, J=8.34 Hz), 7.72-7.52 (4H, m), 7.35 (1H, d, J=8.33 Hz), 7.24 (1H, s), 5.08 (1H, dd, J=14.90, 7.32 Hz), 3.54 (1H, dd, J=15.66, 5.81 Hz), 3.45 (1H, dd, J=15.16, 8.85 Hz). LCMS (APCI): 439.0 ($M+H^+$). Elemental Analysis for ($C_{21}H_{16}BrN_3O_3$•0.35TFA•0.1H_2O) calc: C 54.30, H 3.48, N 8.75; found: C 54.37, H 3.54, N 8.79.

Example 8:



To a methanol solution (5 mL) of **1** (60 mg, 0.167 mmol) was added thionyl chloride (0.5 mL, 6.85 mmol) at –30°C. The mixture was stirred at room temperature for overnight. Excess reagents were evaporated. The residue was purified by prep. HPLC to give the title compound in 36% yield. ^{1}H NMR (CD_3OD): δ 6.89 (1H, s), 6.53-6.46 (3H, m), 6.36 (1H, dd, J=8.59, 1.77 Hz), 6.29 (2H, dd, J=6.07, 3.03 Hz), 6.19-6.10 (4H, m), 3.76 (1H, dd, J=7.58, 6.32 Hz), 2.47 (1H, dd, J=15.16, 4.30 Hz), 2.37 (3H, s), 2.29 (1H, dd, J=15.16, 7.83 Hz). LCMS (APCI): 374.1 ($M+H^+$). Elemental Analysis for ($C_{22}H_{19}N_3O_3$•1TFA•1H_2O) calc: C 57.03, H 4.39, N 8.31; found: C 57.10, H 4.20, N 8.13.

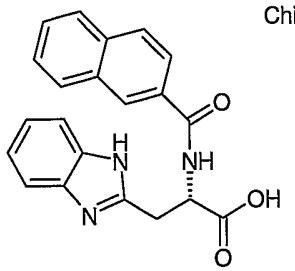
Example 9:



To a 5.5 N HCl solution (50 mL) of 1,2-phenylene diamine dihydrochloride (9.05 g, 50.0 mmol) was added L-aspartic acid (9.98 g, 75.0 mmol). The mixture was refluxed for 72h. It was filtered after cooling down to room temperature. The filtrate was adjusted to pH 1 with solid sodium carbonate. Solid was collected by filtration and recrystalized in 67% ethanol in water (50 mL) to give the title compound in 36% yield. ^{1}H NMR (CD_3OD): δ 6.20-6.13 (2H, m), 6.02-5.94 (2H, m), 3.06 (1H, t, J=7.32 Hz), 2.20 (2H, d, J=7.58 Hz).

LCMS (APCI): 206.1 ($M+H^+$). Elemental Analysis for ($C_{10}H_{11}N_3O_2$•1H_2O) calc: C 49.70, H 5.01, N 17.39; found: C 49.60, H 5.05, N 17.28.

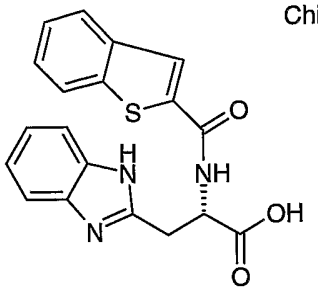
Example 10:



To an acetonitrile/water solution (4 mL/5 mL) of **9** (265 mg, 1.10 mmol) was added 2-naphthoyl chloride (209 mg, 1.10 mmol) and sodium carbonate (408 mg, 3.85 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 74% yield. ^{1}H NMR (DMSO-*d6*): δ 12.74 (1H, brs), 9.27 (1H, d, J=7.58 Hz), 8.59 (1H, s), 8.14 (3H, dd, J=17.94, 9.09 Hz), 8.05 (1H, d, J=8.84 Hz), 7.80-7.70 (2H, m), 7.63 (2H, dd, J=5.81, 3.03 Hz), 7.26 (2H, dd, J=6.06, 3.28

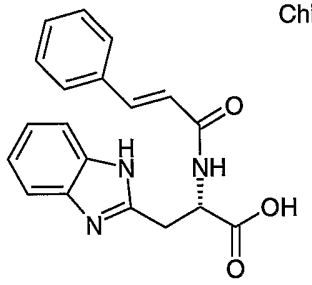
Hz), 5.20 (1H, dd, J=11.36, 8.08 Hz), 3.64 (1H, dd, J=15.16, 5.81 Hz), 3.53 (1H, dd, J=15.16, 8.09 Hz). LCMS (APCI): 360.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{17}N_3O_3 \bullet 0.1H_2O$) calc: C 69.83, H 4.80, N 11.63; found: C 69.64, H 4.80, N 11.70.

Example 11:



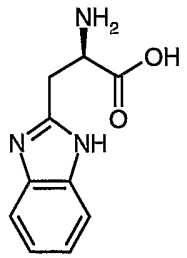
To an acetonitrile/water solution (4 mL/5 mL) of **9** (236 mg, 0.977 mmol) was added benzo[B]thiophene-2-carbonyl chloride (192 mg, 0.977 mmol) and sodium carbonate (362 mg, 3.42 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solids was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 81% yield. ^{1}H NMR (DMSO-*d6*): δ 12.57 (1H, brs), 9.16 (1H, d, J=7.83 Hz), 8.06 (1H, s), 7.95 (1H, d, J=7.33 Hz), 7.89 (1H, d, J=8.59 Hz), 7.45-7.33 (4H, m), 7.08-7.02 (2H, m), 4.93 (1H, dd, J=15.92, 8.09 Hz), 3.41 (1H, dd, J=15.41, 6.06 Hz), 3.28 (1H, dd, J=15.42, 8.34 Hz). LCMS (APCI): 366.1 ($M+H^+$). Elemental Analysis for ($C_{19}H_{15}N_3O_3S$) calc: C 62.45, H 4.14, N 11.50; found: C 62.23, H 4.21, N 11.48.

Example 12:



To an acetonitrile/water solution (5 mL/6 mL) of **9** (301 mg, 1.25 mmol) was added cinnamoyl chloride (208 mg, 1.25 mmol) and sodium carbonate (464 mg, 4.38 mmol). The mixture was stirred at room temperature overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate to give the title compound in 17% yield. ^{1}H NMR (CD_3OD): δ 7.58-7.51 (2H, m), 7.43-7.14 (8H, m), 6.46 (1H, d, J=15.83 Hz), 4.91 (1H, d, J=7.53 Hz), 3.62 (1H, dd, J=15.07, 6.03 Hz), 3.41 (1H, dd, J=15.07, 7.91 Hz). LCMS (APCI): 336.1 ($M+H^+$). Elemental Analysis for ($C_{19}H_{17}N_3O_3 \bullet 0.3H_2O$) calc: C 66.97, H 5.21, N 12.33; found: C 66.73, H 5.07, N 12.24.

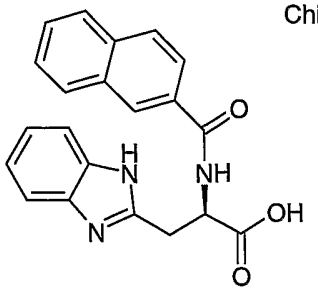
Compound 13a:



To a 5.5 N HCl solution (50 mL) of 1,2-phenylene diamine dihydrochloride (9.05 g, 50.0 mmol) was added H-D-Asp-OH (9.98 g, 75.0 mmol). The mixture was refluxed for 48h. It was filtered after cooling down to room temperature. The filtrate was adjusted to pH 1 with solid sodium carbonate. Solid was collected by filtration to give the title compound in 32% yield. ^{1}H NMR (DMSO-d_6): δ 7.50-7.45 (2H, m), 7.20-7.10 (2H, m), 4.45-4.38 (1H, m), 3.5-3.35 (2H, m). LCMS (APCI): 206.1 ($M+H^+$).

Example 13:

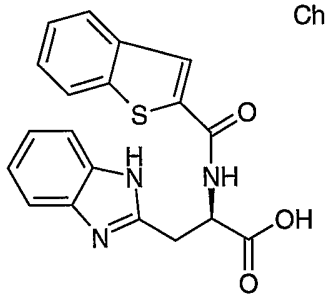
Chiral



To an acetonitrile/water solution (4 mL/5 mL) of **13a** (231 mg, 0.957 mmol) was added 2-naphthoyl chloride (182 mg, 0.957 mmol) and sodium carbonate (355 mg, 3.35 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 54% yield. ^{1}H NMR (DMSO-*d6*): δ 9.24 (1H, d, J=7.83 Hz), 8.57 (1H, s), 8.18-8.00 (4H, m), 7.77-7.69 (2H, m), 7.61 (2H, dd, J=5.81, 3.03 Hz), 7.24 (2H, dd, J=6.06, 3.03 Hz), 5.18 (1H, dd, J=13.90, 7.84 Hz), 3.61 (1H, dd, J=15.16, 5.82 Hz), 3.50 (1H, dd, J=15.16, 8.09 Hz). LCMS (APCI): 360.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{17}N_3O_3 \bullet 0.2H_2O$) calc: C 69.49, H 4.83, N 11.58; found: C 69.38, H 4.90, N 11.74.

Example 14:

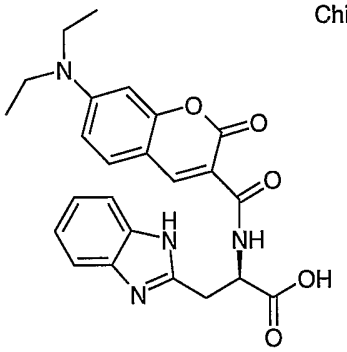
Chiral



To an acetonitrile/water solution (4 mL/5 mL) of **13a** (213 mg, 0.882 mmol) was added benzo[B]thiophene-2-carbonyl chloride (173 mg, 0.882 mmol) and sodium carbonate (327 mg, 3.09 mmol). The mixture was stirred at room temperature overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 84% yield. ^{1}H NMR (DMSO-*d6*): δ 9.38 (1H, d, J=7.84 Hz), 8.29 (1H, s), 8.17 (1H, d, J=8.59 Hz), 8.12 (1H, d, J=6.32 Hz), 7.68-7.56 (4H, m), 7.31-7.24 (2H, m), 5.16 (1H, dd, J=15.92, 8.09 Hz), 3.63 (1H, dd, J=15.16, 5.81 Hz), 3.51 (1H, dd, J=15.41, 8.33 Hz). LCMS (APCI): 366.0 ($M+H^+$). Elemental Analysis for ($C_{19}H_{15}N_3O_3S$) calc: C 62.45, H 4.14, N 11.50; found: C 62.30, H 4.32, N 11.50.

Example 15:

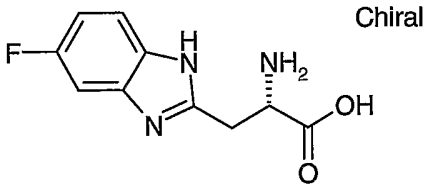
Chiral



To an acetonitrile/water solution (2 mL/2 mL) of **13a** (67 mg, 0.279 mmol) was added N-succinimidyl 7-(diethylamino)coumarin-3-carboxylate (100 mg, 0.279 mmol) and sodium carbonate (74 mg, 0.698 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Purification by prep. HPLC gave the title compound in 48% yield. ^{1}H NMR (CD_3OD): δ 8.52 (1H, s), 7.78-7.72 (2H, m), 7.63-7.57 (2H, m), 7.54 (1H, d, J=9.09 Hz), 6.86-6.81 (1H, m), 6.60 (1H, s), 5.20-

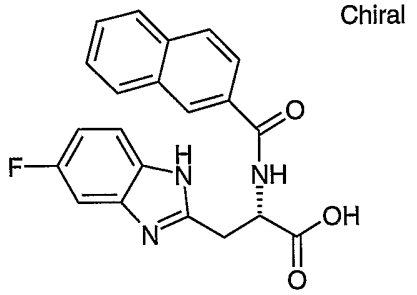
5.13 (1H, m), 3.88 (1H, dd, J=14.65, 6.06 Hz), 3.67 (1H, dd, J=17.43, 10.61 Hz), 3.56 (4H, q, J=7.08 Hz), 1.25 (6H, t, J=7.07 Hz). LCMS (APCI): 449.1 ($M+H^+$). Elemental Analysis for ($C_{24}H_{24}N_4O_5 \bullet 1.2TFA \bullet 0.4H_2O$) calc: C 53.51, H 4.42, N 9.46; found: C 53.63, H 4.49, N 9.36.

Compound 16a:



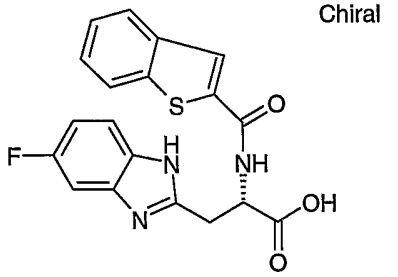
To a 5.5 N HCl solution (40 mL) of 4-fluoro-*o*-phenylene diamine (5.11 g, 40.5 mmol) was added L-aspartic acid (8.09 g, 60.8 mmol). The mixture was refluxed overnight. It was filtered after cooling down to room temperature. The filtrate was adjusted to pH 1 with solid sodium carbonate. Solid was collected by filtration and recrystalized with 67% ethanol in water (50 mL) to give the title compound in 12% yield. ^{1}H NMR (DMSO-d_6): δ 10.37 (1H, br s), 7.53 (1H, dd, J=8.9, 4.9 Hz), 7.35 (1H, dd, J=9.4, 2.2Hz), 7.10-7.00 (1H, m), 4.46 (1H, t, J=6Hz), 3.49 (1H, dd, J=16.4, 5.4Hz), 3.40 (1H, dd, J=16.8, 6.8Hz). LCMS (APCI): 224.1 ($M+H^+$).

Example 16:



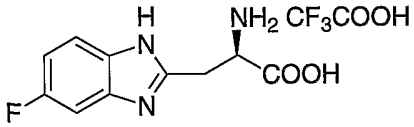
To an acetonitrile/water solution (4 mL/5 mL) of **16a** (241 mg, 0.929 mmol) was added 2-naphthoyl chloride (177 mg, 0.929 mmol) and sodium carbonate (345 mg, 3.25 mmol). The mixture was stirred at room temperature overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 57% yield. ^{1}H NMR (DMSO-D6): δ 12.92 (1H, brs), 9.35 (1H, d, J=8.59 Hz), 8.69 (1H, s), 8.26 (3H, dd, J=18.69, 7.83 Hz), 8.16 (1H, d, J=8.59 Hz), 7.90-7.81 (2H, m), 7.77-7.70 (1H, m), 7.56 (1H, d, J=9.35 Hz), 7.22 (1H, dd, J=9.35 Hz), 5.30 (1H, dd, J=14.66, 7.08 Hz), 3.78-3.56 (2H, m). LCMS (APCI): 378.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{16}FN_3O_3 \bullet 0.2H_2O$) calc: C 66.20, H 4.34, N 11.03; found: C 66.26, H 4.33, N 11.09.

Example 17:



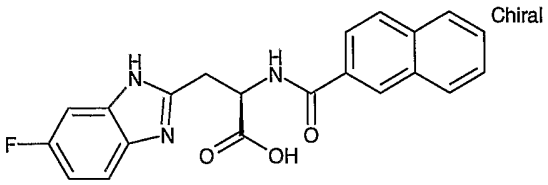
To an acetonitrile/water solution (3 mL/4 mL) of **16a** (223 mg, 0.859 mmol) was added benzo[B]thiophene-2-carbonyl chloride (169 mg, 0.859 mmol) and sodium carbonate (319 mg, 3.01 mmol). The mixture was stirred at room temperature overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 85% yield. ^{1}H NMR (DMSO-D6): δ 9.27-9.16 (1H, m), 8.13 (1H, s), 8.06-7.93 (2H, m), 7.52-7.40 (3H, m), 7.36-7.27 (1H, m), 7.03-6.93 (1H, m), 5.04-4.96 (1H, m), 3.52-3.31 (2H, m). LCMS (APCI): 384.0 ($M+H^+$). Elemental Analysis for ($C_{19}H_{14}FN_3O_3S$) calc: C 59.52, H 3.68, N 10.96; found: C 59.57, H 3.83, N 10.86.

Compound 18a:



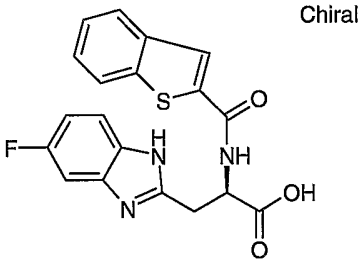
To an aqueous HCl solution (5.5 N, 87mL) was added 4-Fluorobenzene-1,2-diamine (10g, 79.4mmol) and D-Aspartic acid (15.8g, 119mmol). The mixture was heated at reflux for 72h. The mixture was purified with preparative HPLC and recrystallization from EtOAc, affording the title compound (7.5g, 28% yield) as a pale tan solid. ^{1}H NMR (CD_3OD): δ 7.62 (1H, dd, J=8.9, 4.8Hz), 7.36 (1H, dd, J=8.9, 2.3Hz), 7.14 (1H, td, J=9.6, 2.5 Hz), 4.53 (1H, dd, J=7.4, 5.6Hz), 3.67 (1H, dd, J=16.4, 5.8Hz), 3.54 (1H, dd, J=16.2, 7.4Hz). LCMS (APCI): 224 (M+H) (positive).

Example 18:



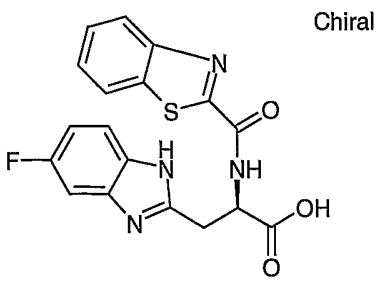
To an acetonitrile/water solution (4 mL/5 mL) of **18a** (214 mg, 0.960 mmol) was added 2-naphthoyl chloride (183 mg, 0.960 mmol) and sodium carbonate (356 mg, 3.36 mmol). The mixture was stirred at room temperature overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 69% yield. ^{1}H NMR (DMSO-D6): δ 12.62 (1H, br), 9.08 (1H, d, J = 7.6 Hz), 8.43 (1H, s), 8.03-7.96 (2H, m), 7.90 (1H, dd, J = 8.6, 1.5 Hz), 7.63-7.56 (2H, m), 7.48-7.45 (1H, m), 7.31-7.28 (1H, m), 6.99-6.93 (1H, m), 5.06-5.01 (1H, m), 3.47 (1H, dd, J = 15.2, 6.1 Hz), 3.36 (1H, dd, J = 15.2, 8.1 Hz). LCMS (APCI): 378.0 ($M+H^+$). Elemental Analysis for ($C_{21}H_{16}FN_3O_3 \bullet 0.65H_2O$) calc: C 64.82, H 4.48, N 10.80; found: C 64.66, H 4.26, N 10.80.

Example 19:



To an acetonitrile/water solution (5 mL/6 mL) of **18a** (391 mg, 1.75 mmol) was added benzo[B]thiophene-2-carbonyl chloride (345 mg, 1.75 mmol) and sodium carbonate (649 mg, 6.13 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 69% yield. ^{1}H NMR (DMSO): δ 12.71 (1H, br), 9.20 (1H, d, J = 7.8 Hz), 8.11 (1H, s), 8.02-8.00 (1H, m), 7.96-7.94 (1H, m), 7.48-7.40 (3H, m), 7.29 (1H, dd, J = 9.6, 2.5 Hz), 6.99-6.93 (1H, m), 5.00-4.93 (1H, m), 3.45 (1H, dd, J = 15.4, 5.8 Hz), 3.33 (1H, dd, J = 15.4, 8.3 Hz). LCMS (APCI): 384.0 ($M+H^+$). Elemental Analysis for ($C_{19}H_{14}FN_3O_3S0.2H_2O$) calc: C 58.97, H 3.75, 10.86; found: C 58.94, H 3.72, N 10.87.

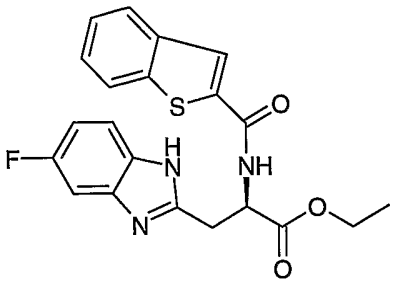
Example 20:



To a dichloromethane solution (20 mL) of 1,3-benzothiazole-2-carboxylic acid (563 mg, 3.14 mmol) were slowly added oxalyl chloride (1194 mg, 9.41 mmol) and 2 drops of N,N-dimethylformamide. It was stirred for 2 hours at room temperature. Evaporation of the solvent gave the crude 1,3-benzothiazole-2-carboxylic chloride. To an acetonitrile/water solution (10 mL/10 mL) of **18a** (700 mg, 3.14 mmol) was added the crude 1,3-benzothiazole-2-carboxylic chloride (3.14 mmol) and sodium carbonate (1165 mg, 11.0 mmol). The mixture was stirred at room temperature for two days. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 4% yield. ^{1}H NMR (DMSO-D6): δ 9.52 (1H, d, J = 8.3 Hz), 8.23 (1H, d, J = 8.8 Hz), 8.16 (1H, d, J = 8.6 Hz), 7.66-7.56 (2H, m), 7.48 (1H, dd, J = 8.9, 4.9 Hz), 7.33-7.29 (1H, m), 7.01-6.94 (1H, m), 5.11-5.04 (1H, m), 3.48-3.46 (2H, m). LCMS (APCI): 385.0 (M+H$^+$). Elemental Analysis for ($C_{18}H_{13}FN_4O_3S$•0.15H_2O) calc: C 55.85, H 3.46, 14.47; found: C 55.83, H 3.37, N 14.28.

Example 21:

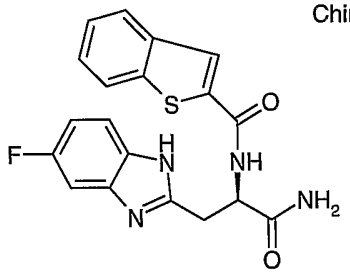
Chiral



To an ethanol solution (5 mL) of **19** (114 mg, 0.298 mmol) was added thionyl chloride (0.5 mL, 6.85 mmol) at –30°C. The mixture was stirred at room temperature for overnight. Excess reagents were evaporated. The residue was purified by prep. HPLC to give the title compound in 62% yield. ^{1}H NMR (CD_3OD): δ 7.86 (1H, s), 7.82-7.79 (2H, m), 7.61 (1H, dd, J = 9.1, 4.3 Hz), 7.40-7.31 (3H, m), 7.26-7.20 (1H, m), 5.01-4.98 (1H, m), 4.14 (2H, q, J = 7.2 Hz), 3.76-3.71 (1H, m), 3.57 (1H, dd, J = 15.2, 7.8 Hz), 1.11 (3H, t, J = 7.2 Hz). LCMS (APCI): 412.0 (M+H$^+$). Elemental Analysis for ($C_{21}H_{18}FN_3O_3S1$•TFA•0.6H_2O) calc: C 51.51, H 3.80, N 7.84; found: C 51.56, H 3.82, N 7.68.

Example 22:

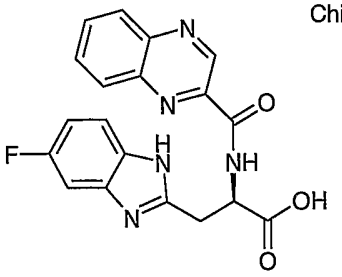
Chiral



Into a methanol solution (2 mL) of **19** (36 mg, 0.0876 mmol) was bubbled ammonia at 0°C for 45 minutes. The mixture was stirred at room temperature for overnight. The crude product was purified by prep. HPLC to give the title compound in 36% yield. ^{1}H NMR (CD_3OD): δ 7.90 (1H, s), 7.82-7.77 (2H, m), 7.62-7.59 (1H, m), 7.38-7.32 (3H, m), 7.24-7.18 (1H, m), 5.11-5.09 (1H, m), 3.72-3.66 (1H, m), 3.48-3.42 (1H, m). LCMS (APCI): 393.1 (M+H$^+$).

Example 23:

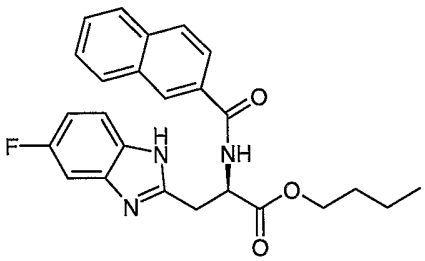
Chiral



To an acetonitrile/water solution (6 mL/7 mL) of **18a** (322 mg, 1.44 mmol) was added 2-quinoxaloyl chloride (278 mg, 1.44 mmol) and sodium carbonate (382 mg, 3.60 mmol). The mixture was stirred at room temperature for overnight. It was then diluted with ethyl acetate (10 mL) and acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 43% yield. ^{1}H NMR (DMSO-D6): δ 9.67 (1H, d, J = 8.6 Hz), 9.48 (1H, s), 8.25-8.19 (2H, m), 8.02-7.99 (2H, m), 7.50 (1H, dd, J = 8.7, 4.9 Hz), 7.33 (1H, dd, J = 9.5, 2.4 Hz), 7.02-6.96 (1H, m), 5.17-5.12 (1H, m), 3.50-3.49 (2H, m). LCMS (APCI): 380.1 (M+H$^+$). Elemental Analysis for ($C_{19}H_{14}FN_5O_3$•0.5H_2O) calc: C 58.76, H 3.89, 18.03; found: C 58.94, H 3.70, N 17.88.

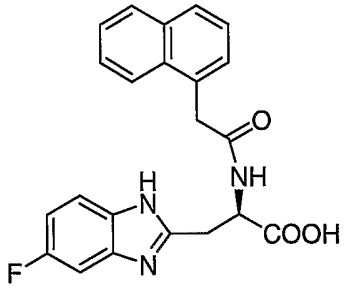
Example 24:

Chiral



To a *t*-butanol solution (5 mL) of **18** (218 mg, 0.578 mmol) was added thionyl chloride (0.6 mL, 8.22 mmol). The reaction mixture was stirred at room temperature for 45 minutes. Excess reagents were evaporated. The residue was purified by prep. HPLC to give the title compound in 52% yield. ^{1}H NMR (DMSO-D6): δ 9.32 (1H, d, J = 7.5 Hz), 8.42 (1H, s), 8.02-7.97 (3H, m), 7.88 (1H, dd, J = 8.5 Hz, 1.7 Hz), 7.73 (1H, dd, J = 9.0, 4.6 Hz), 7.66-7.57 (3H, m), 7.31-7.25 (1H, m), 5.09 (1H, q, J = 7.4 Hz), 4.08-4.00 (2H, m), 3.70 (1H, dd, J = 15.3, 7.0 Hz), 3.56 (1H, dd, J = 15.1, 7.9 Hz), 1.44-1.35 (2H, m), 1.20-1.08 (2H, m), 0.72 (3H, t, J = 7.4 Hz). LCMS (APCI): 434.1 (M+H$^+$). Elemental Analysis for ($C_{25}H_{24}FN_3O_3$•1.45TFA•0.2H_2O) calc: C 55.62, H 4.33, N 6.96; found: C 55.63, H 4.33, N 7.01.

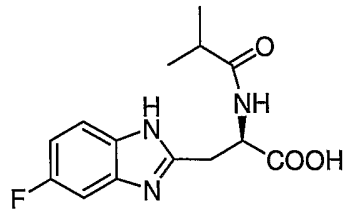
Example 25:



25

To a sodium carbonate solution (1M, 2.5mL) was added the amino acid **18a** (150mg, 0.445mmol), 1-Naphthylacetic anhydride (284mg, 0.804mmol) and acetonitrile (2.5mL). The mixture was stirred at 25°C for 18h. Ice-cooled 5% HCl solution was added to acidify the reaction mixture (pH~2). The precipitate was collected by filtration and washed with EtOAc. Preparative HPLC purification provided 75mg of the title product (29% yield). ^{1}H NMR (DMSO-d_6): δ 8.52 (1H, d, J=7.8Hz), 7.70 (2H, m), 7.58 (1H, m), 7.33-7.23 (2H, m), 7.15-7.05 (4H, m), 6.85 (1H, t, J=9Hz), 4.64 (1H, m), 3.73 (3H, s), 3.15-3.0 (2H, m); LCMS (APCI): 392(M+H$^+$) (positive); 390 (M-H) (negative); HRMS (MALDI) calc for $C_{22}H_{19}N_3O_3F$ (M+H$^+$) 392.1410; found 392.1407; Elemental Analysis for ($C_{22}H_{18}N_3O_3F$• 0.1EtOAc) calc: C 67.22, H 4.74, N 10.50; found: C 67.36, H 4.57, N 10.24.

Example 26:

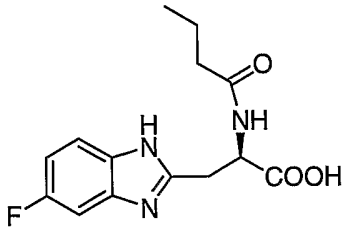


26

To a sodium carbonate solution (1M, 5mL) was added the amino acid **18a** (250mg, 0.742mmol), 2-Methylpropanoic anhydride (150mg, 0.948mmol) and acetonitrile (5mL). The mixture was stirred at 25°C for 15h. Ice-cooled 5% HCl solution was added to acidify the reaction mixture

(pH~2). The precipitate was collected by filtration and washed with EtOAc. Preparative HPLC purification provided 220mg of the title product (99% yield). ^{1}H NMR (DMSO-d_6): δ 8.43 (1H, d, J=8.1Hz), 7.77 (1H, dd, J=8.8, 4.7Hz), 7.61 (1H, dd, J=9.2, 2.4Hz), 7.31 (1H, td, J=9.8, 2.4Hz), 4.95 (1H, q, J=8.1Hz), 3.58 (1H, dd, J=14.9, 6.4Hz), 3.40 (1H, dd, J=14.9, 8.1Hz), 2.54 (1H, hept, J=6.8Hz), 1.13 (3H, d, J=7Hz), 1.06 (3H, d, J=6.8Hz). LCMS (APCI positive): 294 (M+H$^+$); Elemental Analysis for ($C_{14}H_{16}N_3O_3F$• 0.32CF_3COOH) calc: C 53.32, H 4.99, N 12.74; found: C 53.29, H 5.06, N 12.73.

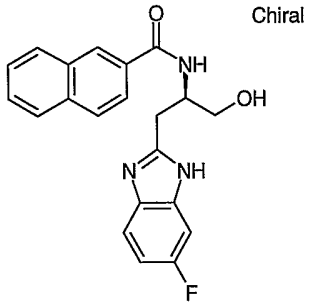
Example 27:



27

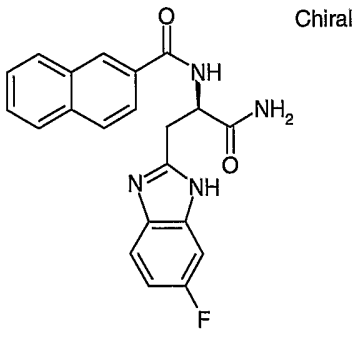
To a sodium carbonate solution (1M, 5mL) was added the amino acid **18a** (230mg, 0.682mmol), Butanoic anhydride (150mg, 0.948mmol) and acetonitrile (5mL). The mixture was stirred at 25°C for 15h. Ice-cooled 5% HCl solution was added to acidify the reaction mixture (pH~2). The precipitate was collected by filtration and washed with EtOAc. Preparative HPLC purification provided 200mg of the title product (quantative). ^{1}H NMR (DMSO-d_6): δ 12.9 (1H, s), 8.27 (1H, d, J=8.1Hz), 7.55 (1H, dd, J=8.8, 4.7Hz), 7.39 (1H, dd, J=9.2, 2.4Hz), 7.09 (1H, td, J=9.8, 2.4Hz), 4.76 (1H, m), 3.36 (1H, dd, J=15, 6.2 Hz), 3.18 (1H, dd, J=15.1, 8.1 Hz), 2.01 (1H, t, J=7.1Hz), 1.40 (1H, hex, J=7.3Hz), 0.72 (1H, t, J=7.4 Hz). LCMS (APCI positive): 294 (M+H$^+$); Elemental Analysis for ($C_{14}H_{16}N_3O_3F$•0.51CF_3COOH) calc: C 51.33, H 4.74, N 11.96; found: C 51.30, H 4.79, N 11.81.

Example 28:



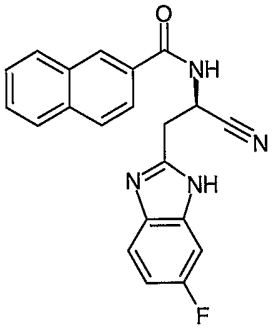
To a tetrahydrofuran solution (3 mL) of **24** (66 mg, 0.152 mmol) was added lithium borohydride (5 mg, 0.229 mmol) and stirred at room temperature for 3 hours. The reaction was quenched with saturated ammonium chloride and purified by prep. HPLC to give the title compound in 13% yield. ^{1}H NMR (CD_3OD): δ 8.18 (1H, s), 7.84-7.76 (4H, m), 7.63-7.57 (2H, m), 7.47-7.36 (3H, m), 7.25-7.18 (1H, m), 4.60-4.52 (1H, m), 3.74-3.71 (2H, m), 3.51 (1H, dd, J = 14.8, 4.6 Hz), 3.28 (1H, dd, J = 14.8, 9.0 Hz), 2.85 (1H, s), 2.72 (1H, s). LCMS (APCI): 3641 (M+H$^+$). HRMS (MALDI) calc for $C_{21}H_{19}N_3O_3F$ (M+H$^+$) 364.1461; found 364.1458.

Compound 29a:



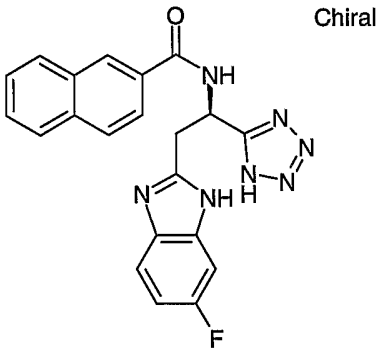
To a methanol solution (25 mL) of **18** (1.03 g, 2.73 mmol) was added thionyl chloride (0.5 mL, 6.85 mmol) at 0°C. The mixture was stirred at room temperature for overnight. Excess reagents were evaporated to give the crude methyl ester. LCMS (APCI): 392.1.1 ($M+H^+$). To a methanol solution (25 mL) of the crude methyl ester was bubbled ammonium at 0°C for 45 minutes. The mixture was stirred at room temperature for overweekend. Methanol was evaporated to give the title compound. LCMS (APCI): 377.1 ($M+H^+$).

Compound 29b:



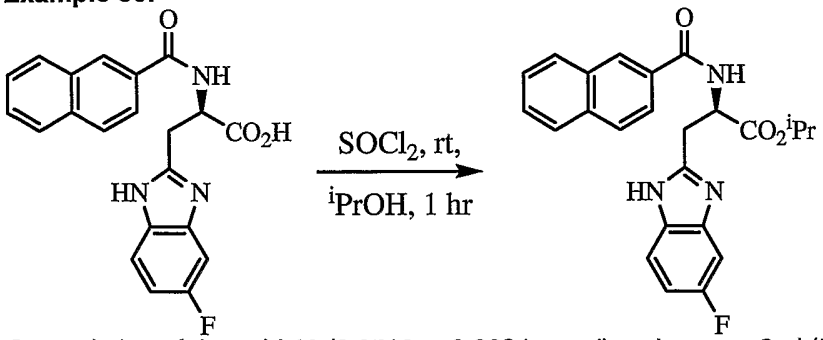
To a tetrahydrofuran solution (25 mL) of **29a** (2.73 mmol) was added trifluoroacetic anhydride (1.29 g, 6.14 mmol) and triethylamine (1.03 g, 10.2 mmol). The mixture was stirred at room temperature for overnight. It was then evaporated to give the crude title compound. ^{1}H NMR (DMSO-d_6): δ 9.61 (1H, d, J=7.6Hz), 8.47 (1H, s), 8.07-7.88 (4H, m), 7.72-7.58 (3H, m), 7.52 (1H, dd, J=9, 2.2Hz), 7.17 (1H, td, J=9.1, 1.9Hz), 5.61 (1H, dd, =15.2, 7.7Hz), 3,76-3.57 (2H, m). LCMS (APCI): 359.1 ($M+H^+$).

Example 29:



To a 1-methyl-2-pyrrolidinone solution (5 mL) of **29b** (70 mg, 0.196 mmol) were added triethylamine hydrochloride (40 mg, 0.294 mmol) and sodium azide (38 mg, 0.587 mmol). The mixture was stirred at 150°C for 3 hours. It was then purified by prep. HPLC to give the title compound in 6% yield. ^{1}H NMR (CD_3OD): δ 8.24 (1H, s), 7.84-7.78 (3H, m), 7.71 (1H, dd, J = 8.7, 1.5 Hz), 7.49-7.44 (2H, m), 7.38 (1H, dd, J = 8.7, 4.6 Hz), 7.13 (1H, dd, J = 9.0, 2.5 Hz), 6.95-6.88 (1H, m), 6.01 (1H, dd, J = 7.9, 6.4 Hz), 3.80-3.71 (1H, m), 3.61 (1H, dd, J = 14.9, 8.3 Hz). LCMS (APCI): 402.1 ($M+H^+$). HRMS (MALDI) calc for $C_{21}H_{17}N_7OF$ ($M+H^+$) 402.1479; found 402.1494.

Example 30:

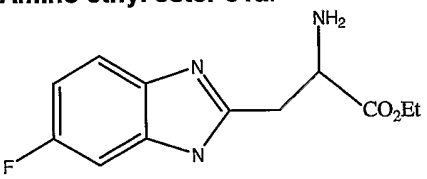


To a solution of the acid **18** (0.2516 g, 0.6684 mmol) and propan-2-ol (5.8 mL), at 0 °C under an nitrogen atmosphere, was added thionyl chloride (0.7 mL) dropwise. The reaction mixture was

allowed to warm to ambient temperature and stirred for 1 hour. The volatiles were removed *in vacuo* and the subsequent residue dissolved in ethyl acetate (25 mL) and saturated aq. sodium bicarbonate (25 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product. This material was purified by preparative HPLC to yield the pure title compound as a colorless oil (0.0586 g, 21%). ^{1}H NMR ($CDCl_3$): δ 8.27 (bs, 1H), 7.97 (d, J = 7.4 Hz, 1H), 7.84-7.76 (m, 4H), 7.53-7.46 (m, 2H), 7.44-7.36 (m, 1H), 7.17-7.14 (m, 1H), 6.92-6.86 (m, 1H), 5.22-5.16 (m, 1H), 5.08-4.99 (m, 1H), 3.65-3.52 (m, 2H), 2.03 (s, 6H); LCMS 420 (M+H).

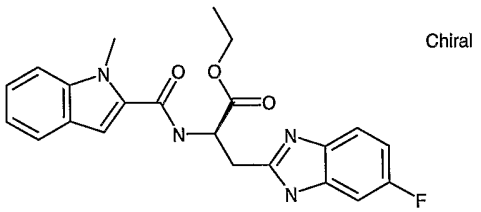
Synthesis of Examples 31-44

Amino ethyl ester 31a:



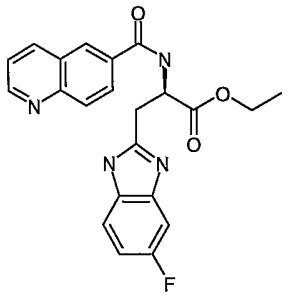
Amino acid 18a (1.25 g, 5.59 mmol) in ethanol (11 mL) was stirred for two hours at room temperature. Thionyl chloride (0.94 mL, 12.86 mmol) was added into the reaction mixture at 0°C. The reaction mixture was stirred for another two hours at 65°C. After cooling down to room temperature, excess thionyl chloride and solvent were removed *in vacuo* to give 0.94g (48%) of reddish brown residue. Crude **amino ethyl ester 31a** was used in the next step without aqueous work up and purification. ^{1}H NMR (DMSO-d_6): δ 0.94 (dd, 3H, J=14.13, 7.16 Hz), 1.04 (dd, 2H, J=13.94, 6.97 Hz), 3.42 (t, 2H, J=6.97 Hz), 4.91 (d, 1H, J=6.78 Hz), 7.37 (td, 1H, J=2.45, 2.07 Hz), 7.66 (t, 1H, J=2.26 Hz), 7.80 (t, 1H, J=4.52 Hz). LCMS 252 (M-H).

Example 31:



To a reaction mixture of amino ethyl ester **31a** (0.28 g, 1.12 mmol) and aryl carboxylic acid (0.20 g, 1.12 mmol) in DMF (3 mL), EDC (0.32 g, 2.68 mmol), DMAP (20.5 mg, 0.17 mmol) and triethyl amine (172 ?L, 1.23 mmol) were added. The reaction mixture was stirred for 16 hours at room temperature. Crude product was purified by prep-HPLC without work up (25_75_60min, 0.1% TFA in water and acetonitrile) given 0.13 g (29%) of oil **31**. ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3H, J-7.06 Hz), 3.44 (m, 2H), 3.91 (s, 3H), 4.07 (q, 2H, J=7.03 Hz), 4.99 (m, 1H), 6.98 (m, 1H), 7.09 (m, 2H), 7.38 (m, 4H), 7.64 (d, 1H, J=8.10 Hz), 9.02 (dd, 1H, J=7.54, 2.83 Hz). LCMS 409 (M+H).

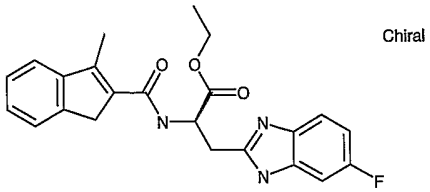
Example 32:



To a reaction mixture of amino ethyl ester **31a** (0.29 g, 1.12 mmol) and aryl carboxylic acid (0.19 g, 1.12 mmol) in DMF (7.5 mL), EDC (2.41 g, 1.30 mmol), HATU (469.0 mg, 1.20 mmol) and triethyl amine (312 µL, 4.25 mmol) were added. The reaction mixture was stirred for 16 hours at room temperature. Crude product was purified by prep-HPLC without work up (20_55_60min, 0.1% TFA in water and acetonitrile) giving 0.16 g (38%) of oil **32**. ^{1}H NMR (DMSO-d_6): δ 1.07 (t, 3H, J=7.16 Hz),

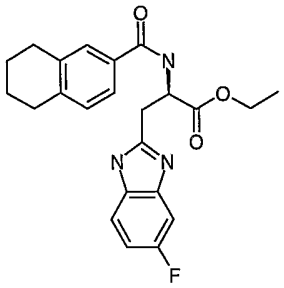
3.58 (m, 2H), 4.11 (q, 2H), J=7.28 Hz), 5.10 (q, 1H, 7.47 Hz), 7.34 (m, 1H) 7.66 (dd, 2H, J=8.29, 4.33 Hz), 7.78 (dd, 1H, J=8.85, 4.71 Hz), 8.13 (m, 2H), 8.53 (m, 2H), 9.03 (d, 1H, J=4.33 Hz), 9.44 (d, 1H, J=7.35 Hz). LCMS 407 (M+H).

Example 33:



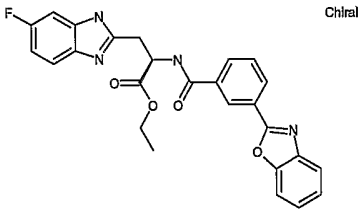
To a reaction mixture of amino ethyl ester **31a** (98.4 m g, 0.39 mmol) and aryl carboxylic acid (68.2 mg, 0.39 mmol) in DMF (2 mL), EDC (113.0 mg, 0.59 mmol), DMAP (7.2 mg, 0.06 mmol) and triethyl amine (60 µL, 0.43 mmol) were added. The reaction mixture was stirred for 16 hours at room temperature. Crude product was purified by prep-HPLC without work up (25_75_60min, 0.1% TFA in water and acetonitrile) giving 66.8 m g (42%) of oil **33** with less than 85% purity. The ethyl ester was carried in the hydrolysis step without further purification.

Example 34:



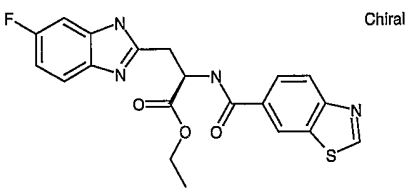
To a reaction mixture of **amino ethyl ester 31a** (0.31 g, 1.23 mmol) and aryl carboxylic acid (0.22 g, 1.23 mmol) in DMF (8.2 mL), EDC (0.35 g, 1.8 mmol), DMAP (22.5 mg, 0.18 mmol) and triethyl amine (342 µL, 2.5 mmol) were added. The reaction mixture was stirred for 16 hours at room temperature. Crude product was purified by prep-HPLC without work up (30_95_60min, 0.1% TFA in water and acetonitrile) giving 0.23 g (45%) of oil **34**. ^{1}H NMR (DMSO-d_6): δ 1.04 (t, 3H, J=7.16 Hz), 1.73 (s, 4H), 2.73 (s, 4H), 3.51 (m, 2H), 4.07 (q, 2H, J=7.03 Hz), 5.00 (q, 1H, J=7.60 Hz), 7.13 (d, 1H, J=8.67 Hz), 7.28 (m, 1H), 7.51 (d, 2H, J=6.22 Hz), 7.60 (d, 1H, J=7.72 Hz), 7.72 (dd, 1H, J=8.76, 4.43 Hz), 8.99 (d, 1H, J=7.16 Hz). LCMS 410 (M+H).

Example 35:



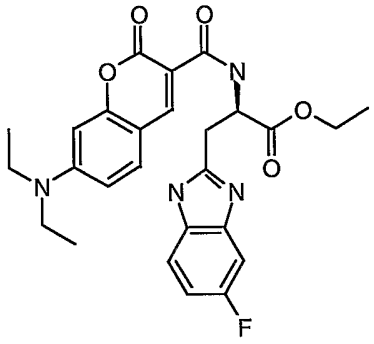
To a reaction mixture of **amino ethyl ester 31a** (0.31 g, 1.24 mmol) and aryl carboxylic acid (0.30 g, 1.24 mmol) in DMF (3 mL), EDC (0.37 g, 1.9 mmol), DMAP (25 mg, 0.19 mmol) and triethyl amine (345 µL, 2.5 mmol) were added. The reaction mixture was stirred for 16 hours at room temperature. Crude product was purified by prep-HPLC without work up (25_60_60min, 0.1% TFA in water and acetonitrile) giving 0.24 g (41%) of oil **35**.

Example 36:



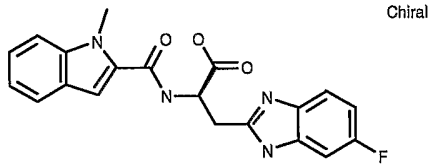
To a reaction mixture of **amino ethyl ester 31a** (0.31 g, 1.24 mmol) and aryl carboxylic acid (0.22 g, 1.24 mmol) in DMF (4 mL), EDC (0.36 g, 1.9 mmol), DMAP (25.0 mg, 0.28 mmol) and triethyl amine (345 µL, 3.72 mmol) were added. The reaction mixture was stirred for 16 hours at room temperature. Crude product was purified by prep-HPLC without work up (10_50_60min, 0.1% TFA in water and acetonitrile) giving 0.30 g (59%) of oil **36**. ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3H, J=7.06 Hz), 3.54 (s, 2H), 4.08 (dd, 3H, J=6.97, 1.13 Hz), 7.32 (dd, 1H, J=9.04, 6.78 Hz), 7.65 (dd, 1H, J=4.14, 0.94 Hz), 7.77 (m, 1H, J=8.48, 7.16, 4.90, 4.90, 4.90 Hz), 7.94 (d, 1H, J=8.48 Hz), 8.17 (d, 1H, J=8.48 Hz), 8.63 (d, 1H, J=1.70 Hz), 9.30 (d, 1H, J=8.29 Hz), 9.55 (s, 1H). LCMS 413 (M+H).

Example 37:



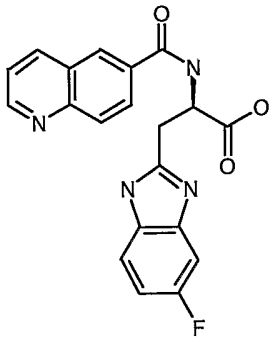
To a reaction mixture of **amino ethyl ester 31a** (0.02 g, 0.28 mmol) and N-succinimidyl 7-(diethylamino) coumarin-3-carboxylate (0.10 g, 0.28 mmol) in DMF (1.4 mL), EDC (0.08 g, 0.42 mmol), and triethyl amine (78 µL, 0.56 mmol) were added. The reaction mixture was stirred for 16 hours at room temperature. Crude product was purified by prep-HPLC without work up (30_70_60min, 0.1% TFA in water and acetonitrile) giving 0.051 g (37%) of oil **37**. ^{1}H NMR (DMSO-d_6): δ 1.11 (t, 6H, J=7.06 Hz), 3.48 (dd, 2H, J=21.29, 7.16 Hz), 4.11 (t, 4H, J=7.06 Hz), 5.06 (dd, 1H, J=7.54, 4.90 Hz), 6.61 (d, 1H, J=1.88 Hz), 6.80 (dd, 1H, J=11.30, 9.04 Hz), 7.24 (dd, 1H, J=16.20, 10.93 Hz), 7.55 (d, 1H, J=9.04 Hz), 7.69 (d, 2H, J=7.35 Hz), 8.60 (s, 1H), 9.31 (d, 1H, J=7.54 Hz). LCMS 495 (M+H).

Example 38:



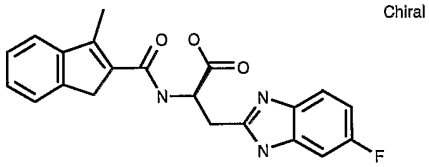
To a solution of **31** (0.12g, 0.23 mmol) in methanol (1.5 mL), 5% NaOH (1.5mL, 1.6 mmol) was added. The reaction mixture was stirred for two and half hours at room temperature then neutralized with 5.5N HCl until pH~7. The solvents were removed *in vacuo*. The residue was dissolved in methanol, and the product was purified by prep-HPLC (20_60_30min with 0.1% AcOH as buffer in water and acetonitrile) to give 4.9 mg (6%) of solid **38**. ^{1}H NMR (DMSO-d_6): δ 3.91 (s, 5H), 4.99 (s, 1H), 7.02 (ddd, 3H, J=29.58, 9.23, 8.85 Hz), 7.26 (dd, 2H, J=9.80, 8.29 Hz), 7.47 (dd, 2H, J=10.36, 7.54 Hz), 7.63 (d, 1H, J=8.10 Hz), 8.92 (d, 1H, J=7.35 Hz). LCMS 381 (M+H).

Example 39:



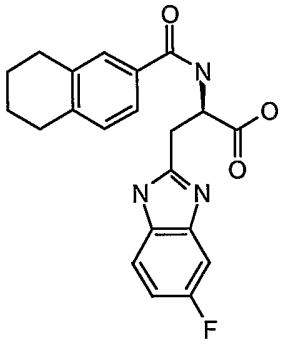
To a solution of **32** (0.16g, 0.40 mmol) in methanol (1.5 mL), 5% NaOH (0.5mL, 0.8 mmol) was added. The reaction mixture was stirred for two and half hours at room temperature then neutralized with 5.5N HCl until pH~7. The solvents were removed *in vacuo*. The residue was dissolved in methanol, and the product was purified by prep-HPLC with 0.1% AcOH as buffer in water and acetonitrile to give 35.5 mg (24%) of solid **57**. ^{1}H NMR (DMSO-d_6): δ 3.56 (m, 2H, J=7.72, 7.72. 6.03, 5.46 Hz), 5.07 (d, 1H, J=6.59 Hz), 7.16 (t, 1H, J=9.14 Hz), 7.49 (d, 1H, J=8.48 Hz), 7.63 (m, 2H), 8.12 (dq, 2H, J=25.81, 8.60 Hz), 8.50 (d, 2H, J=8.10 Hz), 9.01 (s, 1H), 9.29 (d, 1H, J=7.72 Hz). LCMS 379 (M+H).

Example 40:



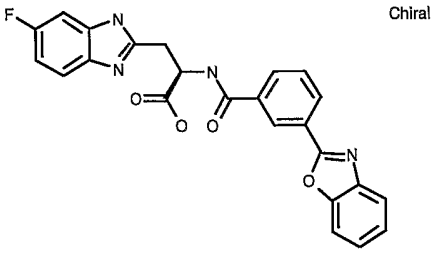
To a solution of **33** (0.067g, 0.16 mmol) in methanol (1.0 mL), 5% NaOH (0.5mL, 0.8 mmol) was added. The reaction mixture was stirred for two and half hours at room temperature then neutralized with 5.5N HCl until pH~7. The solvents were removed *in vacuo*. The residue was dissolved in methanol, and the product was purified by prep-HPLC with 0.1% TFA as buffer in water and acetonitrile to give 15.0 mg (24%) of solid **40**. ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H), 3.34 (d, 2H, J=3.77 Hz), 3.62 (s, 2H), 4.91 (dd, 1H, J=4.71, 3.77 Hz), 7.03 (dd, 1H, J=8.67, 8.29 Hz), 7.32 (d, 3H, J=6.97 Hz), 7.50 (dd, 3H, J=6.22, 4.52 Hz), 8.30 (d, 1H, J=8.10 Hz). LCMS 380 (M+H).

Example 41:



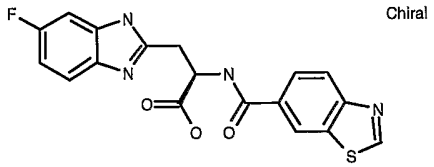
To a solution of **34** (0.23g, 0.56 mmol) in methanol (1.0 mL), 5% NaOH (1.0mL, 1.6 mmol) was added. The reaction mixture was stirred for two and half hours at room temperature then neutralized with 5.5N HCl until pH~7. The solvents were removed *in vacuo*. The residue was dissolved in methanol, and the product was purified by prep-HPLC (20_60_30min with 0.1% AcOH as buffer in water and acetonitrile) to give 52.7 mg (25%) of solid **41**. ^{1}H NMR (DMSO-d_6): δ 1.73 (s, 4H), 2.73 (s, 4H), 3.42 (t, 2H, J=8.19 Hz), 3.60 (dd, 2H, J=6.97, 5.84 Hz), 4.99 (dd, 1H, J=7.54, 5.46 Hz), 7.11 (d, 1H, J=8.48 Hz), 7.22 (td, 1H, J=2.26, 1.41 Hz), 7.52 (dd, 3H, J=6.59, 2.26 Hz), 7.66 (dd, 1H, J=4.71, 4.33 Hz), 8.88 (d,1H, J=7.72 Hz). LCMS 382 (M+H).

Example 42:



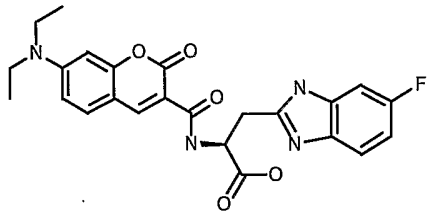
To a solution of **35** (0.24g, 0.51 mmol) in methanol (2.6 mL), 5% NaOH (1.2mL, 1.9 mmol) was added. The reaction mixture was stirred for two and half hours at room temperature then neutralized with 5.5N HCl until pH~7. The solvents were removed *in vacuo*. The residue was dissolved in methanol, and the product was purified by prep-HPLC (25_55_60min with 0.1% TFA as buffer in water and acetonitrile) to give 29.8 mg (13%) of solid **42**. ^{1}H NMR (DMSO-d_6): δ 3.59 (m, 2H, J=6.97, 6.03, 5.84, 4.90, 4.52, 4.71 Hz), 5.09 (t, 1H, J=6.12 Hz), 7.34 (dd, 1H, J=10.55, 1.32 Hz), 7.46 (m, 2H), 7.74 (m, 6H), 8.05 (d, 1H, J=8.67 Hz), 8.37 (d, 1H, J=8.10 Hz), 8.66 (s, 1H), 9.40 (d, 1H, J=8.67 Hz). LCMS 445 (M+H).

Example 43:



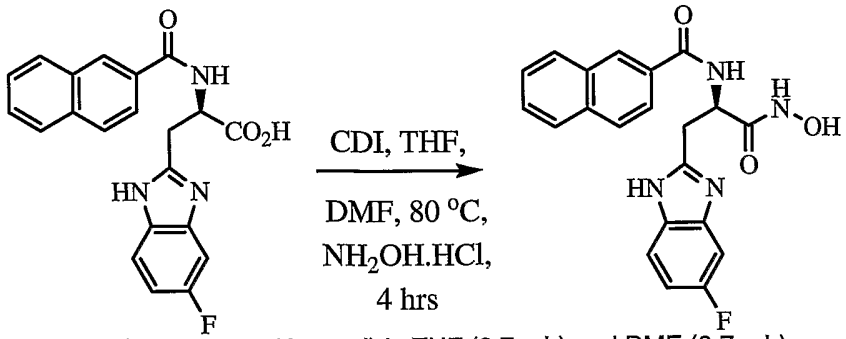
To a solution of **36** (0.30g, 0.73 mmol) in methanol (3.7 mL), 5% NaOH (1.8mL, 2.8 mmol) was added. The reaction mixture was stirred for two and half hours at room temperature then neutralized with 5.5N HCl until pH~7. The solvents were removed *in vacuo*. The residue was dissolved in methanol, and the product was purified by prep-HPLC (25_55_60min with 0.1% AcOH as buffer in water and acetonitrile) to give 40.5 mg (14%) of solid **43**. ^{1}H NMR (DMSO-d_6): δ 3.59 (m, 2H, J=34.66, 8.29, 7.91, 4.90, 4.52, 2.64, 2.45 Hz), 5.09 (dd, 1H, J=12.06, 7.91 Hz), 7.38 (d, 1H, J=1.88 Hz), 7.71 (t, 1H, J=2.45 Hz), 7.82 (t, 1H, J=4.71 Hz), 7.96 (d, 1H, J=8.48 Hz), 8.16 (d, 1H, J=8.67 Hz), 8.64 (s, 1H), 9.26 (d, 1H, J=7.54 Hz), 9.54 (s, 1H). LCMS 385 (M+H).

Example 44:



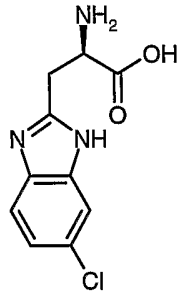
To a solution of **37** (32.6 mg, 0.07 mmol) in methanol (0.5 mL), 5% NaOH (0.2mL, 0.32 mmol) was added. The reaction mixture was stirred for two and half hours at room temperature then neutralized with 5.5N HCl until pH~7. The solvents were removed *in vacuo*. The residue was dissolved in methanol, and the product was purified by prep-HPLC with 0.1% AcOH as buffer in water and acetonitrile to give 10.7 mg (35%) of solid **44**. ^{1}H NMR (DMSO-d_6): δ 0.92 (t, 6H, J=6.88 Hz), 3.17 (d, 6H, J=6.59 Hz), 4.81 (d, 1H, J=6.22 Hz), 6.41 (s, 1H), 6.59 (dd, 1H, J=6.03, 2.07 Hz), 6.84 (d, 1H, J=7.54 Hz), 7.15 (d, 1H, J-12.81 Hz), 7.32 (d, 1H, J=3.96 Hz), 7.49 (d, 1H, J=8.48 Hz), 8.43 (s, 1H), 9.08 (d, 1H, J=7.16 Hz). LCMS 467 (M+H).

Example 45:



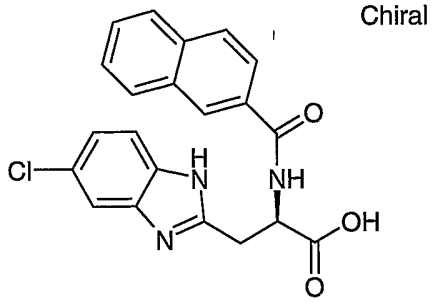
To a solution of the acid (0.25 g, 0.6642 mmol) in THF (8.7 mL) and DMF (0.7 mL) was added CDI (0.2154 g, 1.3284 mmol) and the resulting mixture was heated at 80 °C for 1 hour. The mixture was cooled to ambient temperature and hydroxylamine hydrochloride (0.1385 g, 1.9926 mmol) was added. The reaction mixture was then heated at 80 °C for a further 4 hours and once again allowed to cool to ambient temperature. The mixture was then partitioned between ethyl acetate (25 mL) and 3M aq. hydrochloric acid (25 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were then dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product. This material was then purified by preparative HPLC to afford the pure title compound as a white crystalline solid (0.1121 g, 43%). ^{1}H NMR (d_6-DMSO): δ 8.29 (bs, 1H), 8.00 (d, J = 7.4 Hz, 1H), 7.86-7.78 (m, 4H), 7.56-7.49 (m, 2H), 7.47-7.39 (m, 1H), 7.19-7.16 (m, 1H), 6.95-6.89 (m, 1H), 5.25-5.19 (m, 1H), 5.11-5.02 (m, 1H), 3.58-3.54 (m, 1H); LCMS 393 (M+H).

Compound 46a:



To a 5.5 N HCl solution (54 mL) of 4-chloro-1,2-phenylene diamine (7.74 g, 54.3 mmol) was added H-D-Asp-OH (10.8 g, 81.4 mmol). The mixture was refluxed for 72h. It was filtered after cooling down to room temperature. The filtrate was adjusted to pH 7 with solid sodium carbonate. Solid was collected by filtration and recrystalized with 67% ethanol (50 mL) to give the title compound in 23% yield. ^{1}H NMR (DMSO-d_6): δ 7.81 (1H, d, J=1.8Hz), 7.75 (1H, d, J=8.6Hz), 7.40 (1H, dd, J=8.4, 2.1Hz), 4.05-3.90 (1H, m), 3.64 (1H, dd, J=16.4, 5.6Hz), 3.36 (1H, dd, J=15.9, 7.4Hz). LCMS (APCI): 240.0 (M+H$^+$).

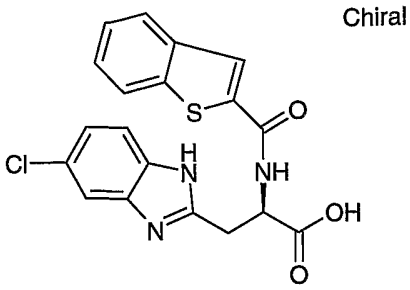
Example 46:



To an acetonitrile/water solution (4 mL/5 mL) of **46a** (210 mg, 0.877 mmol) was added 2-naphthoyl chloride (167 mg, 0.877 mmol) and sodium carbonate (325 mg, 3.07 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 12% yield. ^{1}H NMR

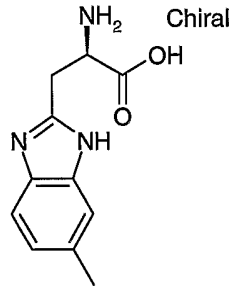
(DMSO-D6): δ 12.73 (1H, brs), 8.45 (1H, s), 8.07-7.96 (3H, m), 7.95-7.88 (1H, m), 7.67-7.48 (4H, m), 7.16 (1H, dd, J=8.48, 1.89 Hz), 5.12-5.03 (1H, m), 3.56-3.33 (2H, m). LCMS (APCI): 394.0 ($M+H^+$). Elemental Analysis for ($C_{21}H_{16}ClN_3O_3 \bullet 0.7H_2O$) calc: C 62.06, H 4.32, N 10.34; found: C 61.82, H 4.06, N 10.27.

Example 47:



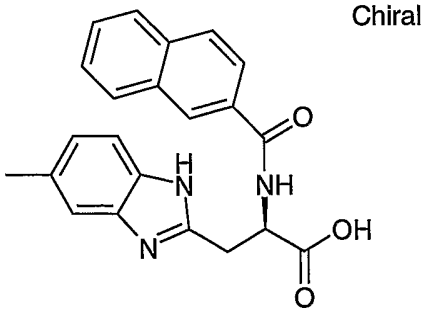
To an acetonitrile/water solution (3 mL/4 mL) of **46a** (170 mg, 0.710 mmol) wwas added benzo[B]thiophene-2-carbonyl chloride (140 mg, 0.710 mmol) and sodium carbonate (263 mg, 2.49 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 28% yield. ^{1}H NMR (DMSO-*d6*): δ 12.78 (1H, brs), 9.23 (1H, d, J=7.92 Hz), 8.13 (1H, s), 8.06-7.93 (2H, m), 7.59-7.41 (4H, m), 7.16 (1H, dd, J=8.47, 1.88 Hz), 5.06-4.97 (1H, m), 3.49 (1H, dd, J=15.45, 6.03 Hz), 3.36 (1H, dd, J=15.07, 8.10 Hz). LCMS (APCI): 400.0 ($M+H^+$). Elemental Analysis for ($C_{19}H_{14}ClN_3O_3S \bullet 0.3H_2O$) calc: C 56.31, H 3.63, N 10.37; found: C 56.35, H 3.66, N 10.34.

Compound 48a:



To a 5.5 N HCl solution (50 mL) of 3,4-diamino toluene (6.11 g, 50.0 mmol) was added H-D-Asp-OH (9.98 g, 75.0 mmol). The mixture was refluxed for overnight. It was filtered after cooling down to room temperature. The filtrate was adjusted to pH 1 with solid sodium carbonate. Solid was collected by filtration and recrystalized with 67% ethanol to give the title compound in 30% yield. ^{1}H NMR (DMSO-d_6): δ 10.0 (1H, br s), 7.62 (1H, d, J=8.3Hz), 7.52 (1H, s), 7.20 (1H, d, J=9Hz), 4.33 (1H, t, J=7Hz), 3.63 (1H, dd, J=16.2, 5.1Hz), 3.45 (1H, dd, J=16.2, 7.3Hz), 2.61 (3H, s). LCMS (APCI): 220.0 ($M+H^+$).

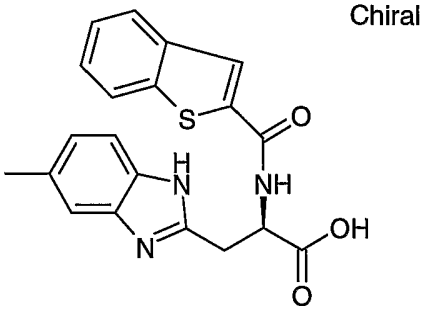
Example 49:



To an acetonitrile/water solution (5 mL/6 mL) of **48a** (247 mg, 1.13 mmol) was added 2-naphthoyl chloride (215 mg, 1.13 mmol) and sodium carbonate (419 mg, 3.96 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration

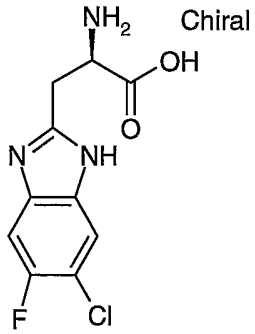
and washed with water (2X) and ethyl acetate (2X) to give the title compound in 7% yield. ^{1}H NMR (DMSO-d6): δ 9.10 (1H, d, J = 7.8 Hz), 8.43 (1H, s), 8.03-7.96 (3H, m), 7.91-7.89 (1H, m), 7.63-7.57 (2H, m), 7.36 (1H, d, J = 8.1 Hz), 5.06-5.00 (1H, m), 3.45 (1H, dd, J = 15.2, 6.1 Hz), 3.32 (1H, dd, J = 15.7, 8.0 Hz), 2.36 (3H, s). LCMS (APCI): 374.1 ($M+H^+$). Elemental Analysis for ($C_{22}H_{19}N_3O_3$0.7HCl) calc: C 66.23, H 4.98, N 10.53; found: C 66.24, H 4.92, N 10.57.

Example 50:



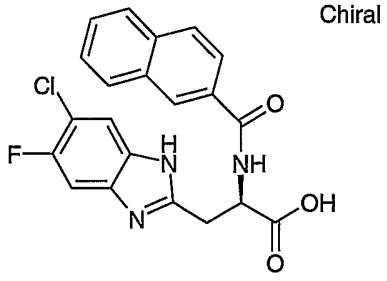
To an acetonitrile/water solution (5 mL/6 mL) of **48a** (207 mg, 0.945 mmol) was added benzo[B]thiophene-2-carbonyl chloride (186 mg, 0.945 mmol) and sodium carbonate (351 mg, 3.31 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 19% yield. ^{1}H NMR (DMSO-d6): δ 9.21 (1H, d, J = 7.8 Hz), 8.11 (1H, s), 8.02-8.00 (1H, m), 7.96-7.94 (1H, m), 7.47-7.40 (2H, m), 7.35 (1H, d, J = 8.1 Hz), 7.26 (1H, s), 6.92-6.94 (1H, m), 4.99-4.95 (1H, m), 3.43 (1H, dd, J = 15.4, 6.1 Hz), 3.31 (1H, dd, J = 15.4, 8.1 Hz), 2.36 (3H, s). LCMS (APCI): 380.0 ($M+H^+$). Elemental Analysis for ($C_{20}H_{17}N_3O_3S$•0.6HCl) calc: C 59.86, H 4.42, 10.47; found: C 60.03, H 4.21, N 10.60.

Compound 51a:



To a 5.5 N HCl solution (30.7 mL) of 4-chloro-1,2-diamino-5-fluoro-benzene (4.93 g, 30.7 mmol) was added H-D-Asp-OH (6.12 g, 46.0 mmol). The mixture was refluxed for overnight. It was filtered after cooling down to room temperature. The filtrate was purified by prep. HPLC to give the title compound. ^{1}H NMR (DMSO-d_6): δ 7.60 (1H, d, J=6.6Hz), 7.42 (1H, d, J=9.4Hz), 3.73 (1H, dd, J=8.9, 4.8Hz), 3.42-3.30 (2H, m). LCMS (APCI): 258.0 ($M+H^+$).

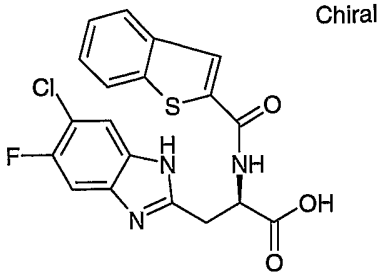
Example 51:



To an acetonitrile/water solution (6 mL/7 mL) of **51a** (460 mg, 1.79 mmol) was added 2-naphthoyl chloride (272 mg, 1.43 mmol) and sodium carbonate (378 mg, 3.57 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solids was collected by

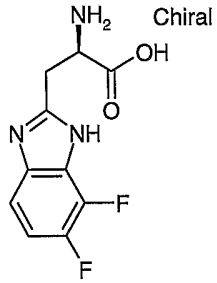
filtration and purified by prep. HPLC to give the title compound in 20% yield. ^{1}H NMR (DMSO-d6): δ 12.73 (1H, br), 9.08 (1H, d, J = 8.1 Hz), 8.42 (1H, s), 8.03-7.86 (4H, m), 7.71-7.53 (4H, m), 5.07-5.00 (1H, m), 3.53-3.33 (2H, m). LCMS (APCI): 412.0 ($M+H^+$). Elemental Analysis for ($C_{21}H_{15}ClFN_3O_3 \bullet 0.25H_2O$) calc: C 60.58, H 3.75, 10.09; found: C 60.60, H 3.81, N 10.12.

Example 52:



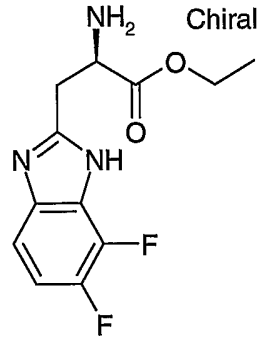
To an acetonitrile/water solution (10 mL/12 mL) of **51a** (785 mg, 3.05 mmol) was added benzo[B]thiophene-2-carbonyl chloride (480 mg, 2.44 mmol) and sodium carbonate (647 mg, 6.10 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solids was collected by filtration and purified by prep HPLC to give the title compound in 13% yield. ^{1}H NMR (DMSO): δ 9.24 (1H, d, J = 7.9 Hz), 8.10 (1H, s), 8.02-7.93 (2H, m), 7.80 (1H, d, J = 6.6 Hz), 7.65 (1H, d, J = 9.6 Hz), 7.48-7.40 (2H, m), 5.04-4.96 (1H, m), 3.56-3.49 (1H, m), 3.42-3.34 (1H, m). LCMS (APCI): 418.0 ($M+H^+$). Elemental Analysis for ($C_{19}H_{13}ClFN_3O_3S \bullet 0.3H_2O$) calc: C 53.92, H 3.24, 9.93; found: C 53.73, H 3.05, N 9.76.

Compound 53a:



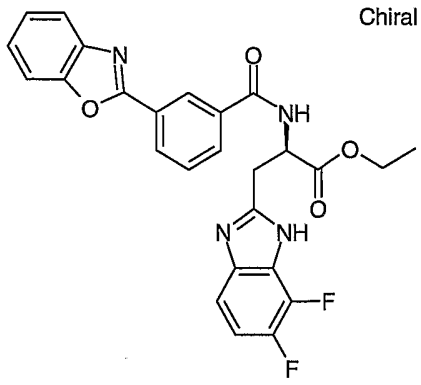
To a 5.5 N HCl solution (12.5 mL) of 1,2-diamino-3,4-difluoro-benzene (1.80 g, 12.5 mmol) was added H-D-Asp-OH (6.12 g, 46.0 mmol). The mixture was refluxed for overweekend. It was filtered after cooling down to room temperature. The filtrate was purified by prep. HPLC to give the title compound in 66% yield. LCMS (APCI): 242.1 ($M+H^+$).

Compound 53b:



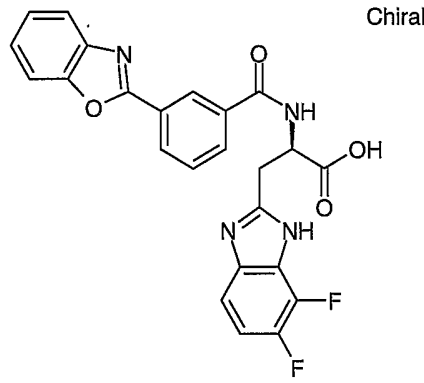
To an ethanol solution (20 mL) of **53a** (1.98 g, 8.22 mmol) was added thionyl chloride (2 mL) at 0°C. The mixture was stirred at 65°C for 2 hours. Excess reagents were evaporated. The residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with cold 1M sodium carbonate and brine. It was then dried over Na_2SO_4 and concentrated to give the title compound in 63% yield. ^{1}H NMR (DMSO-d_6): δ 8.81 (1H, br s), 7.38-7.15 (2H, m), 4.65 (1H, m), 4.20-4.00 (2H, m), 3.52-3.48 (2H, m), 1.05 (3H, t, J=7.1Hz). LCMS (API-ES): 270.2 ($M+H^+$).

Compound 53c:



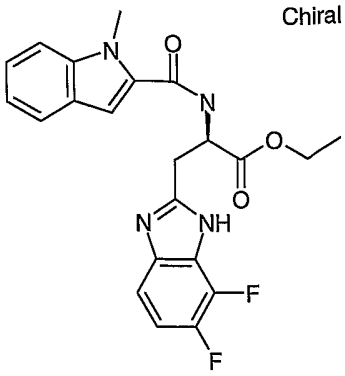
To a N, N-dimethyl-formamide solution (5 mL) of **53b** (149 mg, 0.625 mmol) were added added 3-benzooxazol-2-yl-benzoic acid (149 mg, 0.625 mmol), EDC (179 mg, 0.983 mmol), triethylamine (70 mg, 0.688 mmol) and 4-(dimethylamino)pyridine (11 mg, 0.0938 mmol). The mixture was stirred at room temperature for overnight. It was then purified by prep. HPLC. The fractions containing the product were combined and evaporated. The residue was dissolved in ethyl acetate (20 mL). The ethyl acetate solution was washed with 1M sodium carbonate (10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated to give the title compound in 12% yield. ^{1}H NMR (DMSO-d_6): δ 12.82 (1H, br s), 9.41 (1H, d, J=7.7Hz), 8.69 (1H, s), 8.38 (1H, d, J=7.7Hz), 8.09 (1H, d, J=8.1Hz), 7.9-7.8 (2H, m), 7.75 (1H, t, J=7.8Hz), 7.47 (2H, m), 7.32-7.25 (2H, m), 5.08 (1H, q, J=6.2Hz), 4.11 (2H, q, J=6.6Hz), 3.55-3.40 (2H, m), 1.09 (3H, d, J=7.0Hz).
LCMS (APCI): 491.1 ($M+H^+$).

Example 53:



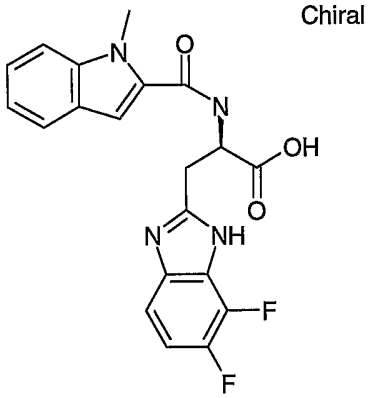
To a methanol solution (1 mL) of **53c** (33 mg, 0.0673 mmol) was added 5% sodium hydroxide (1 mL) at 0°C. The mixture was stirred at room temperature for 3 hours. It was then purified by prep. HPLC to give title compound in 68% yield. ^{1}H NMR (DMSO-d6): δ 12.88 (1H, br), 9.28 (1H, d, J = 7.9 Hz), 8.67 (1H, s), 8.35 (1H, d, J = 7.9 Hz), 8.06 (1H, d, J = 7.9 Hz), 7.85-7.80 (2H, m), 7.72 (1H, t, J = 7.8 Hz), 7.50-7.43 (2H, m), 7.30-7.26 (1H, m), 7.22-7.15 (1H, m), 5.09-5.02 (1H, m), 3.55-3.48 (1H, m), 3.38 (1H, dd, J = 15.1, 8.5 Hz). LCMS (APCI): 463.0 ($M+H^+$). Elemental Analysis for ($C_{24}H_{16}F_2N_4O_4$•0.35TFA) calc: C 59.06, H 3.28, N 11.15; found: C 59.22, H 3.47, N 11.02.

Compound 54a:



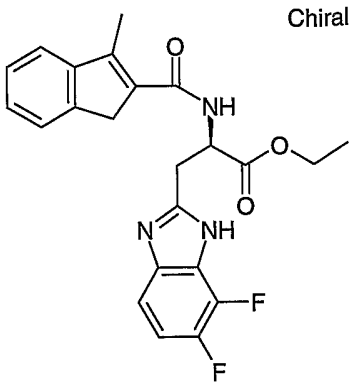
To a N, N-dimethyl-formamide solution (5 mL) of **52b** (198 mg, 0.736 mmol) was added 1-methylindole-2-carboxylic acid (129 mg, 0.736 mmol), EDC (210 mg, 1.10 mmol), triethylamine (82 mg, 0.810 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.110 mmol). The mixture was stirred at room temperature for overnight. It was then purified by prep. HPLC. The fractions containing the product were combined and evaporated. The residue was triturated with water (10 mL) and filtered to give the title compound in 32% yield. ^{1}H NMR (DMSO-d_6): δ 12.79 (1H, br s), 9.07 1H, d, J=7.3Hz), 7.66 (1H, d, J=7.9Hz), 7.40 (1H, d, J=8.7Hz), 7.30 (1H, td, J=6.9, 1.1Hz), 7.26-7.08 (3H, m), 5.04 (1H, q, J=8.3Hz), 4.10 (1H, q, J=7Hz), 3.51-3.35 (2H, m), 3.93 (3H, s), 1.09 (3H, t, J=7.2Hz). LCMS (APCI): 427.1 ($M+H^+$).

Example 54:



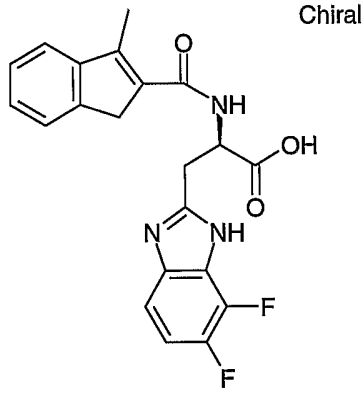
To a methanol solution (2 mL) of **54a** (64 mg, 0.150 mmol) was added 5% sodium hydroxide (2 mL) at 0°C. The mixture was stirred at room temperature for 2.5 hours. It was then purified by prep. HPLC to give title compound in 62% yield. ^{1}H NMR (DMSO-d6): δ 12.78 (1H, s), 8.92 (1H, d, J = 7.8 Hz), 7.62 (1H, d, J = 7.8 Hz), 7.50 (1H, d, J = 8.3 Hz), 7.28-7.24 (2H, m), 7.20-7.13 (1H, m), 7.10-7.07 (2H, m), 5.02-4.96 (1H, m), 3.91 (3H, s), 3.50-3.45 (1H, m), 3.36-3.33 (1H, m). LCMS (APCI): 399.1 ($M+H^+$). Elemental Analysis for ($C_{20}H_{16}F_2N_4O_3$•0.5TFA) calc: C 55.39, H 3.65, N 12.30; found: C 55.09, H 3.79, N 12.25.

Compound 55a:



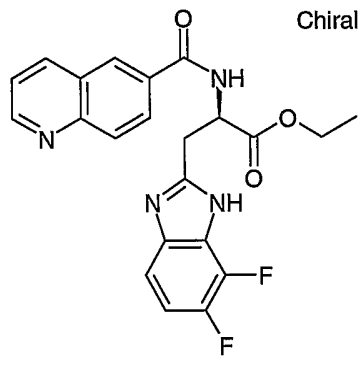
To a N, N-dimethyl-formamide solution (5 mL) of **52b** (211 mg, 0.784 mmol) was added 3-methylindene-2-carboxylic acid (124 mg, 0.713 mmol), EDC (205 mg, 1.07 mmol), triethylamine (90 mg, 0.891 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.107 mmol). The mixture was stirred at room temperature for overnight. It was then diluted with ethyl acetate (30 mL). The ethyl acetate solution was washed with water (2X20 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane), the title compound was obtained in 36% yield. ^{1}H NMR (DMSO-d_6): δ 8.40 and 7.87 (1H, m), 7.55-7.20 (6H, m), 5.46 and 5.34 (1H, m), 4.38-3.60 (7H, m), 2.54 and 2.50 (3H, s), 1.29 and 1.26 (3H, t). LCMS (API-ES): 426.0 ($M+H^+$).

Example 55:



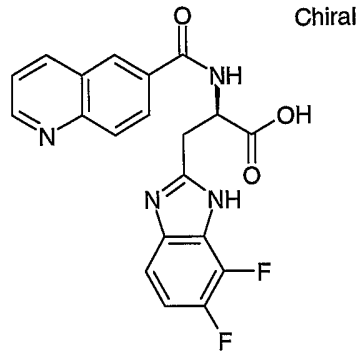
To a methanol solution (2 mL) of **55a** (106 mg, 0.249 mmol) was added 5% sodium hydroxide (2 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. It was then purified by prep. HPLC to give title compound in 56% yield. ^{1}H NMR (DMSO-d6): δ 12.76 (1H, br), 8.23 (1H, d, J = 8.1 Hz), 7.49-7.47 (2H, m), 7.36-7.26 (3H, m), 7.21-7.14 (1H, m), 4.94-4.89 (1H, m), 3.61 (2H, s), 3.44 (1H, dd, J = 15.2, 5.8 Hz), 3.30 (1H, dd, J = 15.2, 8.1 Hz), 2.35-2.34 (3H, m). LCMS (APCI): 398.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{17}F_2N_3O_3 \bullet 0.4H_2O$) calc: C 62.34, H 4.43, N 10.39; found: C 62.18, H 4.26, N 10.28.

Compound 56a:



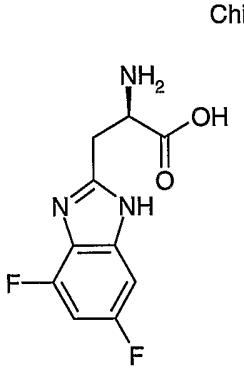
To a N, N-dimethyl-formamide solution (5 mL) of **52b** (243 mg, 0.903 mmol) were added quinoline-6-carboxylic acid (142 mg, 0.821 mmol), EDC (236 mg, 1.23 mmol), triethylamine (104 mg, 1.03 mmol) and 4-(dimethylamino)pyridine (15 mg, 0.123 mmol). The mixture was stirred at room temperature for overnight. It was then diluted with ethyl acetate (30 mL). The ethyl acetate solution was washed with 1M sodium carbonate (20 mL), water (10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. After column chromatography (100% ethyl acetate), the title compound was obtained in 31% yield. ^{1}H NMR (DMSO-d_6): δ 12.80 (1H, br s), 9.31 (1H, d, J=7.6Hz), 9.00 (1H, dd, J=4.3, 1.8Hz), 8.51 (1H, d, J=1.8Hz), 8.48 (1H, dd, J=8.3,1.2Hz), 8.15 (1H, dd, J=7, 1.8Hz), 7.63 (1H, dd, J=8.4, 4.3Hz), 7.26 (1H, br m), 7.22-7.10 (1H, m), 5.08 (1H, q, J=7.3Hz), 4.12-4.05 (2H, m), 3.52 (1H, dd, J=15.2, 6.9Hz), 3.41 (1H, dd, J=15.2, 1.9Hz), 1.07 (3H, t, J=7.1Hz). LCMS (API-ES): 425.1 ($M+H^+$).

Example 56:



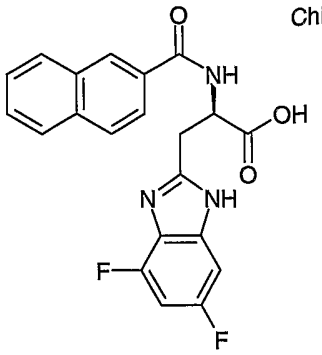
To a methanol solution (3 mL) of **56a** (105 mg, 0.248 mmol) was added 5% sodium hydroxide (3 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. It was then purified by prep. HPLC to give title compound in 62% yield. ^{1}H NMR (DMSO-d6): δ 9.27 (1H, d, J = 7.8 Hz), 9.07 (1H, dd, J = 4.3, 1.5 Hz), 8.63 (1H, d, J = 7.8 Hz), 8.56 (1H, d, J = 1.8 Hz), 8.20 (1H, dd, J = 8.8, 1.8 Hz), 8.12 (1H, d, J = 8.8 Hz), 7.72 (1H, dd, J = 8.3, 4.6 Hz), 7.35-7.32 (1H, m), 7.28-7.21 (1H, m), 5.10-5.05 (1H, m), 3.59-3.54 (1H, m), 3.42 (1H, dd, J = 15.2, 8.3 Hz). LCMS (API-ES): 397.1 ($M+H^+$). Elemental Analysis for ($C_{20}H_{14}F_2N_4O_3$•2.7TFA•0.7H_2O) calc: C 42.45, H 2.57, N 7.80; found: C 42.37, H 2.58, N 7.72.

Compound 57:



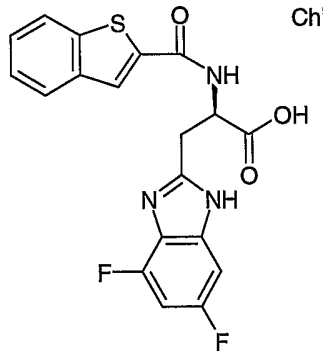
To a 5.5 N HCl solution (7.2 mL) of 1,2-diamino-3,5-difluorobenzene (1.04 g, 7.19 mmol) was added D-aspartic acid (1.44 g, 10.8 mmol). The mixture was refluxed for overnight. The reaction crude was purified by prep. HPLC to give the title compound as an acetic acid salt in 57% yield. ^{1}H NMR (DMSO-d_6): δ 7.22 (1H, dd, J=8.6, 2Hz), 7.02 (1H, td, J=10.6, 2Hz), 4.21 (1H, t, J=6.3Hz), 3.44 (1H, dd, J=16.2, 5.6Hz), 3.29 (1H, dd, J=16.4, 7Hz). LCMS (API-ES): 242.1 ($M+H^+$).

Example 58:



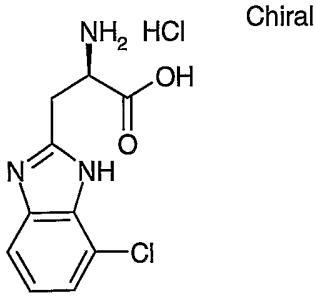
To an acetonitrile/water solution (3 mL/3 mL) of **57** (166 mg, 0.551 mmol) were added 2-naphthoyl chloride (131 mg, 0.689 mmol) and sodium carbonate (234 mg, 2.20 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X). Further purification by prep. HPLC gave the title compound in 11% yield. ^{1}H NMR (DMSO-d_6): δ 12.75 (1H, br s), 9.04 (1H, d, J=7.9Hz), 8.38 (1H, s), 7.98-7.85 (3H, m), 7.84 (1H, dd, J=8.61, 1.8Hz), 7.54 (2H, m), 7.13 (1H, dd, J=8.9, 1.8Hz), 6.93 (1H, td, J=11.1, 1.7Hz), 5.05-4.95 (1H, m), 3.44 (1H, dd, J=15.2, 6.1Hz), 3.31 (1H, dd, J=15.1, 8.3Hz). LCMS (APCI): 396.1 (M+H$^+$). Elemental Analysis for ($C_{21}H_{15}F_2N_3O_3$•0.4H_2O) calc: C 62.65, 3.96, N 10.44; found: C 62.95, H 3.97, N 10.21.

Example 59:



To an acetonitrile/water solution (3 mL/3 mL) of **57** (154 mg, 0.512 mmol) was added benzo[B]thiophene-2-carbonyl chloride (126 mg, 0.640 mmol) and sodium carbonate (217 mg, 2.05 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X). Further purification by prep. HPLC gave the title compound in 22% yield. ^{1}H NMR (DMSO-d_6): δ 12.99 (1H, br s), 9.25 (1H, d, J=7.8Hz), 8.20 (1H, s), 8.12-8.00 (2H, m), 7.52 (2H, m), 7.27 (1H, dd, J=8.8, 1.8Hz), 7.06 (1H, dd, J=10.4, 1.8Hz), 5.04 (1H, dd, J=14.2, 7.9Hz), 3.55 (1H, dd, J=15.2, 6.1Hz), 3.55-3.40 (1H, m). LCMS (APCI): 402.0 (M+H$^+$). Elemental Analysis for ($C_{19}H_{13}F_2N_3O_3S$•0.4H_2O) calc: C 55.85, 3.40, N 10.28; found: C 55.87, H 3.28, N 10.16.

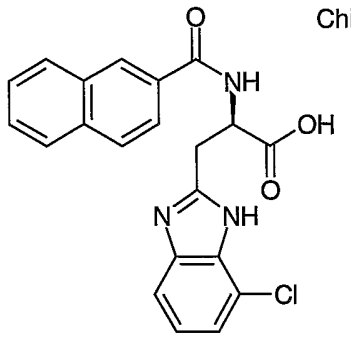
Compound 60a:



To a 5.5 N HCl solution (9 mL) of 1,2-diamino-3-chloro-benzene (1.3 g, 9.12 mmol) was added H-D-Asp-OH (3.6 g, 27.4 mmol). The mixture was refluxed for 72h. It was filtered after cooling down to

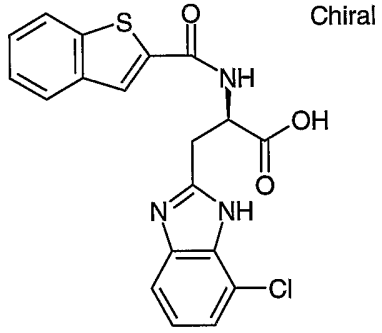
room temperature. The filtrate was purified by prep. HPLC to give the title compound in 41% yield (0.9g). ^{1}H NMR (DMSO-d6): δ 7.52 (1H, dd, J=8.1, 1Hz), 7.28 (1H, dd, J=7.8, 1Hz), 7.20 (1H, t, J=7.8Hz), 4.54 (1H, t, J=6.8Hz), 3.49 (1H, dd, J=16.4, 5.8Hz), 3.39 (1H, dd, J=16.2, 7.1Hz). LCMS (APCI): 240 ($M+H^+$).

Example 60:



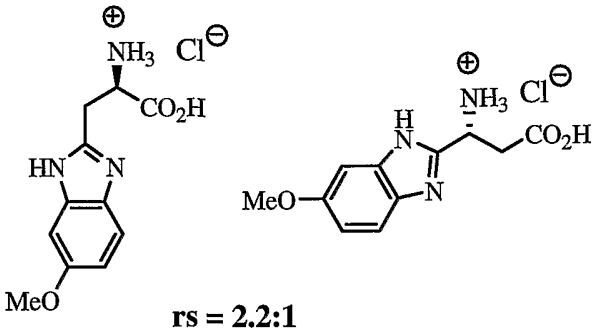
To an acetonitrile/water solution (3 mL/4 mL) of **60a** (216 mg, 0.611 mmol) was added 2-naphthoyl chloride (116 mg, 0.611 mmol) and sodium carbonate (227 mg, 2.14 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 60% yield. ^{1}H NMR (DMSO-d6): δ ?12.79 (1H, br), 9.19 (1H, d, J = 7.8 Hz), 8.44 (1H, s), 8.02-7.96 (3H, m), 7.92 (1H, dd, J = 8.7, 1.6 Hz), 7.64-7.57 (2H, m), 7.45 (1H, d, J = 7.8 Hz), 7.21-7.19 (1H, m), 7.13 (1H, t, J = 7.8 Hz), 5.09-5.04 (1H, m), 3.55-3.49 (1H, m), 3.40 (1H, dd, J = 15.2, 8.1 Hz).
LCMS (API-ES): 394.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{16}ClN_3O_3 \bullet 0.30H_2O$) calc: C 63.18, H 4.19, N 10.53; found: C 63.26, H 4.14, N 10.43.

Example 61:



To an acetonitrile/water solution (3 mL/4 mL) of **60a** (216 mg, 0.611 mmol) was added benzo[B]thiophene-2-carbonyl chloride (120 mg, 0.611 mmol) and sodium carbonate (227 mg, 2.14 mmol). The mixture was stirred at room temperature for overnight. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 55% yield. ^{1}H NMR (DMSO-d6): δ 12.80 (1H, br), 9.23 (1H, d, J = 7.8 Hz), 8.13 (1H, s), 8.02-8.00 (1H, m), 7.95-7.93 (1H, m), 7.48-7.41 (3H, m), 7.21-7.19 (1H, m), 7.12 (1H, t, J = 7.8 Hz), 5.04-4.98 (1H, m), 3.50 (1H, dd, J = 15.2, 6.1 Hz), 3.37 (1H, dd, J = 15.2, 8.3 Hz).
LCMS (API-ES): 400.0 ($M+H^+$). Elemental Analysis for ($C_{19}H_{14}ClN_3O_3S$) calc: C 57.07, H 3.53, 10.51; found: C 56.98, H 3.60, N 10.27.

Compounds 62a & 62b

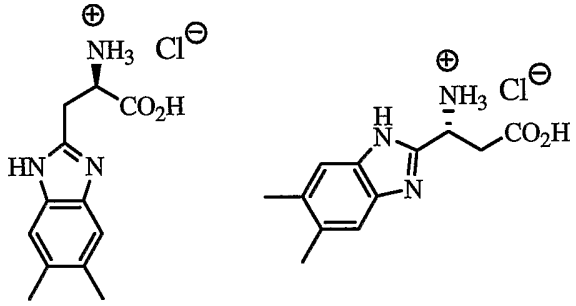


rs = 2.2:1

62a **62b**

A solution of 4-methoxy-*o*-phenylenediamine (5g, 36.1873 mmol), D-aspartic acid (3.211g, 24.1249 mmol), water (14.6 mL) and concentrated hydrochloric acid (10 mL) was refluxed for 3 days and then allowed to cool to ambient temperature. The mixture was evaporated to dryness and the regioisomers partially separated by preparative HPLC.
LCMS 236 (M+H).

Compounds 63a & 63b:

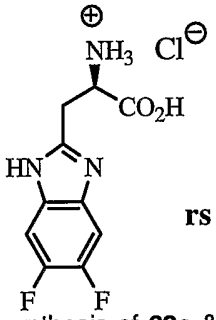


rs = 3.6:1

63a **63b**

Prepared as described in the synthesis of amino acids **62a** & **62b**. For synthesis of amino acids **63a** & **63b**, 4,5-dimethyl-1,2-phenylenediamine (5g, 36.7107 mmol), D-aspartic acid (3.2575g, 24.4738 mmol), water (14.8 mL) and concentrated hydrochloric acid (10.2 mL) were used. The mixture was evaporated to dryness and the regioisomers partially separated by preparative HPLC. LCMS 234 (M+H).

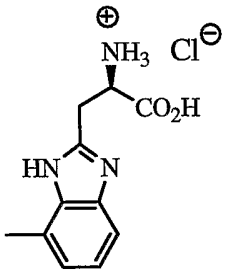
Compound 64a

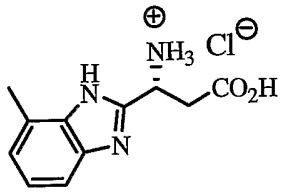


rs = 1:0

Prepared as described in the synthesis of **62a** & **62b**. For synthesis of **64a**, 4,5-difluoro-1,2-phenylenediamine (5g, 34.6933 mmol), D-aspartic acid (3.0785g, 23.1289 mmol), water (14 mL) and concentrated hydrochloric acid (9.6 mL) were used. The mixture was evaporated to dryness and the regioisomers partially separated by preparative HPLC. LCMS 242 (M+H).

Compounds 65a & 65b:



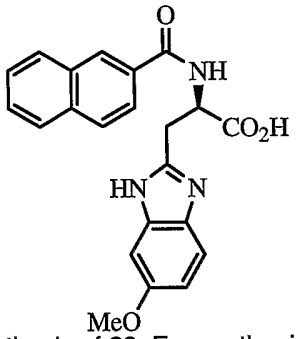


rs = 2.8:1

65a **65b**

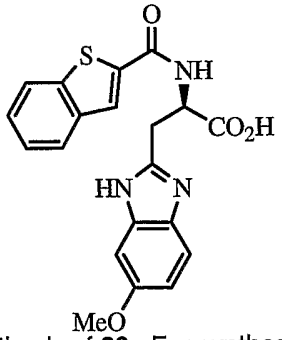
Prepared as described in the synthesis of **62a** & **62b**. For synthesis of **65a** & **65b**, 2,3-diaminotoluene (4.31g, 35.2787 mmol), D-aspartic acid (3.1304g, 23.5191 mmol), water (14.2 mL) and concentrated hydrochloric acid (9.8 mL) were used. The mixture was evaporated to dryness and the regioisomers partially separated by preparative HPLC. LCMS 220 (M+H).

Example 66:



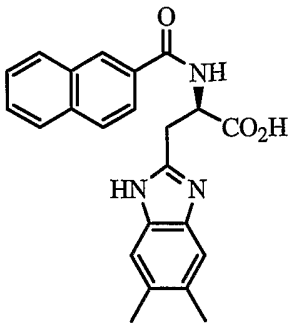
Prepared as described in the synthesis of **60**. For synthesis of **66**, **62a** (0.2g, 0.7360 mmol), 2-naphthoyl chloride (0.1754g, 0.9200 mmol), sodium bicarbonate (0.1855g, 2.208 mmol), water (3 mL), and acetonitrile (3 mL) were used. The crude material was purified by preparative HPLC to yield the pure title compound as a white crystalline solid (0.0602g, 21%). ^{1}H NMR (d_4-methanol): δ 8.26 (s, 1H), 7.87-7.83 (m, 3H), 7.73 (d, J = 8.7 Hz, 1H), 7.53-7.47 (m, 3H), 7.09-7.04 (m, 2H), 5.12-5.07 (m, 1H), 3.81-3.77 (m, 1H), 3.62-3.54 (m, 1H), 3.77 (s, 3H); LCMS 390 (M+H).

Example 67:



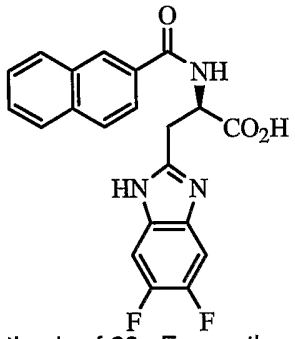
Prepared as described in the synthesis of **60**. For synthesis of **67**, **62a** (0.2g, 0.7360 mmol), benzo[B]thiophene-2-carbonyl chloride (0.1809g, 0.9200 mmol), sodium bicarbonate (0.1855g, 2.208 mmol), water (3 mL), and acetonitrile (3 mL) were used. The crude material was purified by preparative HPLC to yield the pure title compound as a white crystalline solid (0.1251g, 43%). ^{1}H NMR (d_4-methanol): δ 8.00 (s, 1H), 7.93-7.90 (m, 2H), 7.63 (d, J = 8.9 Hz, 1H), 7.50-7.42 (m, 2H), 7.21-7.17 (m, 2H), 5.17 (dd, J = 7.9, 3.4 Hz, 1H), 3.93-3.86 (m, 1H), 3.69 (dd, J = 15.2, 8.2 Hz, 1H), 3.33 (s, 3H); LCMS 396 (M+H).

Example 68:



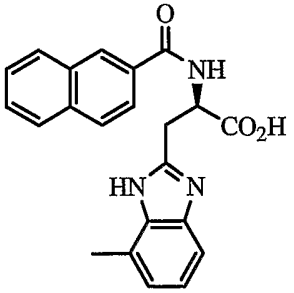
Prepared as described in the synthesis of **60**. For synthesis of **68**, **63a** (0.2g, 0.7414 mmol), 2-naphthoyl chloride (0.1767g, 0.9267 mmol), sodium bicarbonate (0.1869g, 2.242 mmol), water (3 mL), and acetonitrile (3 mL) were used. The crude material was purified by preparative HPLC to yield the pure title compound as a white crystalline solid (0.1838g, 64%). ^{1}H NMR (d_4-methanol): δ 8.36 (s, 1H), 7.98-7.92 (m, 3H), 7.83 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.65-7.56 (m, 2H), 7.50 (s, 2H), 5.22 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.92 (dd, *J* = 15.3, 6.2 Hz, 1H), 3.70 (dd, *J* = 15.1, 8.3 Hz, 1H), 2.44 (s, 6H); LCMS 388 (M+H).

Example 69:



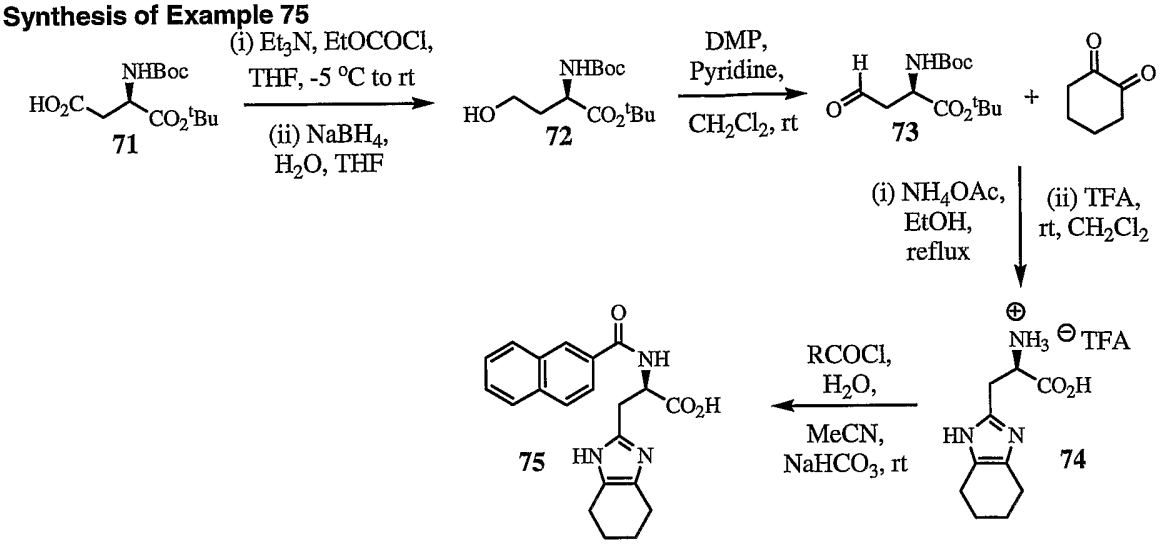
Prepared as described in the synthesis of **60**. For synthesis of **69**, **64a** (0.25g, 0.9003 mmol), 2-naphthoyl chloride (0.2145g, 1.1253 mmol), sodium bicarbonate (0.2269g, 2.7009 mmol), water (4 mL), and acetonitrile (4 mL) were used. The crude material was purified by preparative HPLC to yield the pure title compound as a white crystalline solid (0.2064g, 58%).
^{1}H NMR (d_4-methanol): δ 8.38 (s, 1H), 8.00-7.95 (m, 3H), 7.85 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.68-7.58 (m, 2H), 7.52 (s, 2H), 5.25 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.94 (dd, *J* = 15.2, 6.4 Hz, 1H), 3.73 (dd, *J* = 15.2, 8.0 Hz, 1H); LCMS 396 (M+H).

Example 70:

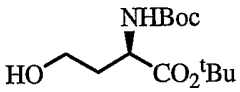


Prepared as described in the synthesis of **60**. For synthesis of **70**, **65a** (0.25g, 0.9775 mmol), 2-naphthoyl chloride (0.2329g, 1.2219 mmol), sodium bicarbonate (0.2464g, 2.9325 mmol), water (4 mL), and acetonitrile (4 mL) were used. The crude material was purified by preparative HPLC to yield the pure title compound as a white crystalline solid (0.1496g, 41%).
^{1}H NMR (d_4-methanol): δ 8.28 (s, 1H), 7.89-7.85 (m, 3H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.56-7.50 (m, 3H), 7.11-7.06 (m, 2H), 5.14-5.09 (m, 1H), 3.84-3.80 (m, 1H), 3.65-3.56 (m, 1H), 2.40 (s, 3H); LCMS 374 (M+H).

Synthesis of Example 75

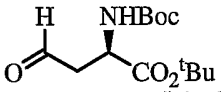


Example 72



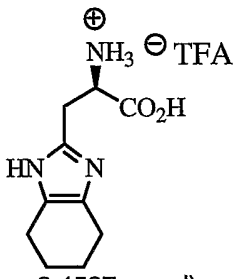
To a solution of the acid (5.0 g, 17.2813 mmol) and triethylamine (2.41 mL, 17.2813 mmol) in THF (17.3 mL), at –5 °C under an atmosphere of nitrogen, was added a solution of ethyl chloroformate (1.73 mL, 18.1454 mmol) in THF (17.3 mL) over a period of 10 minutes. The resulting suspension was stirred at ambient temperature for 30 mins and the resulting mixture filtered and washed with THF (15 mL). The filtrate was added dropwise over 30 minutes to an ice-cold solution of sodium borohydride (1.3620 g, 36.0027 mmol) in water (8.6 mL). The mixture was stirred at ambient temperature for 4 hours and then acidified to pH 2 with 1*N* aq. hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were then washed with 1M aq. sodium bicarbonate (2 x 50 mL), brine (50 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product as a colorless oil (4.5079 g, 95%), which was used without any subsequent purification. LCMS 276 (M+H).

Example 73



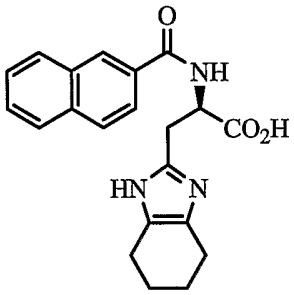
To a solution of the alcohol **72** (4.5079 g, 16.3715 mmol) in CH_2Cl_2 (185 mL), was added pyridine (3.99 mL, 49.1145 mmol) and DMP (10.4160 g, 24.5573 mmol). The resulting solution was allowed to stir at ambient temperature for 2 hours and then diluted with diethyl ether (100 mL). The volatiles were then partially removed on the rotary evaporator and the residue taken up in diethyl ether (100 mL). This was then washed with 1:1 10% aq. sodium thiosulfate:satd. aq. sodium bicarbonate (100 mL), followed by water (50 mL), and satd. aq. sodium chloride (50 mL). The aqueous washings were then back-extracted with diethyl ether (2 x 50 mL) and the combined organic extracts dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product (4.1119 g, 92%) as a white crystalline solid that was used immediately. LCMS 274 (M+H).

Example 74



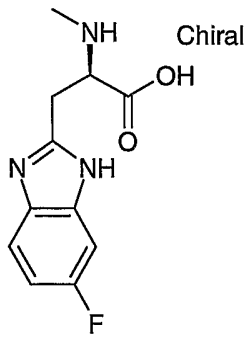
To a solution of the aldehyde **73** (0.9444 g, 3.4537 mmol) and 1,2-cyclohexanedione (0.3873 g, 3.457 mmol) in ethyl alcohol (35 mL) was added ammonium acetate (1.5973 g, 20.7222 mmol). The resulting solution was refluxed for 2 hours and then allowed to cool to ambient temperature. The reaction mixture was added to ethyl acetate (50 mL) and washed with satd. aq. sodium chloride (50 mL). The aqueous layer was then extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product (0.9057 g, 72%) as a yellow waxy solid. LCMS 366 (M+H).
A solution of the crude ester (0.9057 g, 2.4782 mmol) in CH_2Cl_2 (11.2 mL) was treated with trifluoroacetic acid (5.7 mL) dropwise. The resulting mixture was allowed to stir at ambient temperature for 16 hours and was then evaporated to dryness. The crude product was isolated as a brown crystalline solid (0.8001 g, 100%) and was used without further purification. LCMS 210 (M+H).

Example 75:



A solution of the amino acid **74** (0.8001g, 2.4748 mmol), 2-naphthoyl chloride (0.7077g, 3.7122 mmol), sodium bicarbonate (1.0395g, 12.3740 mmol), water (10.5 mL), and acetonitrile (10.5 mL) was stirred at ambient temperature for 3 hrs. The solution was washed with ethyl acetate (100 mL), which was discarded, and then acidified with 1M aq. hydrochloric acid and further extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were then dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product. The crude material was then purified by preparative HPLC to yield the pure title compound as a cream colored solid (0.1570g, 18%). ^{1}H NMR (d_6-DMSO): δ 8.26 (s, 1H), 7.87-7.83 (m, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.54-7.48 (m, 2H), 7.09-7.04 (m, 2H), 5.12-5.07 (m, 1H), 3.82-3.78 (m, 1H), 3.63-3.54 (m, 1H), 1.87 (d, J = 12.6 Hz, 2H), 1.55-1.48 (m, 3H), 1.31-1.13 (m, 3H); LCMS 364 (M+H).

Compound 76a:

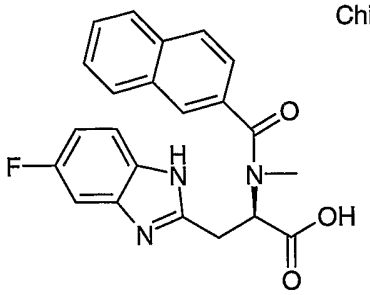


To a 5.5 N HCl solution (11 mL) of 4-fluoro-1,2-phenylene diamine (1.32 g, 10.9 mmol) was added N-methyl-D-aspartic acid (2.00 g, 13.6 mmol). The mixture was refluxed for overnight. It was filtered after cooling down to room temperature. The filtrate was washed with ethyl acetate (10 mL) and

concentrated to give the title compound. ^{1}H NMR (CD_3OD): δ 7.88 (1H, dd, J=9.1, 4.3Hz), 7.65 (1H, dd, J=8.1, 2.5Hz), 7.47 (1H, td, J=9.4, 4.3Hz), 4.74 (1H, dd, J=10.5, 4.5Hz), 4.09 (1H, dd, J=15.3, 4.4Hz), 3.81 (1H, dd, J=15.2, 10.5Hz), 2.98 (3H, s). LCMS (APCI): 238.1 ($M+H^+$).

Example 76:

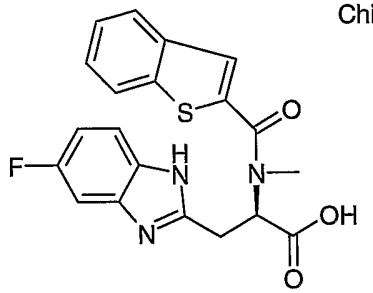
Chiral



To an acetonitrile/water solution (4 mL/5 mL) of **76a** (277 mg, 1.01 mmol) were added 2-naphthoyl chloride (193 mg, 1.01 mmol) and sodium carbonate (375 mg, 3.54 mmol). The mixture was stirred at room temperature for overweekend. It was then acidified with 1M HCl and diluted with ethyl acetate. The water phase was purified by prep. HPLC to give the title compound in 4% yield. ^{1}H NMR (CD_3OD): δ 7.84-7.77 (3H, m), 7.70-7.66 (2H, m), 7.50-7.40 (3H, m), 7.28-7.24 (2H, m), 5.18-5.14 (1H, m), 3.91-3.86 (1H, m), 3.68-3.62 (1H, m), 3.04 (3H, s).
LCMS (APCI): 392.1 ($M+H^+$). HRMS (MALDI) calc for $C_{22}H_{19}N_3O_3F$ ($M+H^+$) 392.1410; found 392.1402.

Example 77:

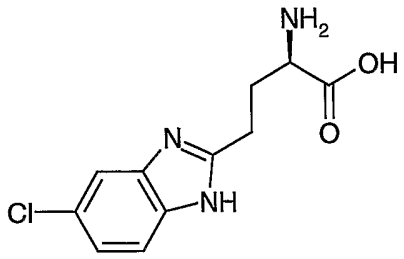
Chiral



To an acetonitrile/water solution (4 mL/5 mL) of **76a** (288 mg, 1.05 mmol) were added benzo(b)thiophene-2-carbonyl (207 mg, 1.05 mmol) and sodium carbonate (390 mg, 3.68 mmol). The mixture was stirred at room temperature for overweekend. It was then acidified with 1M HCl and diluted with ethyl acetate. The water phase was purified by prep. HPLC to give the title compound in 4% yield. ^{1}H NMR (CD_3OD): δ 7.81-7.76 (2H, m), 7.63-7.58 (2H, m), 7.38-7.32 (3H, m), 7.24-7.18 (1H, m), 5.15-5.12 (1H, m), 3.85-3.78 (1H, m), 3.63-3.56 (1H, m), 3.33 (3H, s).
LCMS (APCI): 398.0 ($M+H^+$). HRMS (MALDI) calc for $C_{20}H_{17}N_3O_3FS$ ($M+H^+$) 398.0975; found 398.0962.

Compound 78a:

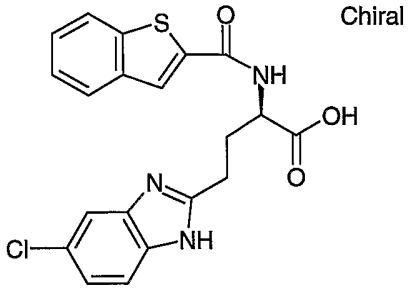
Chiral



To a 5.5 N HCl solution (41.1 mL) of 4-chloro-1,2-phenylene diamine (5.86 g, 41.1 mmol) was added D-glutamic acid (9.07 g, 61.6 mmol). The mixture was refluxed for 72h. A small portion of the reaction mixture was purified by prep. HPLC to give the title compound. ^{1}H NMR (DMSO-d_6): δ 7.76

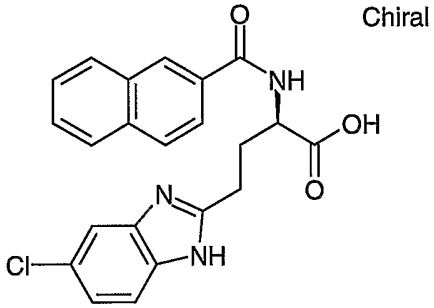
(1H, J=1.8Hz), 7.68 (1H, d, J=8.7Hz), 7.38 (1H, dd, J=1.9Hz), 4.13 (1H, t, J=6.4Hz), 3.25-3.13 (2H, m), 2.42-2.30 (2H, m). LCMS (APCI): 254.0 ($M+H^+$).

Example 78:



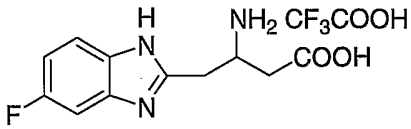
To an acetonitrile/water solution (3 mL/4 mL) of **78a** (145 mg, 0.572 mmol) was added benzo[B]thiophene-2-carbonyl chloride (113 mg, 0.572 mmol) and sodium carbonate (212 mg, 2.00 mmol). The mixture was stirred at room temperature for overweekend. It was then acidified with 1M HCl. Solid was collected by filtration and washed with water (2X) and ethyl acetate (2X) to give the title compound in 30% yield. ^1H NMR (CD_3OD): δ 7.80-7.72 (3H, m), 7.38-7.27 (4H, m), 7.04 (1H, dd, J = 8.7, 2.1 Hz), 4.56 (1H, dd, J = 9.2, 4.7 Hz), 3.00 (2H, t, J = 7.5 Hz), 2.55-2.44 (1H, m), 2.35-2.22 (1H, m). LCMS (APCI): 414.0 ($M+H^+$). Elemental Analysis for ($C_{20}H_{16}ClN_3O_3S•1H_2O$) calc: C 55.62, H 4.20, 9.73; found: C 55.48, H 4.21, N 9.60.

Example 79:



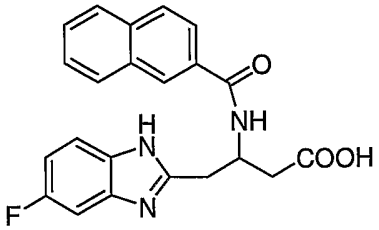
To an acetonitrile/water solution (3 mL/4 mL) of **78a** (173 mg, 0.682 mmol) was added 2-naphthoyl chloride (130 mg, 0.682 mmol) and sodium carbonate (253 mg, 2.39 mmol). The mixture was stirred at room temperature for overweekend. It was then diluted with ethyl acetate and acidified with 1M HCl. Solid was collected by filtration and purified by prep. HPLC to give the title compound in 14% yield. ^1H NMR (DMSO-*d6*): δ 9.01 (1H, d, J = 7.6 Hz), 8.44 (1H, s), 8.00-7.92 (4H, m), 7.66-7.57 (4H, m), 7.27 (1H, dd, J = 8.5, 1.6 Hz), 4.58-4.53 (1H, m), 3.13-3.09 (2H, m), 2.53-2.49 (1H, m), 2.39-2.32 (1H, m). LCMS (APCI): 408.1 ($M+H^+$). HRMS (MALDI) calc for $C_{22}H_{19}N_3O_3Cl$ ($M+H^+$) 408.1115; found 408.1087.

Compound 80a:



To an aqueous HCl solution (5.5 N, 5mL) was added 4-Fluorobenzene-1,2-diamine hydrochloride (0.572g, 4.53mmol) and 3-Aminopentanoic acid (1g, 6.8mmol). The mixture was heated at reflux for 20h. After being cooled down to 25°C, the mixture was purified by preparative HPLC to afford 0.8g of the title compound (50% yield). LCMS (APCI positive): 238 ($M+H^+$).

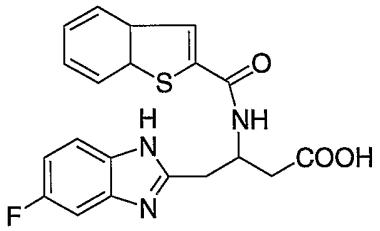
Example 80:



80

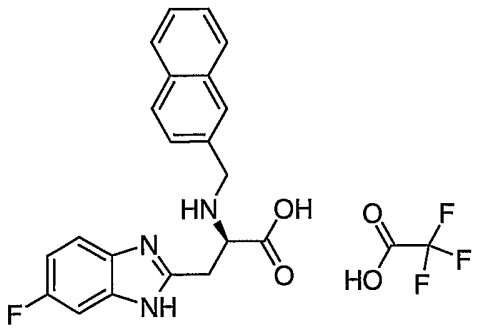
To a sodium carbonate solution (1M, 1.5mL) was added the amino acid **80a** (112mg, 0.319mmol), 2-Naphthoyl chloride (90mg, 0.473mmol) and acetonitrile (1.5mL). The mixture was stirred at 25°C for 15h. Preparative HPLC purification provided 30mg of the title product (24% yield). ^{1}H NMR (DMSO-d_6): δ 12.5 (1H, br s), 8.89 (1H, d, J=8.1Hz), 8.10 (1H, s), 8.09-8.06 (1H, m), 8.04-8.0 (1H, m), 7.77 (1H, dd, J=8.3, 4.3Hz), 7.65 (1H, d, J=7.3Hz), 7.5 (2H, m), 7.34 (1H, t, J=9Hz), 4.85 (1H, m), 3.48-3.3 (2H, m), 2.82 (2H, m). LCMS (APCI positive): 392 ($M+H^+$); Elemental Analysis for ($C_{22}H_{18}N_3O_3F \bullet 1.26CF_3COOH \bullet 0.28H_2O$) calc: C 54.52, H 3.70, N 7.78; found: C 54.58, H 3.73, N 7.70.

Example 81



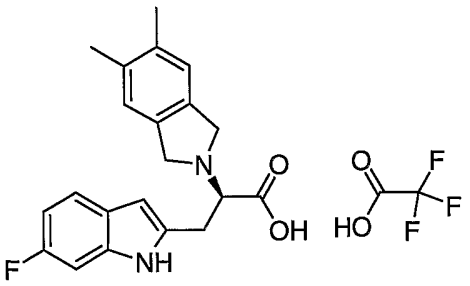
To a sodium carbonate solution (1M, 1.5mL) was added the amino acid **80a** (112mg, 0.319mmol), 1-Benzothiophene-2-carbonyl chloride (93mg, 0.48mmol) and acetonitrile (1.5mL). The mixture was stirred at 25°C for 15h. Preparative HPLC purification provided 35mg of the title product (27% yield). ^{1}H NMR (DMSO-d_6): δ 8.58 (1H, d, J=8.1Hz), 8.21 (1H, s), 7.9-7.83 (3H, m), 7.68 (1H, dd, J=8.6, 1.5Hz), 7.59 (1H, dd, J=8.8, 4.3Hz), 7.48 (2H, m), 7.16 (1H, t, J=9Hz), 4.75 (1H, m), 3.3-3.1 (2H, m), 2.65 (2H, d, J=7.0Hz). LCMS (APCI positive): 398 ($M+H^+$); Elemental Analysis for ($C_{20}H_{16}N_3O_3FS \bullet 1.18CF_3COOH \bullet 0.3H_2O$) calc: C 49.97, H 3.34, N 7.82; found: C 50.00, H 3.39, N 7.78.

Example 82



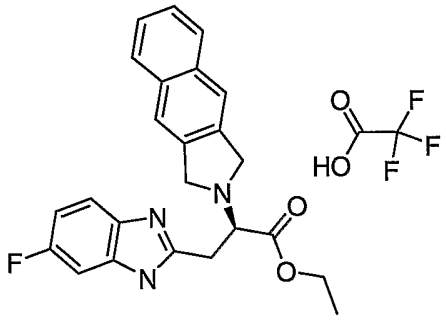
N,O-bis(trimethylsilyl)acetamide (0.135 g; 0.66 mmole) was added to a solution of 3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine **18a** (0.074 g; 0.33 mmole) in DMA (1.0 mL). The mixture was allowed to stir at RT for 6h. 2-(bromomethyl)naphthalene (0.074 g; 0.33 mmole) and *N,N*-diisopropylethylamine (0.216 g; 1.7 mmole) were added. The reaction was stirred at room temperature for 3h and then heated at 60 °C overnight. Water was added, and the solvents were removed. The residues were purified by HPLC to afford a solid. ^{1}H NMR (DMSO-d_6): □ 2.75-3.75 region obscured by water peak, 4.43 (m, overlap, 3H), 6.53 (br s, 1H), 7.05 (m, 1H), 7.36 (dd, J = 10 Hz, 3 Hz, 1H), 7.52-7.57 (m, overlap, 3H), 7.61 (d, J = 8 Hz, 1H), 7.89-7.98 (m, overlap, 4H) LC/MS: 364 (M + H).

Example 83



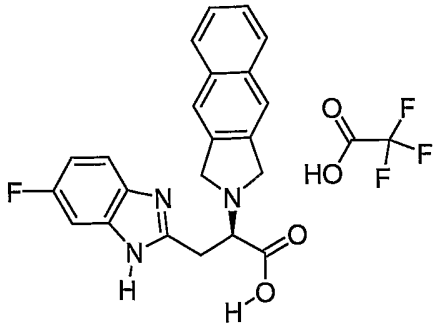
Ethyl 3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine (0.04 g; 0.16 mmole) was dissolved in THF, and 1,2-di(chloromethyl)-4,5-dimethylbenzene (0.033 g; 0.16 mmole) and sodium carbonate (0.034 g; 0.32 mmole) were added. The reaction was allowed to stir at 60 °C overnight. After the solvent was removed, DMSO and TFA were added (8 mL volume), and the precipitate was collected. The precipitate was dissolved in DMSO (3 mL) and LiOH (60 mg; 2.5 mmole) was added. After stirring, the precipitate was collected, and purification by HPLC provided a white solid. LC/MS: 353 (M + H).

Example 84



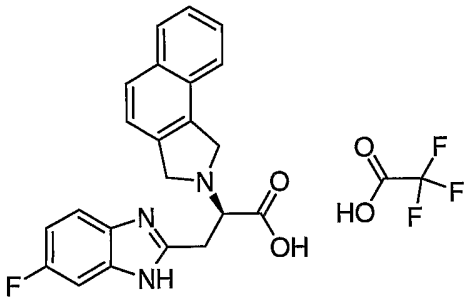
To a solution of ethyl 3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine **18b** (0.125 g; 0.5 mmole) dissolved in THF (4 mL) was added 2,3-*bis*(bromomethyl)naphthalene (0.157 g; 0.5 mmole) in THF (2 mL). Sodium carbonate (0.105 mg; 1.0 mmole) was added, and the reaction was allowed to stir at 60 °C overnight. Water (10 mL) was added, and the residue was triturated. Acetonitrile was added, and the solvents were removed. HCl (1.0 N ; 4 mL) was added, and the aqueous layer was extracted with EtOAc. The aqueous layer was collected and lyophilized to afford the crude as the hydrochloride salt (0.172 g; 79%). Purification by HPLC provided a white solid as a TFA salt (0.079 g; 31%). ^{1}H NMR (DMSO-d_6): □ 1.10 (t, J = 7.1 Hz, 3H), 3.62 (d, J = 7.5 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.39 (d, J = 13.2 Hz, 2H), 4.51 (d, J = 13.2 Hz, 2H), 4.55 (t, J = 7.5 Hz, 1H), 7.25 (dt, J= 9.1, 2.4, 1H), 7.46 (dd, J = 6.2, 3.2 Hz, 2H), 7.56 (dd, J = 9.0 Hz, 2.4 Hz, 1H), 7.71 (dd, J = 9.1, 4.6, 1H), 7.78, (s, 2H), 7.87 (dd, J = 6.2, 3.3, 2H). Anal. Calcd. For $C_{26}H_{23}F_4N_3O_5 \cdot H_2O$: C, 58.31; H, 4.67; N, 7.85. Found: C, 58.30; H, 4.34; N, 7.69. LC/MS: 404 (M + H).

Example 85



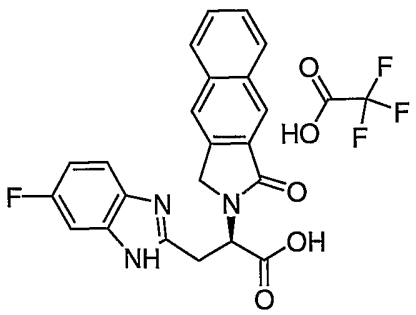
2-(1,3-Dihydro-benzo[f]isoindol-2-yl)-3-(6-fluoro-1H-benzoimidazol-2-yl)-propionic acid ethyl ester; compound with trifluoro-acetic acid (0.05 ; 0.097 mmole) was dissolved in DMF (1 mL), and aqueous LiOH (4 M, 0.25 mL, 1.0 mmole) was added. After stirring, aqueous HCl (4 M, 0.25 mL; 1.0 mmole) was added, and the precipitate was collected. Purification by HPLC provided a white solid. ^{1}H NMR (DMSO-d_6): □ 3.53 (m, overlap with water peak), 4.50 (d, J = 12 Hz, overlap with m, combined 3H), 4.60 (d, J = 12 Hz, 2H), 7.15 (m, 1H), 7.47 (m, overlap, 3H), 7.61 (dd, J = 8 Hz, 4 Hz, 1H), 7.79 (s, 2H), 7.86 (m, 2H). Anal. Calcd. For $C_{24}H_{19}F_4N_3O_4 \cdot 1.5H_2O$: C, 55.81; H, 4.26; N, 8.14. Found: C, 55.76; H, 4.19; N, 8.14. LC/MS: 376 (M + H).

Example 86:



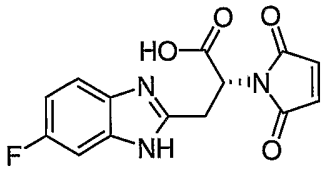
Ethyl 3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine hydrochloride **18b** (0.0861 g; 0.3 mmole) was dissolved in THF (1 mL), and 1,2-bis(bromomethyl)naphthalene (0.0942 g; 0.3 mmole) and sodium carbonate (0.100 mg; 0.95 mmole) were added. The reaction was allowed to stir at 60 °C overnight. After the solvent was removed, the residue was dissolved in DMF (1 mL), and LiOH (0.030g, 1.25 mmole) was added. Purification by HPLC provided a solid. Anal. Calcd. For $C_{22}H_{18}FN_3O_2 \cdot 1.2CF_3CO_2H \cdot 1.5H_2O$: C, 55.26; H, 4.00; N, 7.92. Found: C, 55.16; H, 3.88; N, 7.69. LC/MS: 376 (M + H).

Example 87:



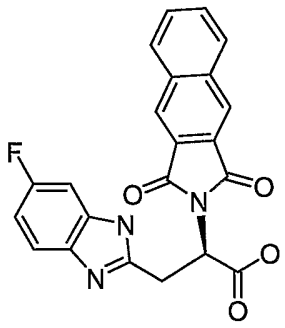
2-(1,3-Dioxo-1,3-dihydro-benzo[f]isoindol-2-yl)-3-(6-fluoro-1H-benzoimidazol-2-yl)-propionic acid (0.025 g; 0.06 mmole) was dissolved in AcOH (2 mL), and zinc dust (0.06 g; 0.923 mmole) was added. The mixture was heated to 85 °C. The solvent was removed by evaporation. DMSO (4 mL) was added, and the solution was filtered. The reaction mixture was lyophilized to afford the desired product, and the product was purified by HPLC. ^{1}H NMR (DMSO-d_6): □ 3.54 (dd, J = 14 Hz, J = 10 Hz, 1H), 3.66 (dd, J = 14 Hz, 6 Hz, 1H), 4.66 (d, J = 18 Hz, 1H), 4.84 (d, J = 18 Hz, 1H), 5.43 (dd, J = 10 Hz, 6 Hz, 1H), 6.95 (m, 1H), 7.27 (d, J = 8 Hz, 1H), 7.45 (dd, J = 10 Hz, 6 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.62 (t, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 8.10 (s, d overlap, 2H), 8.27 (s, 1H). Anal. Calcd. For $C_{24}H_{17}F_4N_3O_5 \cdot 0.5H_2O$: C, 56.21; H, 3.44; N, 8.20. Found: C, 56.72; H, 3.37; N, 8.25. LC/MS: 390 (M + H).

Example 88:



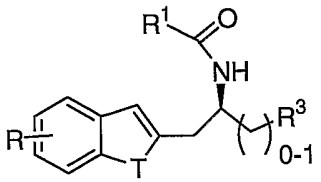
N,O-bis(trimethylsilyl)acetamide (0.223 g; 1.0 mmole) was added to a solution of amino acid **18a** (0.112 g; 0.5 mmole) in NMP (1.0 mL), and the mixture was allowed to stir at room temperature overnight. Maleic anhydride (0.05 g; 0.51 mmole) was added, and the reaction was allowed to stir at room temperature. An aqueous HCl solution (5.0 equiv) was added, and the mixture was allowed to stir. The solvents were removed to afford a white solid (0.15 g; 98 %). LC/MS: 304 (M + H).

Example 89:



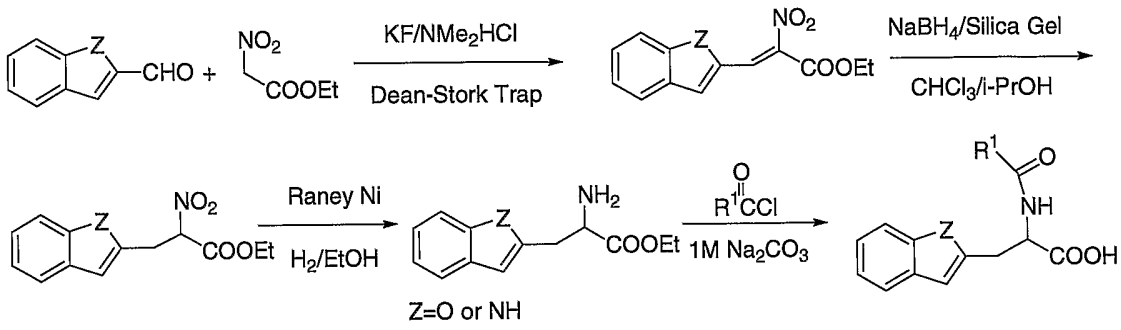
2-Amino-3-(6-fluoro-1H-benzoimidazol-2-yl)-propionic acid 18a (0.263 g; 0.93 mmole) was dissolved in water (10 mL), and sodium carbonate (0.17 g; 1.60 mmole) and 1,3-dioxo-1,3-dihydro-benzo[f]isoindole-2-carboxylic acid ethyl ester (0.275 g; 1.02 mmole; prepared from the reaction of 2,3-naphthalenedicarboximide with ethyl chloroformate) were added. The reaction was briefly heated with a heat gun and then allowed to stir at room temperature overnight. The precipitate was removed by filtration, and the filtrate was made acidic by the addition of aqueous HCl (4 N; 0.6 mL). The precipitate was collected, washed with water, and lyophilized to afford the product (0.306 g; 75%; based on HCl salt). Anal. Calcd. For $C_{22}H_{14}FN_3O_4 \cdot 0.5H_2O$: C, 64.03; H, 3.64; N, 10.18. Found: C, 64.63; H, 3.52; N, 10.18. LC/MS: 404 (M + H).

Synthesis of Examples 90 and 91

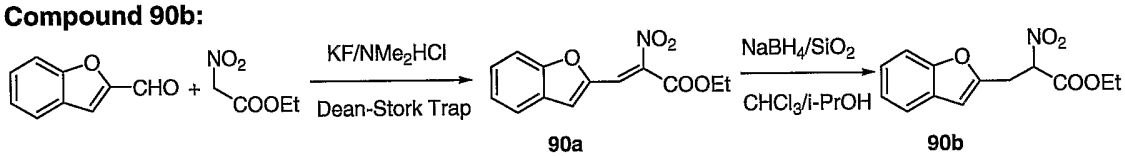


T = O or NH

R^3 = COOH, tetrazole



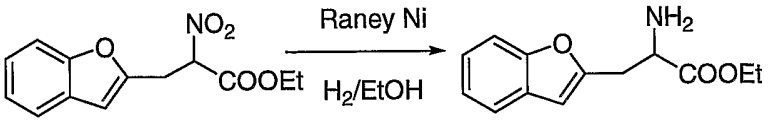
Compound 90b:



90a **90b**

To a toluene solution (60mL) of 1-Benzofuran-2-carbaldehyde (2g, 13.7mmol) and Ethyl nitroacetate (2.19g, 16.4mmol) was added KF (119mg, 2.06mmol) and Dimethylamine hydrochloride (2.23g, 27.4mmol). The mixture was heated at reflux with a Dean-Stork trap to remove water. After being heated for 18h, the solution was cooled down and concentrated. The residue was re-dissolved in methylene chloride (50mL). The resulted solution was washed with water (3x25mL), dried ($MgSO_4$) and evaporated *in vacuo* to dryness. The yellow syrup (**90a**, 3.9g) was dissolved in a co-solvent of chloroform (150mL) and isopropanol (45mL). With stirring, silica gel powder (30g) was added, followed by slow addition of $NaBH_4$ (2.59g, 68.5mmol). The slurry was stirred for 2h, acetic acid (3mL) was then added drop-wise. All solid was filtered off. The filtrate was washed with water (3x50mL), dried (Na_2SO_4) and concentrated. The residue was purified with silica gel flash column chromatography (30% EtOAc in hexanes), affording the title compound (**90b**, 3g, 83% yield) as an oil. ^1H NMR ($CDCl_3$): δ 7.55-7.40 (4H, m), 6.57 (1H, s), 5.58 (1H, dd, J=9.3, 5.5Hz), 4.32 (2H, q, J=7.1Hz), 3.80 (1H, dd, J=15.8, 9.4Hz), 3.67 (1H, dd, J=15.7, 5.5Hz), 1.30 (3H, t, J=7.4Hz).

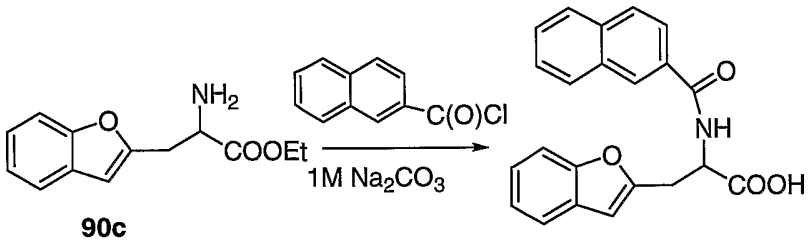
Compound 90c:



90b **90c**

To an ethanol solution (8mL) of the nitroester (**90b**, 680mg, 2.59mmol) was added Raney Nickel (0.6g, 50%). The suspension was kept under hydrogen atmosphere (1atm) for 6h at 25°C. The catalyst was then removed by filtration. The filtrate was evaporated *in vacuo* to dryness, affording 650mg (quantitative) of the title compound as an oil. LCMS (APCI positive): 234 ($M+H^+$).

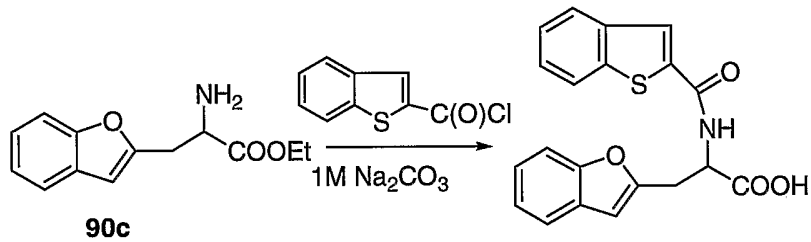
Example 90:



90c **90**

To a sodium carbonate solution (1M, 5mL) was added the amino ester **90c** (150mg, 0.643mmol), 2-Naphthoyl chloride (147mg, 0.773mmol) and acetonitrile (5mL). The mixture was stirred at 25°C for 12h. Preparative HPLC purification provided 90mg of the title product (39% yield). ^{1}H NMR (DMSO-d_6): δ 12.85 (1H, br s), 8.93 (1H, d, J=7.8Hz), 8.34 (1H, s), 7.93-7.85 (3H, m), 7.80 (1H, dd, J=8.6, 6.8Hz), 7.50 (2H, m), 7.45-7.36 (2H, m), 7.11 (1H, td, J=7.3, 1.5Hz), 7.06 (1H, td, J=7.4, 1.1Hz), 6.60 (1H, s), 4.83-4.75 (1H, m), 3.35-3.25 (2H, m). LCMS (APCI positive): 360 (M+H$^+$); Elemental Analysis for ($C_{22}H_{17}NO_4$•0.3H_2O) calc: C 72.44, H 4.86, N 3.84; found: C 72.36, H 4.79, N 3.92.

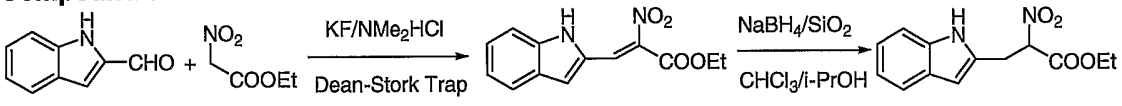
Example 91:



90c **91**

To a sodium carbonate solution (1M, 5mL) was added the amino ester **90c** (150mg, 0.643mmol), 1-Benzothiophene-2-carbonyl chloride (151.7mg, 0.772mmol) and acetonitrile (5mL). The mixture was stirred at 25°C for 12h. Preparative HPLC purification provided 100mg of the title product (43% yield). ^{1}H NMR (DMSO-d_6): δ 13.1 (1H, br s), 9.26 (1H, d, J=8.0Hz), 8.24 (1H, s), 8.12-8.03 (2H, m), 7.65-7.56 (2H, m), 7.54 (2H, m), 7.31 (1H, td, J=7.3, 1.5Hz), 7.25 (1H, td, J=7.3, 1.2Hz), 6.78 (1H, s), 4.95-4.87 (1H, m), 3.40-3.25 (2H, m).). LCMS (APCI positive): 366 (M+H$^+$); Elemental Analysis for ($C_{20}H_{15}NO_4S$•0.26H_2O) calc: C 64.91, H 4.23, N 3.78, S 8.66; found: C 65.00, H 4.32, N 3.93, S 8.38.

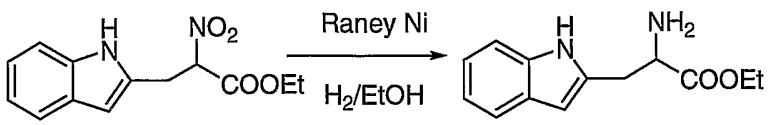
Compound 91b:



91a **91b**

Prepared as described in the synthesis of **90b**. For synthesis of **91a**, 1*H*-indole-2-carbaldehyde (0.5g, 3.45mmol), Ethyl nitroacetate (0.551g, 4.14mmol), KF (30.1mg, 0.518mmol), Dimethylamine hydrochloride (0.563g, 6.9mmol) and tolune (38mL) were used. For reduction of **91a**, silica gel powder (7.5g), $NaBH_4$ (0.65g, 17mmol), chloroform (20mL) and isopropanol (6mL) were used. The residue was purified with column chromatography (30% EtOAc in hexanes), affording the title compound **111b** (120mg, 13% yield) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.7-7.15 (4H, m), 6.50 (1H, s), 4.59-4.50 (3H, m), 3.77-3.74 (2H, m), 1.53 (3H, t, J=7Hz).

Compound 91c:

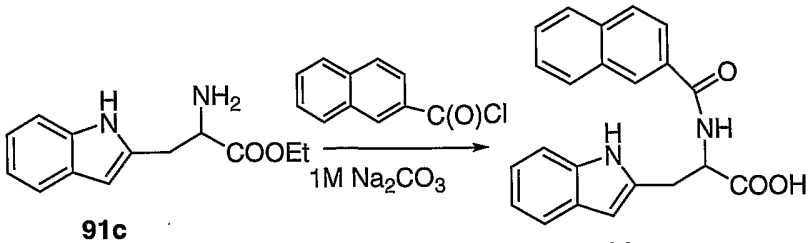


91b **91c**

Prepared as described in the synthesis of **90c** using the nitroester **91b** (120mg, 0.46mmol), Raney Nickel (15mg, 50%) and ethanol (2mL). The title compound (65mg, 52% yield) was obtained

as an oil. ^{1}H NMR ($CDCl_3$): δ 9.51 (1H, s), 7.50-7.46 (1H, m), 7.30-7.25 (1H, m), 7.12-6.98 (2H, m), 6.24 (1H, s), 4.26 (1H, m), 4.12-4.05 (2H, m), 3.43-3.36 (2H, m), 1.22 (3H, t, J=7.1Hz).

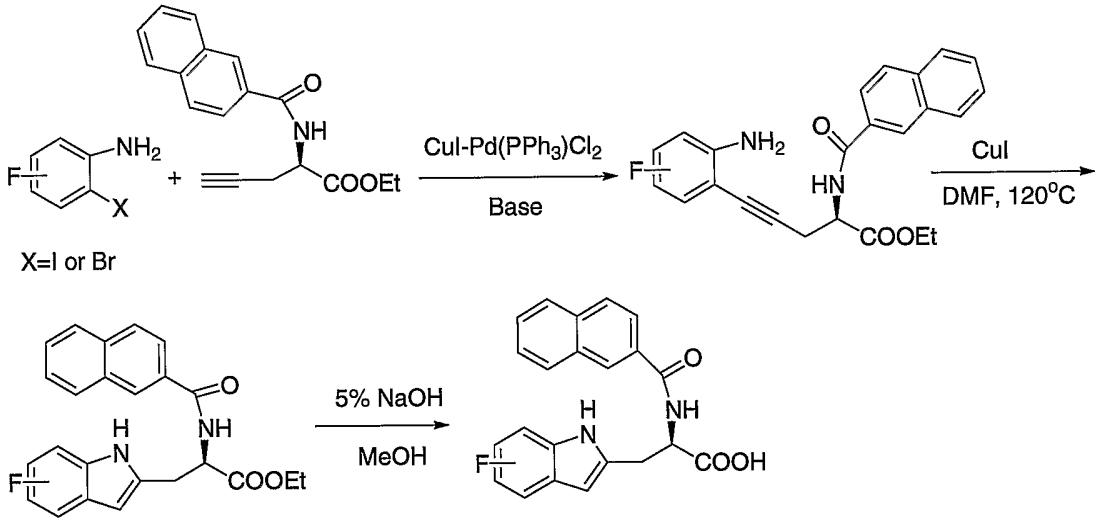
Example 91:



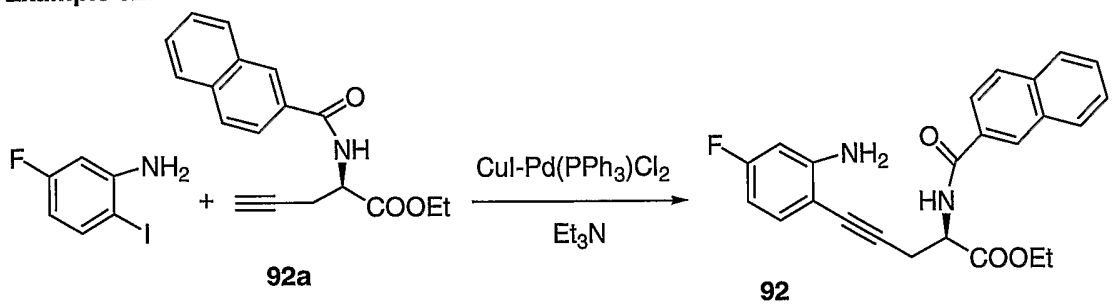
91c **91**

Prepared as described in the synthesis of **90** using sodium carbonate solution (1M, 5mL), the amino ester **90c** (40mg, 0.172mmol), 2-Naphthoyl chloride (65.7mg, 0.345mmol) and acetonitrile (1mL). Preparative HPLC purification provided 35mg of the title product (57% yield). ^{1}H NMR (DMSO-d_6): δ 12.78 (1H, br s), 11.02 (1H, s), 8.89 (1H, d, J=7.9Hz), 8.41 (1H, s), 8.01-7.92 (3H, m), 7.88 (1H, dd, J=8.6, 1.5Hz), 7.57 (2H, m), 7.36 (1H, d, J=7.5Hz), 7.25 (1H, d, J=8.1Hz), 6.95 (1H, d, J=7.5Hz), 6.86 (1H, t, J=7.1Hz), 6.23 (1H, s), 4.88-4.80 (1H, m), 3.38-3.23 (2H, m). LCMS (APCI positive): 359 ($M+H^+$). HRMS (MALDI) calc for $C_{22}H_{19}N_2O_3$ ($M+H^+$) 359.1390; found 359.1400.

Synthesis of Fluoroindoles:



Example 92:

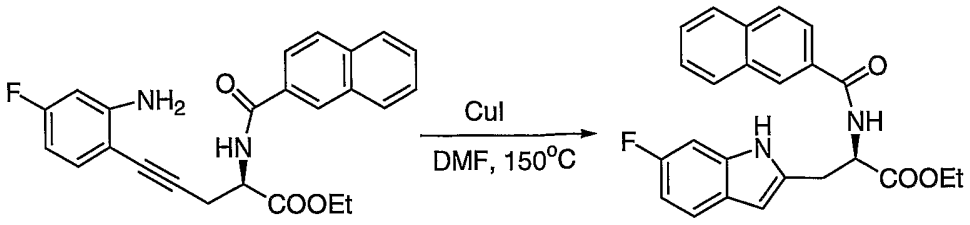


92a **92**

To a triethylamine solution (22.5mL) of 5-fluoro-2-iodoaniline (401.3mg, 1.69mmol) was added the alkyne **92a** (500mg, 1.69mmol), $Pd(PPh_3)_2Cl_2$ (24mg, 0.034mmol), CuI (6.45mg, 0.034mmol) and DMF (3mL). After stirred 15h at 25°C, the solution was concentrated *in vacuo*. The residue was purified with silica gel column chromatography (15-20% EtOAc in hexanes) giving the title compound (570mg, 83% yield) as a solid. ^{1}H NMR ($CDCl_3$): δ 8.36 (1H, s), 7.94-7.85 (4H, m),

7.56 (1H, m), 7.19-7.12 (2H, m), 6.36-6.31 (2H, m), 5.10 (1H, m), 4.41 (2H, br s), 4.34-4.28 (2H, m), 3.25 (1H, dd, J=17.2, 4.9Hz), 3.13 (1H, dd, J=17.2, 4.6Hz), 1.35 (3H, t, J=7.2Hz). LCMS (APCI positive): 405 ($M+H^+$).

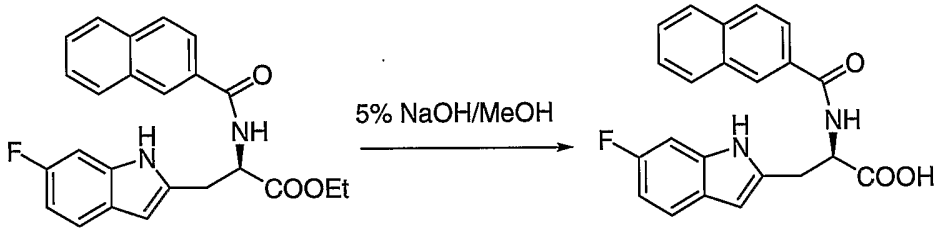
Example 93:



92 **93**

To a DMF solution (18mL) of ethylene glycol (3.5g) was added **92** (250mg, 0.619mmol) and CuI (117.8mg, 0.619mmol). The mixture was degassed *in vacuo*, flushed with nitrogen and heated at refluxed for 2h. The solution was concentrated *in vacuo*. Silica gel column chromatography purification (20% EtOAc in hexanes) provided the title compound (220mg, 88% yield) as a solid. ^1H NMR ($CDCl_3$): δ 9.18 (1H, s), 7.81-7.69 (4H, m), 7.55-7.40 (3H, m), 7.09 (1H, d, J=7.3Hz), 6.99 (1H, dd, J=9.6Hz), 6.87-6.80 (1H, m), 6.26 (1H, d, J=1.2Hz), 5.14 (1H, dd, J=12.6, 4.5Hz), 4.23 (2H, m), 3.5-3.35 (2H, m), 1.24 (3H, t, J=7.3Hz). LCMS (APCI positive): 405 ($M+H^+$).

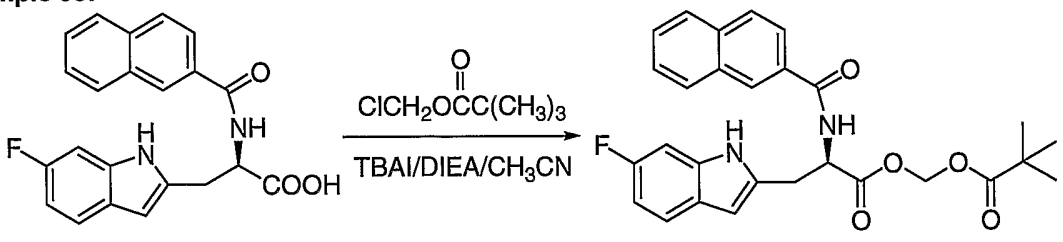
Example 94:



93 **94**

To a methanol solution (3mL) of the ester **93** (215mg, 0.532mmol) was added 10% NaOH solution (3mL). After stirred at 25°C for 15h, the solution was acidified (pH~3) with ice-cooled 10% HCl solution. The suspension was extracted with EtOAc (3x15mL). The combined organic layers were washed (brine, 1x25mL), dried ($MgSO_4$) and concentrated. The residue was purified with column chromatography (50-100% EtOAc in hexanes) and by recrystallization from methylene chloride (8mL), affording the title compound (155mg, 77% yield) as pale tan solid. ^1H NMR (DMSO-*d6*): δ 12.65 (1H, br s), 11.01 (1H, s), 8.78 (1H, d, J=8.1Hz), 8.30 (1H, s), 7.89-7.81 (3H, m), 7.76 (1H, dd, J=8.6, 1.5Hz), 7.46 (2H, m), 7.23 (1H, dd, J=8.6, 5.6Hz), 6.93 (1H, dd, J=10.1, 2.3Hz), 6.61 (1H, m), 6.13 (1H, s), 4.72 (1H, m), 3.25-3.10 (2H, m). LCMS (APCI positive): 376 ($M+H^+$). Elemental Analysis for ($C_{22}H_{17}FN_2O_3 \bullet 0.3H_2O$) calc: C 69.21, H 4.65, N 7.34; found: C 69.19, H 4.68, N 7.26.

Example 95:

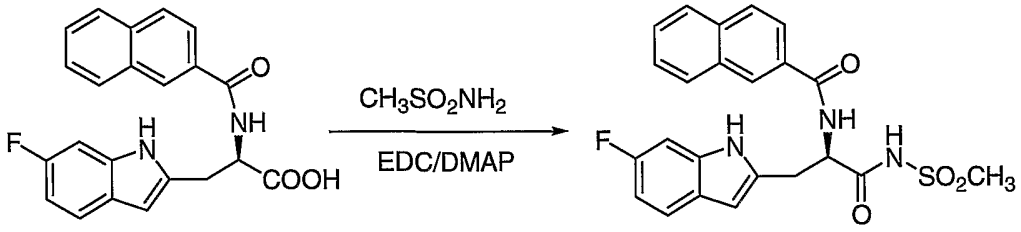


94 **95**

To an acetonitrile solution (1mL) of **94** (50mg, 0.123mmol) was added Diisopropylethylamine (DIEA, 0.3mL), Chloromethyl pivalate (100μL) and Tetrabutylammonium iodide (TBAI, 5mg) at 0°C. The mixture was stirred at 25°C for 15h and concentrated *in vacuo*. The residue was purified with column chromatography (20% EtOAc in hexanes) affording the title compound (2mg, 3.3% yield) as

an oil. ^{1}H NMR (DMSO-*d6*): δ 8.19 (1H, s), 7.85-7.78 (3H, m), 7.70 (1H, dd, J=8.6, 1.8Hz), 7.52-7.43 (2H, m), 7.27 (1H, dd, J=8.5, 5.3 Hz), 6.89 (1H, dd, J=9.6, 2.0Hz), 6.64 (1H, dd, J=8.6, 2.3Hz), 6.62 (1H, dd, J=8.5, 2.2Hz), 6.21 (1H, s), 5.77 (1H, d, J=5.5Hz), 5.72 (1H, d, J=5.5Hz), 4.94 (1H, dd, J=9.4, 5.9Hz), 3.35 (1H, dd, J=15.5, 5.9Hz), 3.26 (1H, dd, J=14.9, 9.3Hz), 1.05 (9H, s). LCMS (APCI positive): 392(M+H$^+$); HRMS (MALDI) calc for $C_{28}H_{28}N_2O_5F$ (M+H$^+$) 491.1976; found 491.1982.

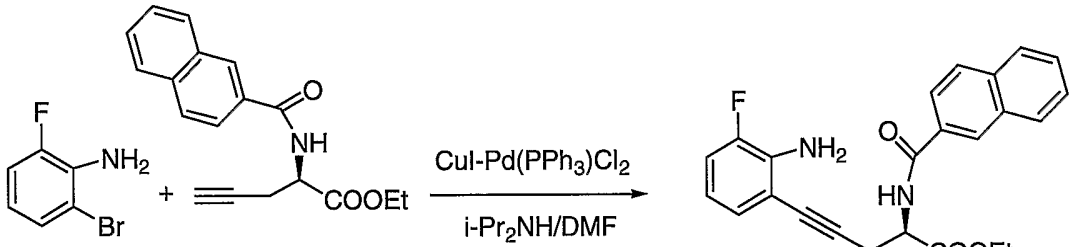
Example 96:



94 **96**

To a methylene chloride solution (2mL) of **94** (50mg, 0.123mmol) was added Methanesulfonamide (63mg, 0.665mmol), EDC (76.7mg, 0.4mmol) and N,N-Dimethyl-4-aminopyridine (DMAP, 20mg). The mixture was stirred at 25°C for 18h and diluted with EtOAc (25mL). The solution was washed with brine (2x20mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified with HPLC affording the title compound (5mg, 8% yield) as a solid. ^{1}H NMR (CD_3OD): δ 10.37 (1H, br s), 8.25 (1H, s), 7.83 (2H, m), 7.76 (1H, dd, J=8.6, 1.8Hz), 7.55-7.40 (2H, m), 7.33-7.25 (1H, m), 6.93 (1H, dd, J=10.9, 2.1Hz), 6.67 (1H, m), 6.26 (1H, s), 4.84 (1H, m), 3.35-3.25 (2H, m), 3.11 (3H, s). HRMS (MALDI) calc for $C_{23}H_{21}N_3O_4FS$ (M+H$^+$) 454.1237; found 454.1234.

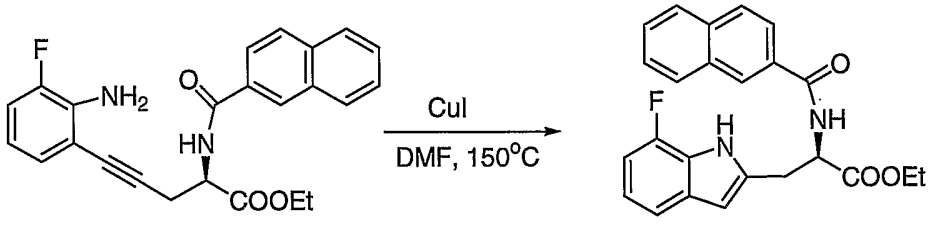
Example 97:



92a **97**

To a DMF solution (6.3mL) of 6-fluoro-2-bromoaniline (247mg, 1.3mmol) was added the alkyne **92a** (350mg, 1.19mmol), $Pd(PPh_3)_2Cl_2$ (33mg, 0.047mmol), CuI (17.8mg, 0.09mmol) and i-Pr_2NH (2.1mL). The mixture was degassed *in vacuo*, flushed with nitrogen and heated at 90°C for 30min. The resulted solution was concentrated *in vacuo*. The residue was purified with silica gel column chromatography (15% EtOAc in hexanes) giving the title compound (300mg, 62% yield) as a solid. ^{1}H NMR ($CDCl_3$): δ 9.18 (1H, s), 8.37 (1H, s), 7.95-7.86 (4H, m), 7.56 (2H, m), 7.23 (1H, d, J=7.6Hz), 7.00 (1H, d, J=7.8Hz), 6.97-6.90 (1H, m), 6.59-6.52 (1H, m), 5.12 (1H, m), 4.39-4.30 (4H, m), 3.27 (1H, dd, J=7.2, 4.8Hz), 1.31 (3H, t, J=7.1Hz). LCMS (APCI positive): 405 (M+H$^+$).

Example 98:

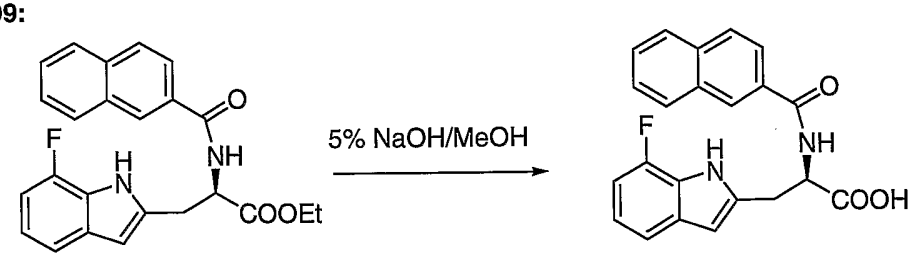


97 **98**

To a DMF solution (18mL) of ethylene glycol (3.5g) was added **97** (300mg, 0.743mmol) and CuI (141mg, 0.743mmol). The mixture was degassed *in vacuo*, flushed with nitrogen and heated at refluxed for 2h. The solution was concentrated *in vacuo*. Silica gel column chromatography

purification (20% EtOAc in hexanes) provided the title compound (220mg, 73% yield) as a solid. ^{1}H NMR ($CDCl_3$): δ 8.74 (1H, br s), 8.28 (1H, d, J=1.3 Hz), 7.92-7.84 (3H, m), 7.81 (1H, dd, J=8.5, 1.7Hz), 7.60-7.50 (2H, m), 7.30 (1H, d, J=7.8Hz), 7.01-6.95 (2H, m), 6.87 (1H, dd, J=11.1, 7.1Hz), 6.34 (1H, m), 5.2-5.14 (1H, m), 4.35-4.25 (2H, m), 3.53-3.50 (2H, m), 1.31 (3H, t, J=7.3Hz).

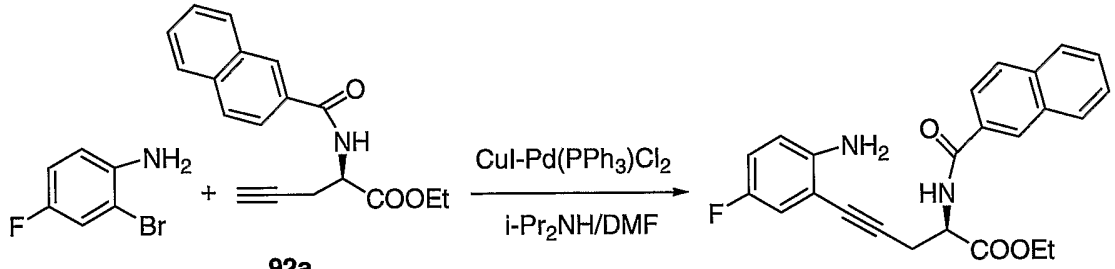
Example 99:



98 **99**

To a methanol solution (5mL) of the ester **98** (290mg, 0.72mmol) was added 10% NaOH solution (5mL). After stirred at 25°C for 6h, the solution was acidified (pH~3) with ice-cooled 10% HCl solution. The suspension was extracted with EtOAc (4x15mL). The combined organic layers were washed (brine, 1x25mL), dried ($MgSO_4$) and concentrated. The residue was triturated with warm hexanes (10mL). The title compound (250mg, 92% yield) was obtained as pale tan solid. ^{1}H NMR (DMSO-*d6*): δ 12.63 (1H, br s), 11.35 (1H, s), 8.78 (1H, d, J=8.1Hz), 8.28 (1H, s), 7.89-7.80 (3H, m), 7.75 (1H, dd, J=8.4, 1.5Hz), 7.45 (2H, m), 7.07 (1H, d, J=7.5Hz), 6.75-6.63 (2H, m), 6.20 (1H, m), 4.80-4.72 (1H, m), 3.28-3.10 (2H, m). Elemental Analysis for ($C_{22}H_{17}N_2O_3F \bullet 0.39H_2O$) calc: C 68.92, H 4.67, N 7.31; found: C 68.92, H 4.55, N 7.22.

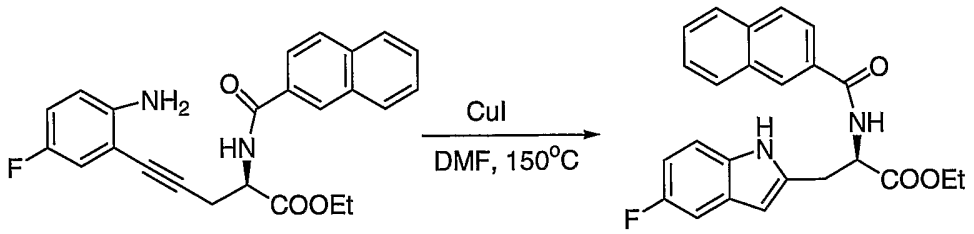
Example 100:



92a **100**

To a DMF solution (7mL) of 4-fluoro-2-bromoaniline (258mg, 1.36mmol) was added the alkyne **92a** (400mg, 1.36mmol), $Pd(PPh_3)_2Cl_2$ (38mg, 0.054mmol), CuI (20.6mg, 0.11mmol) and i-Pr_2NH (2 mL). The mixture was degassed *in vacuo*, flushed with nitrogen and heated at 90°C for 1h. The resulted solution was diluted with EtOAc (30mL), washed with brine (2x25mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified with silica gel column chromatography (15% EtOAc in hexanes) giving the title compound (320mg, 58% yield) as a solid.). LCMS (APCI positive): 405 ($M+H^+$).

Example 101:

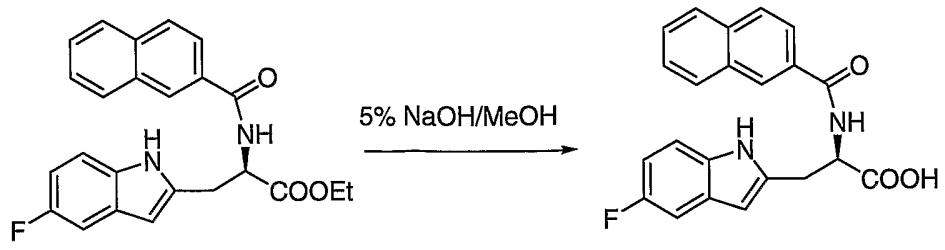


100 **101**

To a DMF solution (7.4mL) of **100** (300mg, 0.74mmol) was added CuI (141mg, 0.74mmol). The mixture was degassed *in vacuo*, flushed with nitrogen and heated at refluxed for 3h. The solution was concentrated *in vacuo*. The residue was dissolved in EtOAc (50mL). The resulted solution was washed with brine (2x25mL), dried with $MgSO_4$ and concentrated. Silica gel column chromatography purification (15% EtOAc in hexanes) provided the title compound (220mg, 73%

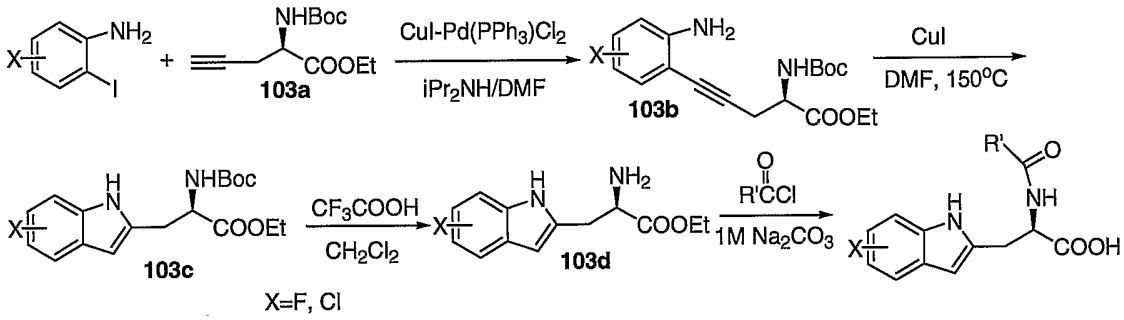
yield) as a solid. ^{1}H NMR ($CDCl_3$): δ 8.71 (1H, br s), 8.24 (1H, s), 7.9-7.84 (3H, m), 7.79 (1H, dd, J=8.5, 1.7Hz), 7.6-7.5 (2H, m), 7.23 (1H, dd, J=8.8, 4.5Hz), 7.18 (1H, dd, J=9.6, 2.6Hz), 7.02 (1H, d, J=7.1Hz), 6.89 (1H, td, J=9.4, 2.6Hz), 6.27 (1H, d, J=1.3Hz), 5.14 (1H, m), 4.29 (2H, m), 3.47 (2H, m), 1.30 (3H, t, J=7.1Hz). LCMS (APCI positive): 405 ($M+H^+$).

Example 102:

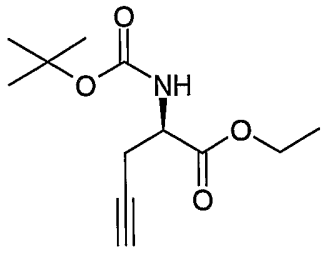


101 **102**

To a methanol solution (5mL) of the ester **101** (200mg, 0.495mmol) was added 10% NaOH solution (5mL). After stirred at 25°C for 15h, the solution was acidified (pH~3) with ice-cooled HCl. The suspension was extracted with EtOAc (3x20mL). The combined organic layers were washed (brine, 1x25mL), dried ($MgSO_4$) and concentrated. Recrystallization from methylene chloride/hexanes (10:1) provided the title compound (150mg, 81% yield) as a brown solid. ^{1}H NMR (DMSO-*d6*): δ 12.70 (1H, s), 11.09 (1H, s), 8.86 (1H, d, J=7.9Hz), 8.36 (1H, s), 7.96-7.88 (3H, m), 7.83 (1H, dd, J=8.6, 1.8Hz), 7.53 (2H, m), 7.19 (1H, dd, J=8.9, 4.8Hz), 7.08 (1H, dd, J=10.1, 2.5Hz), 6.74 (1H, td, J=9.4, 2.6Hz), 6.20 (1H, s), 4.78 (1H, m), 3.35-3.20 (2H, m). LCMS (APCI positive): 377 ($M+H^+$). Elemental Analysis for ($C_{22}H_{17}FN_2O_3 \bullet 0.34H_2O$) calc: C 69.86, H 5.12, N 6.98; found: C 69.96, H 5.21, N 6.90.



Compound 103a:

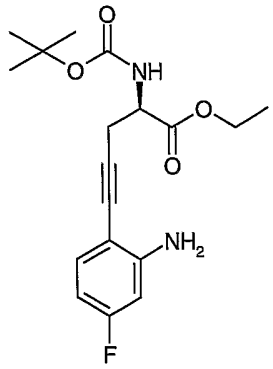


103a

To a dichloromethane solution (100 mL) of **174a** (6.98 g, 39.3 mmol) was added di-*t*-butyldicarbonate (12.9 g, 59.0 mmol) and triethylamine (11.9 g, 118 mmol). The mixture was stirred at room temperature overnight. It was then washed with cold 1M sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 84% yield.

^{1}H NMR ($CDCl_3$): δ 5.37 (1H, br d, J=7.4Hz), 4.50-4.42 (1H, m), 4.32-4.20 (2H, m), 2.82-2.70 (2H, m), 1.47 (9H, s), 1.32 (1H, t, J=7Hz).

Compound 103b:



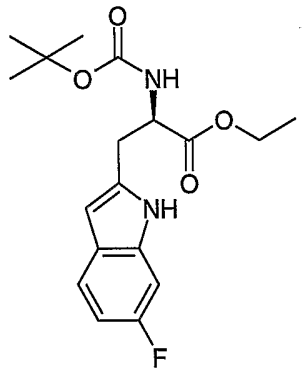
103b

To a N, N-dimethyl-formamide solution (45 mL) of **103a** (3.99 g, 16.1 mmol) was added 5-fluoro-2-iodoaniline (3.82 g, 16.1 mmol), diisopropylamine (15 mL), dichlorobis(triphenylphosphine)-palladium (II) (452 mg, 0.644 mmol) and CuI (246 mg, 1.29 mmol). The mixture was stirred at 90°C for 16 minutes after three circles of nitrogen/vacuum flush. DMF was removed in vacuo and the residue was diluted with dichloromethane (100 mL). It was then washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 89% yield.

^{1}H NMR ($CDCl_3$): δ 7.5-7.3 (1H, m), 6.9-6.7 (1H, m), 6.58 (1H, br m), 5.57 and 5.47 (1H, m), 4.63 (1H, m), 4.35-4.20 (2H, m), 3.08-3.04 (2H, m), 1.48 and 1.45 (9H, s), 1.31 and 1.28 (3H, t).

LCMS (API-ES): 373.1 ($M+Na^+$).

Compound 103c:

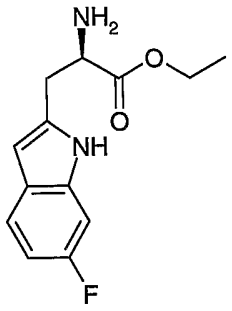


103c

To a N, N-dimethyl-formamide solution (50 mL) of **103b** (5.03 g, 14.4 mmol) was added CuI (2.74 g, 14.4 mmol). The mixture was stirred at 150°C for 4 hours after three circles of nitrogen/vacuum flush. It was filtered through a pad of celite. The filtrate was evaporated and the residue was diluted with dichloromethane (100 mL). It was then washed with water (2X50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 77% yield.

^{1}H NMR ($CDCl_3$): δ 8.40 (1H, br s), 7.45 (1H, dd, J=8.6, 5.3Hz), 7.02 (1H, dd, J=9.9, 2.3Hz), 6.92-6.80 (1H, m), 6.27 (1H, s), 5.18 (1H, br s), 4.63 (1H, br s), 4.29-4.20 (2H, m), 3.30-3.26 (2H, m), 1.45 (9H, s), 1.27 (3H, t). LCMS (API-ES): 373.1 ($M+Na^+$).

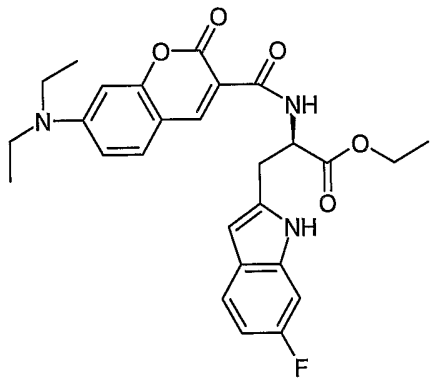
Compound 103d:



103d

To a dichloromethane solution (50 mL) of **103c** (3.89 g, 11.1 mmol) was added trifluoroacetic acid (15 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. It was then concentrated and the residue was diluted with ethyl acetate (100 mL). It was then washed with cold 1M sodium bicarbonate (2X50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (3% methanol in dichloromethane), the title compound was obtained in 88% yield. ^1H NMR (CD_3OD): δ 7.39 (1H, dd, J=8.8, 5.5Hz), 7.00 (1H, dd, J=9.6, 2.3Hz), 6.82-6.70 (1H, m), 6.23 (1H, s), 4.15 (2H, q, J=7.1Hz), 3.81 (1H, m), 3.17 (1H, dd, J=14.4, 6.1Hz), 3.05 (1H, dd, J=14.7, 7.1Hz), 1.18 (1H, t, J=7Hz). LCMS (APCI): 251.1 ($M+H^+$).

Example 103:

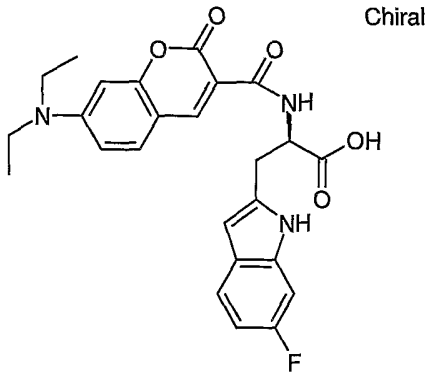


Chiral

103

To a dichloromethane solution (5 mL) of **103d** (175 mg, 0.699 mmol) were added N-succinimidyl 7-(diethylamino)coumarin-3-carboxylate (200 mg, 0.559 mmol), triethylamine (85 mg, 0.839 mmol) and 4-(dimethylamino)pyridine (10 mg, 0.0839 mmol). The mixture was stirred at room temperature overnight. It was then diluted with dichloromethane (20 mL) and washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (30-50% ethyl acetate in hexane), the title compound was obtained in 92% yield.
^1H NMR (CD_3Cl): δ 9.60-9.46 (1H, m), 8.94-8.78 (1H, m), 7.79-7.66 (1H, m), 7.63-7.53 (1H, m), 7.30-6.96 (4H, m), 6.48 (1H, s), 5.23 (1H, d, J=5.30 Hz), 4.45-4.32 (2H, m), 3.71-3.59 (4H, m), 3.58-4.48 (2H, m), 1.51-1.34 (9H, m). LCMS (API-ES): 494.1 ($M+H^+$). HRMS (MALDI) calc for $C_{27}H_{29}N_3O_5F$ ($M+H^+$) 494.2091; found 494.2104.

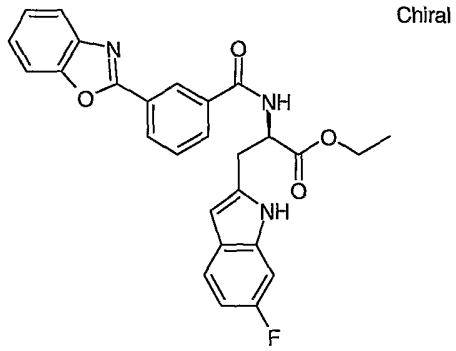
Example 104:



104

To a methanol solution (2.5 mL) of **103** (224 mg, 0.454 mmol) was added 5% sodium hydroxide (2.5 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. It was then purified by prep. HPLC to give title compound in 6% yield. ^{1}H NMR (DMSO-D6): δ 13.00 (1H, s), 11.09 (1H, d, J = 1.5 Hz), 9.07 (1H, d, J = 7.3 Hz), 8.65 (1H, s), 7.67 (1H, d, J = 9.1 Hz), 7.38 (1H, dd, J = 8.6, 5.6 Hz), 7.03 (1H, dd, J = 10.0, 2.2 Hz), 6.81-6.75 (2H, m), 6.61 (1H, d, J = 2.2 Hz), 6.20 (1H, s), 4.86-4.81 (1H, m), 3.47 (4H, q, J = 7.1 Hz), 3.30-3.18 (2H, m), 1.12 (6H, t, J = 7.1 Hz). LCMS (APCI): 466.1 (M+H$^+$). HRMS (MALDI) calc for $C_{25}H_{25}N_3O_5F$ (M+H$^+$) 466.1778; found 466.1776.

Example 105:

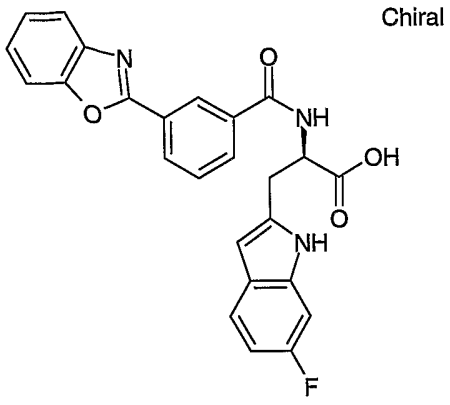


105

To a N, N-dimethyl-formamide solution (15 mL) of **103d** (482 mg, 1.93 mmol) were added 3-benzooxazol-2-yl-benzoic acid (691 mg, 2.89 mmol), EDC (920 mg, 4.83 mmol), triethylamine (780 mg, 7.72 mmol) and 4-(dimethylamino)pyridine (58 mg, 0.475 mmol). The mixture was stirred at room temperature for 48h. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (30-50% ethyl acetate in hexane) and prep. HPLC purification, the title compound was obtained in 4% yield.

^{1}H NMR (DMSO-d6): δ 11.17 (1H, s), 9.22 (1H, d, J = 7.3 Hz), 8.68 (1H, s), 8.35 (1H, d, J = 7.8 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.85-7.81 (2H, m), 7.72 (1H, t, J = 7.8 Hz), 7.49-7.36 (3H, m), 7.07 (1H, dd, J = 10.1, 2.0 Hz), 6.78-6.73 (1H, m), 6.26 (1H, s), 4.90-4.84 (1H, m), 4.11 (2H, q, J = 6.9 Hz), 3.32-3.30 (2H, m), 1.11 (3H, t, J = 7.1 Hz). LCMS (APCI): 472.1 (M+H$^+$). HRMS (MALDI) calc for $C_{27}H_{23}N_3O_4F$ (M+H$^+$) 472.1673; found 472.1677.

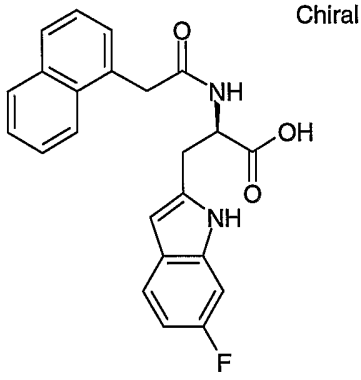
Example 106:



106

To a methanol solution (2 mL) of **105** (33 mg, 0.0701 mmol) was added 5% sodium hydroxide (1 mL) at 0°C. The mixture was stirred at room temperature for 4 hours. It was then purified by prep. HPLC to give title compound in 45% yield. ^{1}H NMR (DMSO-D6): δ 11.15 (1H, br), 9.10 (1H, d, J = 7.9 Hz), 8.67 (1H, s), 8.34 (1H, d, J = 7.7 Hz), 8.06 (1H, d, J = 7.9 Hz), 7.86-7.81 (2H, m), 7.71 (1H, t, J = 7.8 Hz), 7.49-7.35 (3H, m), 7.08-7.04 (1H, m), 6.79-6.71 (1H, m), 6.25 (1H, s), 4.88-4.80 (1H, m), 3.35-3.26 (2H, m). LCMS (APCI): 444.1 ($M+H^+$). HRMS (MALDI) calc for $C_{25}H_{19}N_3O_4F$ ($M+H^+$) 444.1360; found 444.1350.

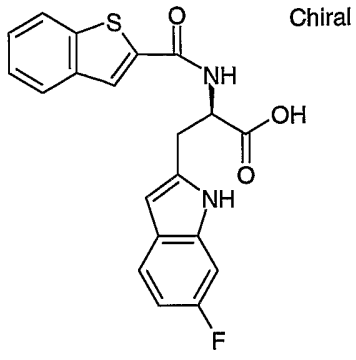
Example 107:



107

To an acetonitrile/water solution (3 mL/3 mL) of **103d** (143 mg, 0.572 mmol) were added 1-naphthylacetic anhydride (303 mg, 0.855 mmol), and sodium hydroxide (92 mg, 2.29 mmol). The mixture was stirred at room temperature for 48h. It was acidified with 1M HCl and diluted with ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (50-100% ethyl acetate in hexane) and prep. HPLC purification, the title compound was obtained in 22% yield. ^{1}H NMR (DMSO-d6): δ 12.81 (1H, br), 11.07 (1H, s), 8.62 (1H, d, J = 8.1 Hz), 7.90-7.85 (2H, m), 7.76-7.74 (1H, m), 7.45-7.38 (2H, m), 7.31-7.22 (3H, m), 7.05 (1H, dd, J = 9.9, 2.0 Hz), 6.83-6.78 (1H, m), 6.19 (1H, s), 4.63-4.57 (1H, m), 3.90 (2H, s), 3.23-3.18 (1H, m), 3.05 (1H, dd, J = 14.9, 9.9 Hz). LCMS (APCI): 391.1 ($M+H^+$). Elemental Analysis for ($C_{23}H_{19}FN_2O_3$) calc: C 70.76, H 4.91, N 7.18; found: C 70.75, H 4.80, N 7.31.

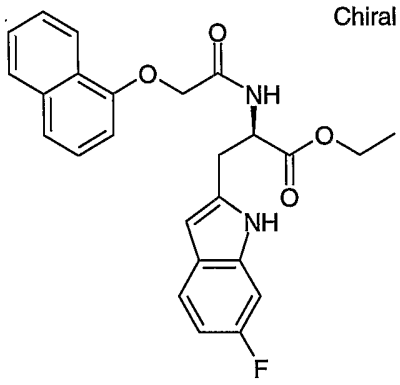
Example 108



108

To an acetonitrile/water solution (3 mL/3 mL) of **103d** (187 mg, 0.748 mmol) were added benzo[B]thiophene-2-carbonyl chloride (162 mg, 0.823 mmol), and sodium hydroxide (120 mg, 2.99 mmol). The mixture was stirred at room temperature for 4 hours. It was acidified with 1M HCl and diluted with ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (50-100% ethyl acetate in hexane) and prep. HPLC purification, the title compound was obtained in 59% yield. ^1H NMR (DMSO-d6): δ 12.88 (1H, br), 11.14 (1H, s), 9.07 (1H, d, J = 8.1 Hz), 8.15 (1H, s), 8.01-7.93 (2H, m), 7.46-7.35 (3H, m), 7.05 (1H, dd, J = 10.1, 1.8 Hz), 6.77-6.72 (1H, m), 6.25 (1H, s), 4.80-4.74 (1H, m), 3.30-3.20 (2H, m). LCMS (APCI): 383.0 ($M+H^+$). Elemental Analysis for ($C_{20}H_{15}FN_2O_3S \bullet 0.1H_2O$) calc: C 62.52, H 3.99, N 7.29; found: C 62.15, H 3.94, N 7.65.

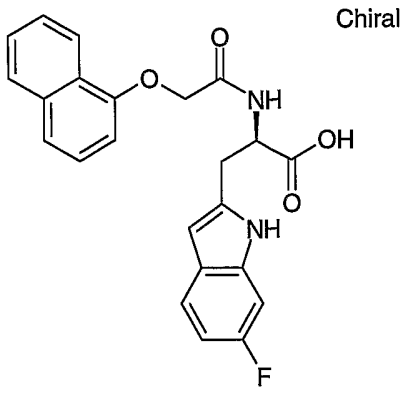
Example 109:



109

To a N, N-dimethyl-formamide solution (8 mL) of **103d** (210 mg, 0.84 mmol) was added (1-naphthoxy)acetic acid (332 mg, 1.64 mmol), EDC (470 mg, 2.45 mmol), triethylamine (347 mg, 3.44 mmol) and 4-(dimethylamino)pyridine (17 mg, 0.17 mmol). The mixture was stirred at room temperature for 72h. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (30-40% ethyl acetate in hexane), the title compound was obtained in 37% yield. ^1H NMR (DMSO-d_6): δ 11.14 (1H, br s), 8.58 (1H, d, J=7.8Hz), 8.21 (1H, d, J=8.1Hz), 7.88 (1H, d, J=8.3Hz), 7.60-7.45 (3H, m), 7.42 (1H, dd, J=8.6, 5.3Hz), 7.25 (1H, t, J=7.8Hz), 7.07 (1H, dd, J=10.1, 2.3Hz), 6.84-6.75 (2H, m), 6.25 (1H, s), 4.82-4.68 (1H, m), 4.71 (1H, AB), 4.12 (1H, q, J=7.3Hz), 3.30-3.20 (2H, m), 1.15 (3H, t, J=7.1Hz). LCMS (APCI): 435.1 ($M+H^+$).

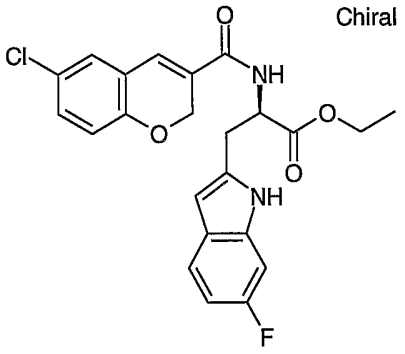
Example 110:



110

To a methanol solution (2 mL) of **109** (132 mg, 0.304 mmol) was added 5% sodium hydroxide (2 mL) at 0°C. The mixture was stirred at room temperature for 4 hours. It was then purified by prep. HPLC to give title compound in 73% yield. ^{1}H NMR (DMSO-D6): δ 12.91 (1H, br), 11.10 (1H, s), 8.41 (1H, d, J = 7.8 Hz), 8.18 (1H, d, J = 7.8 Hz), 7.85 (1H, d, J = 8.3 Hz), 7.54-7.50 (1H, m), 7.48-7.44 (2H, m), 7.39 (1H, dd, J = 8.6, 5.6 Hz), 7.21 (1H, t, J = 8.1 Hz), 7.04 (1H, dd, J = 10.2, 2.2 Hz), 6.81-6.76 (2H, m), 6.23 (1H, s), 4.75-4.63 (3H, m), 3.30-3.16 (2H, m). LCMS (APCI): 407.1 ($M+H^+$). Elemental Analysis for ($C_{23}H_{19}FN_2O_4 \bullet 0.1H_2O$) calc: C 65.09, H 4.99, N 6.60; found: C 65.32, H 4.87, N 6.54.

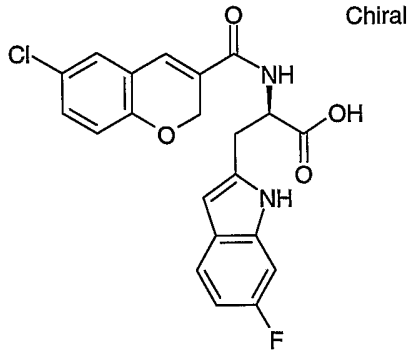
Example 111:



111

To a N, N-dimethyl-formamide solution (8 mL) of **103d** (216 mg, 0.864 mmol) was added 6-Cl-2-H-1-benzopyran-3-carboxylic acid (364 mg, 1.73 mmol), EDC (414 mg, 2.16 mmol), triethylamine (436 mg, 4.32 mmol) and 4-(dimethylamino)pyridine (26 mg, 0.22 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 65% yield. ^{1}H NMR ($CDCl_3$): δ 8.50 (1H, br s), 7.46 (1H, dd, J=8.6, 5.3Hz), 7.18 (1H, dd, J=8.6, 2.5Hz), 7.10-7.00 (2H, m), 6.92-6.85 (2H, m), 6.80 (1H, d, J=8.5Hz), 6.54 (1H, d, J=6.8Hz), 6.27 (1H, br s), 5.08-4.90 (3H, m), 4.36-4.27 (2H, m), 3.38 (2H, d, J=5.3Hz), 1.34-1.25 (3H, m). LCMS (APCI): 443.0 ($M+H^+$).

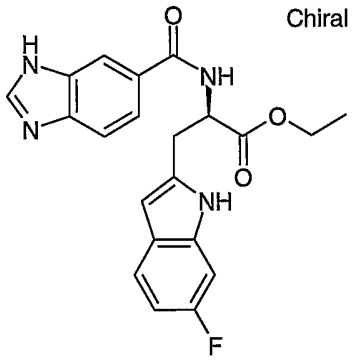
Example 112:



112

To a methanol solution (3 mL) of **111** (250 mg, 0.565 mmol) was added 5% sodium hydroxide (3 mL) at 0°C. The mixture was stirred at room temperature for 4 hours. It was then purified by prep. HPLC to give title compound in 68% yield. ^{1}H NMR (DMSO-d6): δ 12.80 (1H, br), 11.09 (1H, s), 8.56 (1H, d, J = 7.8 Hz), 7.38 (1H, dd, J = 8.6, 5.6 Hz), 7.30 (1H, d, J = 2.5 Hz), 7.26-7.23 (2H, m), 7.07-7.04 (1H, m), 6.86 (1H, d, J = 8.6 Hz), 6.79-6.74 (1H, m), 6.22 (1H, s), 4.86 (2H, s), 4.69-4.64 (1H, m), 3.26 (1H, dd, J = 15.0, 4.7 Hz), 3.18-3.12 (1H, m).
LCMS (APCI): 415.0 ($M+H^+$). Elemental Analysis for ($C_{21}H_{16}ClFN_2O_4 \bullet 0.5H_2O$) calc: C 59.51, H 4.04, N 6.61; found: C 59.35, H 4.17, N 6.46.

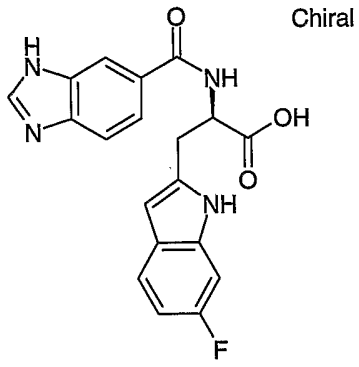
Example 113:



113

To a N, N-dimethyl-formamide solution (7 mL) of **113d** (166 mg, 0.664 mmol) were added 5-benzimidazolecarboxylic acid (215 mg, 1.33 mmol), EDC (318 mg, 1.66 mmol), triethylamine (335 mg, 3.32 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.17 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold saturated ammonium chloride (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% methanol in dichloromethane), the title compound was obtained in 29% yield. ^{1}H NMR (DMSO-d_6): δ 12.69 (1H, d, J=7.3Hz), 11.16 (1H, br s), 8.82 (1H, br s), 8.32 (1H, s), 7.70 (1H, m), 7.38 (1H, dd, J=8.9, 5.6Hz), 7.06 (1H, dd, J=9.9, 1.8Hz), 6.79-6.70 (1H, m), 6.26 (1H, s), 4.81 (1H, q, J=7.6Hz), 4.09 (2H, q, J=6.3Hz), 3.30-3.25 (2H, m), 1.10 (3H, t, J=7.1Hz).
LCMS (APCI): 395.1 ($M+H^+$).

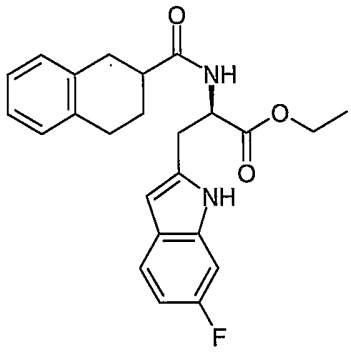
Example 114:



114

To a methanol solution (3 mL) of **113** (73 mg, 0.185 mmol) was added 5% sodium hydroxide (2 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. It was then purified by prep. HPLC to give title compound in 82% yield. ^{1}H NMR (DMSO-d_6): δ 12.5 (1H, br s), 10.98 (1H, s), 8.90 (1H, br s), 8.74 (1H, d, J=7.8Hz), 8.05 (1H, s), 7.72 (1H, d, J=8.5Hz), 7.61 (1H, d, J=8.6Hz), 7.19 (1H, dd, J=8.6, 5.6Hz), 6.88 (1H, dd, J=10.1, 2.7Hz), 6.58 (1H, m), 6.08 (1H, s), 4.68-4.60 (1H, m), 3.20-3.06 (2H, m). LCMS (APCI): 367.1 ($M+H^+$). Elemental Analysis for ($C_{19}H_{15}FN_4O_3$•1TFA•0.75H_2O•0.2ether) calc: C 51.41, H 3.86, N 11.01; found: C 51.71, H 3.88, N 10.83.

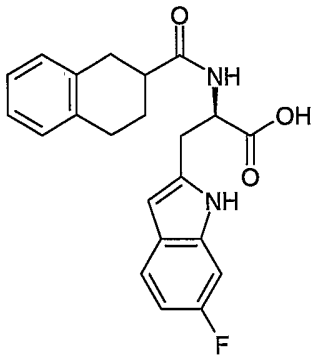
Example 115:



115

To a N, N-dimethyl-formamide solution (7 mL) of **103d** (184 mg, 0.736 mmol) were added 1,2,3,4-tetrahydro-2-naphthoid acid (259 mg, 1.47 mmol), EDC (353 mg, 1.84 mmol), triethylamine (372 mg, 3.68 mmol) and 4-(dimethylamino)pyridine (22 mg, 0.184 mmol). The mixture was stirred at room temperature for overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (20% ethyl acetate in hexane) and, the title compound was obtained in 83% yield. ^{1}H NMR ($CDCl_3$): δ 8.50 (1H, br s), 7.41 (1H, dd, J=8.6, 5.3Hz), 7.12-6.95 (4H, m), 6.84 (1H, m), 6.23 (1H, br d), 4.92 (1H, m), 4.30-4.18 (2H, m), 3.30-3.25 (2H, m), 2.98-2.80 (4H, m), 2.54 (1H, m), 1.26 (3H, m). LCMS (APCI): 409.1 ($M+H^+$).

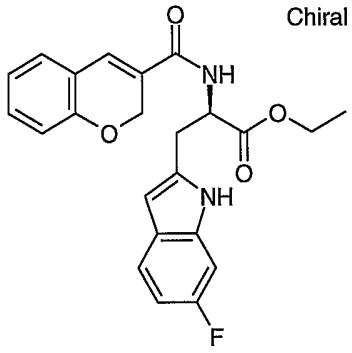
Example 116:



116

To a methanol solution (4 mL) of **115** (242 mg, 0.593 mmol) was added 5% sodium hydroxide (3 mL) at 0°C. The mixture was stirred at room temperature for 4 hours. It was then purified by prep. HPLC to give title compound in 67% yield. ^{1}H NMR (DMSO-d_6): δ 12.76 (1H, br s), 11.10 (1H, s), 8.30 (1H, m), 7.50-7.42 (1H, m), 7.14-6.92 (5H, m), 6.88-6.78 (1H, m), 6.26 (1H, s), 4.68-4.62 (1H, m), 3.25-3.08 (2H, m), 2.76-2.65 (3H, m), 1.96-1.82 (1H, m), 1.65 (1H, m). LCMS (APCI): 381.1 ($M+H^+$). Elemental Analysis for ($C_{22}H_{21}FN_2O_3 \bullet 0.4H_2O$) calc: C 68.17, H 5.67, N 7.23; found: C 67.93, H 5.61, N 7.45.

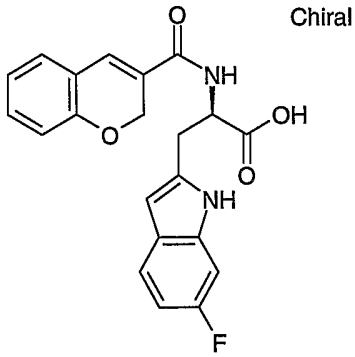
Example 117:



117

To a N, N-dimethyl-formamide solution (8 mL) of **103d** (203 mg, 0.812 mmol) was added 2*H*-chromene-3-carboxylic acid (429 mg, 2.44 mmol), EDC (583 mg, 3.05 mmol), triethylamine (615 mg, 6.09 mmol) and 4-(dimethylamino)pyridine (37 mg, 0.305 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane) and, the title compound was obtained in 60% yield. ^{1}H NMR ($CDCl_3$): δ 8.49 (1H, br s), 7.43 (1H, dd, J=8.9, 5.5Hz), 7.20 (1H, m), 7.05 (1H, dd, J=7.8, 1.7Hz), 7.01 (1H, dd, J=7.2, 2.3Hz), 7.0-6.8 (4H, m), 6.53 (1H, d, J=7.2Hz), 6.24 (1H, br s), 5.01-4.90 (3H, m), 4.30-4.21 (2H, m), 3.35 (1H, d, J=5.3Hz), 1.28 (3H, m). LCMS (APCI): 409.1 ($M+H^+$).

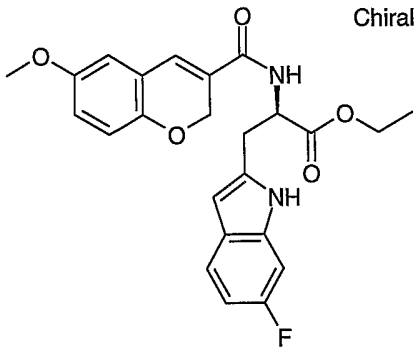
Example 118:



118

To a methanol solution (4 mL) of **117** (198 mg, 0.485 mmol) was added 5% sodium hydroxide (3 mL) at 0°C. The mixture was stirred at room temperature overnight. It was then purified by prep. HPLC to give title compound in 82% yield. ^{1}H NMR (DMSO-d_6): δ 12.79 (1H, br s), 11.11 (1H, s), 8.55 (1H, d, J=7.9Hz), 7.40 (1H, dd, J=8.6, 5.4Hz), 7.31 (1H, s), 7.29-7.19 (2H, m), 7.10-7.04 91H, m), 6.96 (1H, t, J=14.9, 7.2Hz), 6.84 (1H, d, J=7.7Hz), 6.78 (1H, dd, J=11.1, 12.5Hz), 6.23 (1H, s), 4.85 (2H, s), 4.70-4.63 (1H, m), 3.28-3.10 (2H, m). LCMS (APCI): 381.1 (M+H$^+$). Elemental Analysis for ($C_{21}H_{17}FN_2O_4$•0.6H_2O) calc: C 64.48, H 4.69, N 7.16; found: C 64.80, H 4.74, N 6.93.

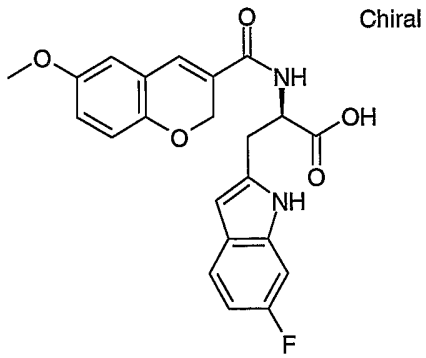
Example 119:



119

To a N, N-dimethyl-formamide solution (8 mL) of **103d** (198 mg, 0.792 mmol) were added 6-methoxy-2*H*-chromene-3-carboxylic acid (492 mg, 2.38 mmol), EDC (569 mg, 2.97 mmol), triethylamine (600 mg, 5.94 mmol) and 4-(dimethylamino)pyridine (36 mg, 0.30 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-30% ethyl acetate in hexane), the title compound was obtained in 95% yield. ^{1}H NMR ($CDCl_3$): δ 8.49 (1H, br s), 7.43 (1H, dd, J=8.7, 5.3Hz), 7.01 (1H, dd, J=9.8, 2.2Hz), 6.89 (1H, m), 6.85 (1H, m), 6.78 (2H, m), 6.60 (1H, m), 6.51 (1H, d, J=6.6Hz), 6.23 (1H, br s), 5.00-4.89 (3H, m), 4.32-4.20 (2H, m), 3.80-3.72 (3H, s), 3.35 (2H, d, J=5.3Hz), 1.28 (3H, m). LCMS (APCI): 439.1 (M+H$^+$).

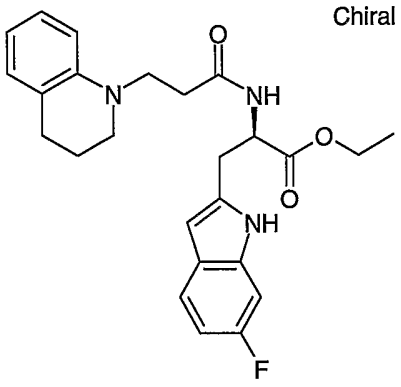
Example 120:



120

To a methanol solution (6 mL) of **119** (325 mg, 0.742 mmol) was added 5% sodium hydroxide (5 mL) at 0°C. The mixture was stirred at room temperature for 4 hours. It was then purified by prep. HPLC to give title compound in 72% yield. ^{1}H NMR (DMSO-D6): δ 12.83 (1H, brs), 11.15 (1H, s), 8.56 (1H, d, J = 7.93 Hz), 7.45 (1H, dd, J = 8.50, 5.48 Hz), 7.32 (1H, s), 7.12 (1H, dd, J = 10.20, 2.27 Hz), 6.93-6.79 (4H, m), 6.28 (1H, s), 4,83 (2H, s), 4.75-4.71 (1H, m), 3.76 (3H, s), 3.47-3.17 (2H, m). LCMS (APCI): 411.1 (M+H$^+$). Elemental Analysis for ($C_{22}H_{19}FN_2O_5$•0.5H_2O) calc: C 63.00, H 4.81, N 6.68; found: C 63.26, H 4.90, N 6.40.

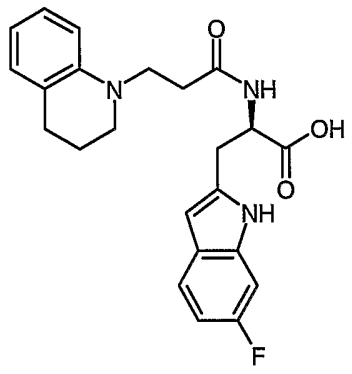
Example 121:



121

To a N, N-dimethyl-formamide solution (10 mL) of **103d** (198 mg, 0.792 mmol) were added 3-(3,4-dihydro-2*H*-quinolin-1-yl)-propionic acid hydrochloride (479 mg, 1.98 mmol), EDC (455 mg, 2.38 mmol), triethylamine (719 mg, 7.13 mmol) and 4-(dimethylamino)pyridine (24 mg, 0.20 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (20-30% ethyl acetate in hexane), the title compound was obtained in 77% yield. LCMS (APCI): 438.2 ($M+H^+$).

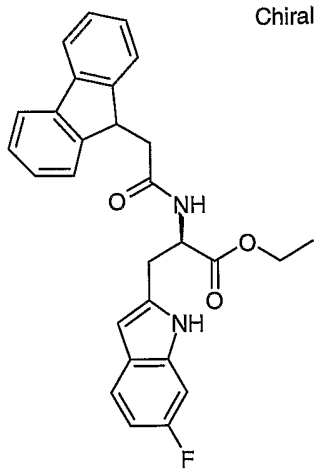
Example 122:



122

To a methanol solution (5 mL) of **121** (260 mg, 0.595 mmol) was added 5% sodium hydroxide (4 mL) at 0°C. The mixture was stirred at room temperature for 1.5 hours. It was then purified by prep. HPLC to give title compound in 86% yield. ^1H NMR (DMSO-d6): δ 10.86 (1H, s), 8.15 (1H, d, J = 8.08 Hz), 7.18 (1H, dd, J = 8.59, 5.56 Hz), 6.86 (1H, dd, J = 10.23, 2.15 Hz), 6.78-6.71 (1H, m), 6.64 (1H, d, J=6.82 Hz), 6.62-6.56 (1H, m), 6.33 (1H, d, J=8.34 Hz), 6.26 (1H, t, J = 7.33 Hz), 5.99 (1H, d, J=1.01 Hz), 4.45-4.37 (1H, m), 3.20 (2H, q, J=6.00 Hz), 3.01-2.76 (4H, m), 2.34-2.24 (2H, m), 2.16-2.09 (2H, m), 1.56-1.45 (2H, m). LCMS (APCI): 410.1 ($M+H^+$). Elemental Analysis for ($C_{23}H_{24}FN_3O_3 \bullet 0.6TFA \bullet 0.5H_2O$) calc: C 59.70, H 5.30, N 8.61; found: C 59.98, H 5.39, N 8.47.

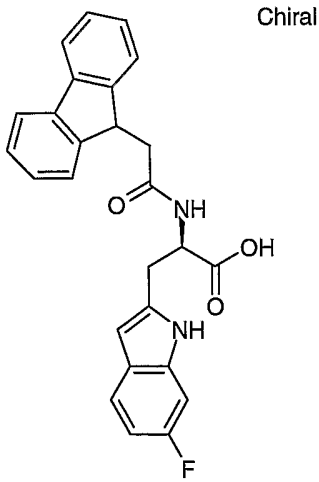
Example 123:



123

To a N, N-dimethyl-formamide solution (6 mL) of **103d** (133 mg, 0.532 mmol) was added (9H-fluoren-9-yl)-acetic acid (149 mg, 0.665 mmol), EDC (255 mg, 1.33 mmol), triethylamine (322 mg, 3.19 mmol) and 4-(dimethylamino)pyridine (16 mg, 0.13 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (20 mL), cold 1M HCl (20 mL), cold saturated sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-30% ethyl acetate in hexane), the title compound was obtained in 36% yield. ^{1}H NMR (DMSO-d_6): δ 11.16 (1H, s), 8.56 (1H, s), 7.82 (1H, t, J=6.8Hz), 7.49 (1H, d, J=7.3Hz), 7.40 (1H, dd, J=8.6, 5.5Hz), 7.36-7.26 (3H, m), 7.21 (1H, t, J=7.6Hz), 7.09 (1H, dd, J=10.1, 2.3Hz), 6.98 (1H, t, J=7.3Hz), 6.22 (1H, s), 4.88-4.80 (1H, m), 4.32-4.29 (1H, m), 4.13 (2H, q, J=7.1Hz), 3.20 (1H, dd, J=15.1, 5.5Hz), 3.07 (1H, dd, J=14.6, 9.6Hz), 2.53 (2H, d, J=7.3Hz), 1.15 (3H, t, J=7.1Hz). LCMS (APCI): 457.1 ($M+H^+$).

Example 124:

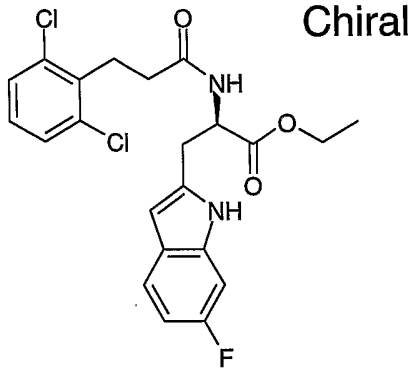


124

To a methanol solution (2 mL) of **123** (84 mg, 0.184 mmol) was added 5% sodium hydroxide (1 mL) at 0°C. The mixture was stirred at room temperature overnight. It was then purified by prep. HPLC to give title compound in 53% yield. ^{1}H NMR (DMSO-d_6): δ 12.86 (1H, br s), 11.14 (1H, s), 8.45 (1H, d, J=7.8Hz), 7.82 (1H, t, J=7.3Hz), 7.54 (1H, d, J=7.4Hz), 7.41 (1H, dd, J=8.6, 5.5Hz), 7.35 (1H, t,

J=7.3Hz), 7.33-7.25 (2H, m), 7.21 (1H, t, J=7.5Hz), 7.10 (1H, dd, J=10.3, 2.3Hz), 6.94 (1H, t, J=7.6Hz), 6.85-6.78 (1H, m), 6.24 (1H, s), 4.88-4.78 (1H, m), 4.32 (1H, d, J=7.6Hz), 3.26 (1H, dd, J=15.2, 4.5Hz), 3.06 (1H, dd, J=15.1, 10.3Hz), 2.54 (2H, m). LCMS (APCI): 429.1 ($M+H^+$). Elemental Analysis for ($C_{26}H_{21}FN_2O_3 \bullet 0.3H_2O$) calc: C 71.97, H 5.02, N 6.46; found: C 72.04, H 5.01, N 6.45.

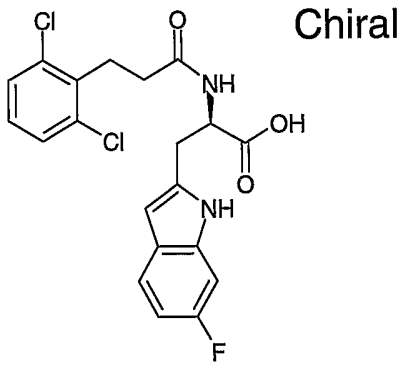
Example 125:



125

To a N, N-dimethyl-formamide solution (3 mL) of **103d** (58 mg, 0.232 mmol) was added 3-(2,6-dichloro-phenyl)-propionic acid (76 mg, 0.348 mmol), EDC (133 mg, 0.696 mmol), triethylamine (164 mg, 1.62 mmol) and 4-(dimethylamino)pyridine (7 mg, 0.058 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (30 mL). The ethyl acetate solution was washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-30% ethyl acetate in hexane), the title compound was obtained in 78% yield. ^{1}H NMR (DMSO-d_6): δ 11.08 (1H, s), 8.43 (1H, d, J=7.6Hz), 7.42 (2H, d, J=8.3Hz), 7.38 (1H, dd, J=8.6, 5.6Hz), 7.28-7.22 (1H, m), 7.05 (1H, dd, J=9.8, 2.3Hz), 6.82-6.72 (1H, m), 6.16 (1H, d, J=1Hz), 4.64-4.56 (1H, m), 4.09-4.00 (2H, m), 3.18-2.96 (4H, m), 2.40-2.25 (2H, m), 1.07 (3H, t, J=7.1Hz). LCMS (APCI): 451.0 ($M+H^+$).

Example 126:

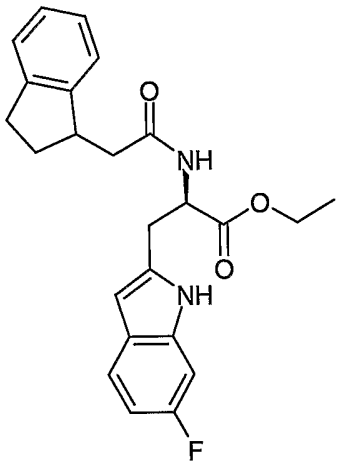


126

To a methanol solution (2 mL) of **125** (79 mg, 0.175 mmol) was added 5% sodium hydroxide (1 mL) at 0°C. The mixture was stirred at room temperature overnight. It was then acidified with 1M HCl and extracted with ethyl acetate (3X20mL). The ethyl acetate extract was concentrated and purified by prep. HPLC to give title compound in 81% yield. ^{1}H NMR (DMSO-d_6): δ 12.73 (1H, s), 11.06 (1H, s), 8.32 (1H, d, J=7.8Hz), 7.44 (1H, s), 7.42 (1H, s), 7.42 (1H, s), 7.39 (1H, dd, J=8.6, 5.5Hz), 7.06 (1H,

dd, J=10.1, 2.2Hz), 6.82-6.72 (1H, m), 6.20 (1H, d, J=1Hz), 4.62-4.55 (1H, m), 3.18 (1H, dd, J=14.7, 5.1 Hz), 3.08-2.95 (3J, m), 2.35-2.28 (2H, m). LCMS (APCI): 423.0 ($M+H^+$).
Elemental Analysis for ($C_{20}H_{17}Cl_2FN_2O_3 \bullet 0.3H_2O \bullet 0.15CH_3CN$) calc: C 56.30, H 4.16, N 6.95; found: C 56.17, H 3.96, N 6.94.

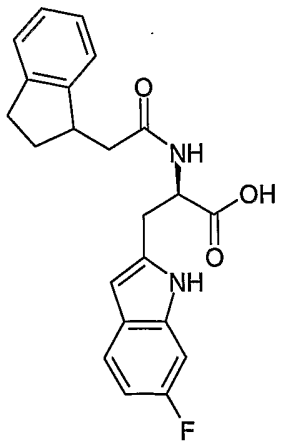
Example 127:



127

To a N, N-dimethyl-formamide solution (3 mL) of **103d** (67 mg, 0.268 mmol) was added 3341-055 (115 mg, 0.653 mmol), EDC (231 mg, 1.21 mmol), triethylamine (271 mg, 2.68 mmol) and 4-(dimethylamino)pyridine (8 mg, 0.067 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (30 mL). The ethyl acetate solution was washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-30% ethyl acetate in hexane), the title compound was obtained in 57% yield. ^{1}H NMR (DMSO-d_6): δ 11.10 (1H, d, J=8.3Hz), 8.44 (1H, d, J=7.8Hz), 7.39 (1H, dd, J=8.3, 5.5Hz), 7.18-7.02 (3H, m), 6.81-6.72 (1H, m), 6.20 (1H, s), 4.69 (1H, m), 4.11-4.05 (2H, m), 3.40-3.34 (1H, m), 3.17 (1H, dd, J=14.9, 5.5Hz), 3.04 (1H, dd, J=14.9, 9.6Hz), 2.80-2.50 (3H, m), 2.20-2.13 (1H, m), 2.10-1.90 (1H, m), 1.62-1.40 (1H, m), 1.11 (3H, t, J=7Hz). LCMS (APCI): 409.1 ($M+H^+$).

Example 128:

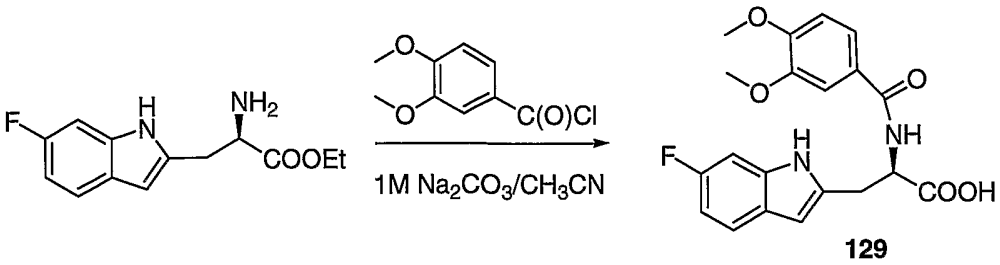


128

To a methanol solution (3 mL) of **127** (60 mg, 0.147 mmol) was added 5% sodium hydroxide (1 mL) at 0°C. The mixture was stirred at room temperature overnight. It was then purified by prep. HPLC to give title compound in 46% yield. ^{1}H NMR (DMSO-d_6): δ 12.83 (1H, s), 11.17 (1H, s), 8.39 (1H, d, J=8.1Hz), 7.48 (1H, dd, J=8.6, 5.6Hz), 7.28-7.10 (4H, m), 7.00-6.80 (3H, m), 6.30 (1H, s), 4.82-4.70

(1H, m), 3.30 (1H, dd, J=14.9, 5Hz), 3.12 (1H, dd, J=15, 9.9Hz), 2.95-2.70 (2H, m), 2.67-2.60 (1H, m), 2.18-2.00 (1H, m), 1.70-1.45 (1H, m). LCMS (APCI): 381.1 ($M+H^+$). HRMS (MALDI) calc for $C_{22}H_{22}N_2O_3F(M+H^+)$ 381.1614; found 381.1612.

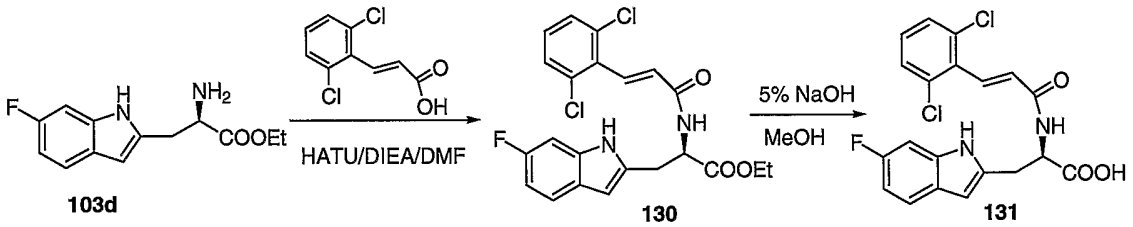
Example 129:



129

To a sodium carbonate solution (1M, 1.5mL) was added the amino ester **103d** (53mg, 0.212mmol), 3,4-Dimethoxybenzoyl chloride (50mg, 0.25mmol) and acetonitrile (1.5mL). The mixture was stirred at 25°C for 12h. Preparative HPLC purification provided 30mg of the title product (37% yield). ^1H NMR (DMSO-*d6*): δ 12.81 (1H, br s), 11.18 (1H, s), 8.66 (1H, d, J=7.9Hz), 7.53 (1H, dd, J=8.4, 2Hz), 7.47-7.40 (2H, m), 7.16-7.09 (1H, m), 7.07 (1H, d, J=8.3Hz), 6.82 (1H, m), 6.31 (1H, s), 4.87-4.82 (1H, m), 3.86 (3H, s), 3.84 (3H, s), 3.40-3.27 (2H, m). LCMS (APCI negative): 386 (M-H). HRMS (MALDI) calc for $C_{20}H_{19}N_2FO_5$ ($M+H^+$) 387.1351; found 387.1359.

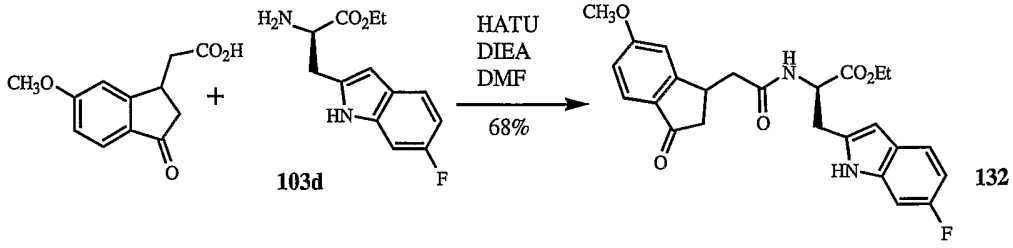
Examples 130 and 131:



103d **130** **131**

To a DMF solution (1mL) of the Aminoester **103d** (75mg, 0.3mmol) was added (2*E*)-3-(2,6-Dichlorophenyl)prop-2-enoic acid (65.1mg, 0.3mmol), diisopropylethylamine (DIEA, 116mg, 0.9mmol) and HATU (114.1mg, 0.3mmol) at 0°C. After 2h at 0°C, the mixture was diluted with EtOAc (25mL). The solution was washed with ice-cooled concentrated potassium carbonate solution (1x25mL) and 5% HCl solution (1x25mL), dried over $MgSO_4$ and concentrated. The residue was dissolved in MeOH (1.5mL). At 0°C, 10% NaOH solution was added. After stirred at 25°C for 12h, the mixture was acidified with ice-cooled 10% HCl solution (pH~2). The suspension was extracted with EtOAc (2x20mL). Combined organic layers were washed with water (1x40mL), dried ($MgSO_4$) and concentrated. Preparative HPLC purification provided 94mg (74% yield) of **131**. ^1H NMR (DMSO-*d6*): δ 11.04 (1H, s), 8.69 (1H, d, J=7.9Hz), 7.49 (1H, s), 7.47 (1H, s), 7.43-7.28 (2H, m), 7.00 (1H, dd, J=10.1, 2.1Hz), 6.75-6.68 (2H, m), 6.16 (1H, s), 4.69-4.63 (1H, m), 3.17 (1H, dd, J=14.9, 5.1Hz), 3.04 (1H, dd, J=15.2, 9.1Hz). LCMS (APCI positive): 421 ($M+H^+$). Elemental Analysis for ($C_{20}H_{15}Cl_2FN_2O_3$•1.55H_2O•0.06EtOAc) calc: C 53.49, H 4.12, N 6.10, Cl 15.60; found: C 53.68, H 3.77, N 6.06; Cl 5.24.

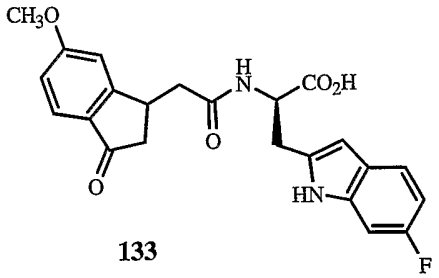
Example 132: Ethyl (2*S*)-2-[(6-fluoro-1*H*-indol-2-yl)methyl]-5-(6-methoxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl)-4-oxopentanoate



103d **132**

Following a similar procedure as example **131**, **132** was synthesized from amine **103d** (0.08g, 0.34 mmol) and 5-methoxy-1-indanone-3-acetic acid (0.08g, 0.34 mmol) to give 0.10g (68%) of an off-white amorphous solid: ^{1}H NMR (DMSO-d_6) mixture of diastereomers δ 11.10-11.09 (1H, m), 8.48-8.46 (1H, m), 7.53-7.50 (1H, m), 7.40-7.36 (1H, m), 7.15-7.13 (1H, m), 7.07-7.04 (1H, m), 6.95 (1H, d, J = 8.4 Hz), 6.80-6.75 (1H, m), 6.17 (1H, s), 4.66-4.63 (1H, m), 4.09-4.03 (2H, m), 3.80, 3.82 diastereomers (3H, s), 3.65-3.55 (1H, m), 3.17-3.12 (1H, m), 3.07-3.03 (1H, m), 2.76-2.61 (2H, m), 2.35-2.18 (2H, m), 1.12-1.06 (3H, m). MS 453 (M+H).

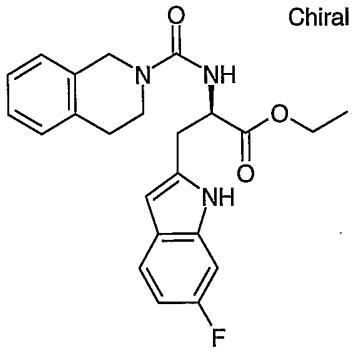
Example 133: (2*S*)-2-[(6-Fluoro-1*H*-indol-2-yl)methyl]-5-(6-methoxy-3-oxo-2,3-dihydro-1*H*-inden-1-yl)-4-oxopentanoic acid



133

Following a similar procedure as example **131**, **133** was synthesized from **112** (0.10g, 0.22 mmol) to give 0.078g (83%) of a tan solid: mp = >100 °C (dec); ^{1}H NMR (DMSO-d_6) mixture of diastereomers: δ 12.69 (1H, br), 11.07, 11.05 (diast., 1H, s), 8.34 (1H, J = 7.8 Hz), 7.52-7.49 (1H, m), 7.40-7.35 (1H, m), 7.14 (1H, s), 7.06-7.03 (1H, m), 6.96-6.92 (1H, m), 6.80-6.75 (1H, m), 6.18 (1H, s), 4.64-4.61 (1H, m), 3.82, 3.79 (diast., 3H, s), 3.60-3.57 (1H, m), 3.21-3.14 (1H, m), 3.05-2.97 (1H, m), 2.74-2.59 (2H, m), 2.34-2.18 (2H, m). HRMS calcd for $C_{23}H_{22}N_2O_5F$ 425.1507 (M+H), found 425.1503. Elemental Analysis for ($C_{23}H_{21}N_2O_5F$•0.5H_2O) calc: C 63.73, H 5.12, N 6.46; found: C 63.82, H 5.14, N 6.16.

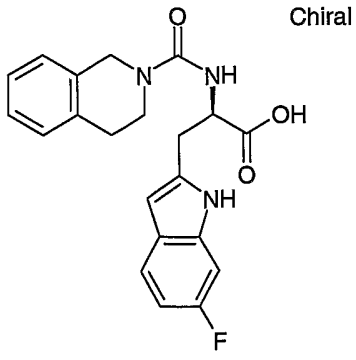
Example 134:



134

To a dichloromethane solution (10 mL) of 1,2,3,4-tetrahydro-isoquinoline (160 mg, 1.20 mmol) at –70°C was added phosgene (20% in toluene, 1.40 mmol) and triethylamine (202 mg, 2.00 mmol). The mixture was slowly warmed to room temperature and stirred for 1 hour. To the reaction mixture were added **103d** (250 mg, 1.00 mmol), triethylamine (149 mg, 1.50 mmol) and 4-(dimethylamino)pyridine (18 mg, 0.15 mmol). The mixture was stirred at room temperature overnight. It was then diluted with dichloromethane (20 mL) and washed with cold 1M HCl (20 mL), cold 1M sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (30-50% ethyl acetate in hexane), the title compound was obtained in 73% yield. ^{1}H NMR ($CDCl_3$): δ 7.43 (1H, dd, J=8.6, 5.3Hz), 7.28-7.10 (4H, m), 7.01 (1H, dd, J=9.9, 2.6Hz), 6.90-6.80 (1H, m), 4.91 (1H, m), 4.60-4.50 (2H,m), 4.30-4.20 (2H, m), 3.68-3.56 (2H, m), 3.40-3.30 (2H, m), 2.88 (2H, m), 1.28 (3H, t, J=7Hz). LCMS (APCI): 410.1 ($M+H^+$).

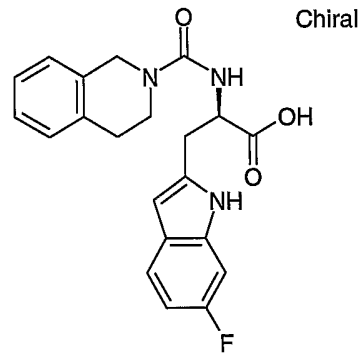
Example 135:



135

To a methanol solution (4 mL) of **134** (290 mg, 0.709 mmol) was added 5% sodium hydroxide (4 mL) at 0°C. The mixture was stirred at room temperature for 3 hours. Methanol was evaporated and the residue was extracted with ethyl acetate (3 X 20 mL). The combined ethyl acetate extract was washed with brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5 to 10% methanol in dichloromthane) and prep. HPLC purification, the title compound was obtained in 44% yield. ^{1}H NMR (DMSO-d6): δ 12.51 (1H, br), 11.04 (1H, s), 7.35 (1H, dd, J = 8.5, 5.7 Hz), 7.15-7.09 (4H, m), 7.03 (1H, dd, J = 10.0, 1.9 Hz), 6.79-6.73 (2H, m), 6.19 (1H, s), 4.45-4.40 (3H, m), 3.56-3.49 (2H, m), 3.19-3.06 (2H, m), 2.76-2.64 (2H, m). LCMS (APCI): 382.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{20}FN_3O_3 \bullet 0.55H_2O$) calc: C 64.45, H 5.44, N 10.74; found: C 64.67, H 5.35, N 10.74.

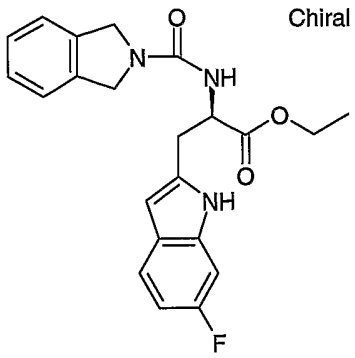
Example 136:



136

To a methanol solution (4 mL) of **135** (290 mg, 0.709 mmol) was added 5% sodium hydroxide (4 mL) at 0°C. The mixture was stirred at room temperature for 3 hours. Methanol was evaporated and the residue was extracted with ethyl acetate (3 X 20 mL). The combined ethyl acetate extract was washed with brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5 to 10% methanol in dichloromthane) and prep. HPLC purification, the title compound was obtained in 44% yield. ^{1}H NMR (DMSO-d6): δ 12.51 (1H, br), 11.04 (1H, s), 7.35 (1H, dd, J = 8.5, 5.7 Hz), 7.15-7.09 (4H, m), 7.03 (1H, dd, J = 10.0, 1.9 Hz), 6.79-6.73 (2H, m), 6.19 (1H, s), 4.45-4.40 (3H, m), 3.56-3.49 (2H, m), 3.19-3.06 (2H, m), 2.76-2.64 (2H, m). LCMS (APCI): 382.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{20}FN_3O_3 \bullet 0.55H_2O$) calc: C 64.45, H 5.44, N 10.74; found: C 64.67, H 5.35, N 10.74.

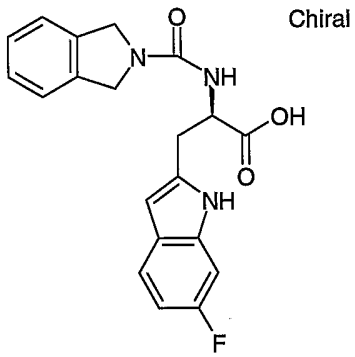
Example 137:



137

To a dichloromethane solution (8 mL) of phosgene (769 uL, 20% in toluene, 1.45 mmol) at –70°C was added triethylamine (234 mg, 2.32 mmol) and isoindoline (138 mg, 1.16 mmol). The mixture was slowly warmed to room temperature and stirred for 1 hour. To the reaction mixture were added **103d** (245 mg, 0.980 mmol), triethylamine (147 mg, 1.45 mmol) and 4-(dimethylamino)pyridine (18 mg, 0.15 mmol). The mixture was stirred at room temperature for 72h. It was then diluted with ethyl acetate (30 mL) and washed with cold 1M HCl (20 mL), cold 1M sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (20-40% ethyl acetate in hexane), the title compound was obtained in 57% yield. ^{1}H NMR ($CDCl_3$): δ 7.44 (1H, dd, J=8.6, 5.3Hz), 7.4-7.2 (4H, m), 7.03 (1H, dd, J=9.8, 2.2Hz), 6.86 (1H, m), 4.98 (1H, m), 4.71 (4H, m), 4.25 (2H, m), 3.37 (2H, m), 1.28 (3H, t, J=7Hz). LCMS (APCI): 396.1 ($M+H^+$).

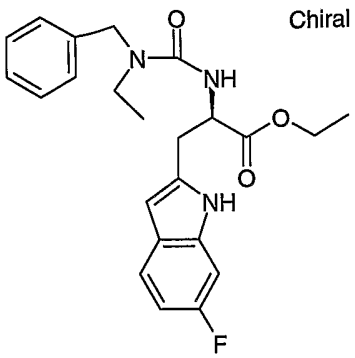
Example 138:



138

To a methanol solution (3 mL) of **137** (217 mg, 0.549 mmol) was added 5% sodium hydroxide (3 mL) at 0°C. The mixture was stirred at room temperature overnight. Methanol was evaporated and the residue was extracted with ethyl acetate (3 X 20 mL). The combined ethyl acetate extract was washed with brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5 to 10% methanol in dichloromethane) and prep. HPLC purification, the title compound was obtained in 35% yield. ^{1}H NMR (DMSO-d6): δ 12.59 (1H, br), 11.05 (1H, s), 7.37 (1H, dd, J = 8.6, 5.6 Hz), 7.33-7.25 (4H, m), 7.05 (1H, dd, J = 10.0, 2.1 Hz), 6.79-6.72 (1H, m), 6.56 (1H, d, J = 8.1 Hz), 6.23 (1H, s), 4.63-4.45 (5H, m), 3.24-3.13 (2H, m). LCMS (APCI): 368.1 ($M+H^+$). Elemental Analysis for ($C_{20}H_{18}FN_3O_3 \bullet 0.3H_2O$) calc: C 64.44, H 5.03, N 11.27; found: C 64.23, H 4.87, N 11.22.

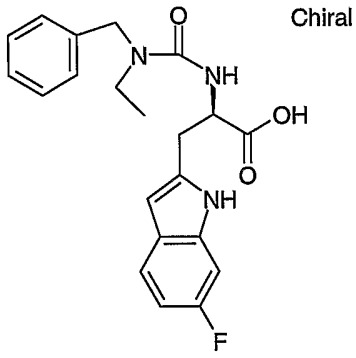
Example 139:



139

To a dichloromethane solution (10 mL) of triethylamine (202 mg, 2.00 mmol) at –70°C was added phosgene (740 uL, 20% in toluene, 1.40 mmol) and N-ethylbenzylamine (162 mg, 1.20 mmol). The mixture was slowly warmed to room temperature and stirred for 1 hour. To the reaction mixture were added **103d** (200 mg, 0.800 mmol), triethylamine (162 mg, 1.60 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol). The mixture was stirred at room temperature for 72h. It was then diluted with dichloromethane (30 mL) and washed with cold 1M HCl (20 mL), cold 1M sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (20-30% ethyl acetate in hexane), the title compound was obtained in 70% yield. ^{1}H NMR ($CDCl_3$): δ 7.37 (1H, dd, J=8.6, 5.6Hz), 7.30-7.20 (4H, m), 7.17 (1H, dd, J=7.1, 3.3Hz), 6.94 (1H, dd, J=9.8, 2.3Hz), 6.81 (1H, m), 4.86 (1H, m), 4.42 (2H, s), 4.22-4.12 (2H, m), 3.36-3.18 (4H, m), 1.25 (3H, m). LCMS (APCI): 412.1 ($M+H^+$).

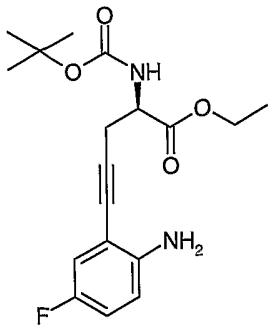
Example 140:



140

To a methanol solution (4 mL) of **139** (242 mg, 0.593 mmol) was added 5% sodium hydroxide (3 mL) at 0°C. The mixture was stirred at room temperature for 3 hours. It was then purified by prep. HPLC to give title compound in 72% yield. ^{1}H NMR (DMSO-d_6): δ 12.62 (1H, br s), 11.09 (1H, s), 7.44 (1H, dd, J=8.3, 5.5Hz), 7.27-7.10 (7H, m), 6.88-6.80 (1H, m), 6.61 (1H, d, J=8.3Hz), 6.24 (1H, s), 4.60-4.50 (1H, m), 4.43 (2H, s), 3.26-3.13 (4H, m), 0.95 (3H, t, J=6.8Hz). LCMS (APCI): 384.1 ($M+H^+$). Elemental Analysis for ($C_{21}H_{22}FN_3O_3$•0.5H_2O) calc: C 64.27, H 5.91, N 10.71; found: C 64.16, H 5.78, N 10.44.

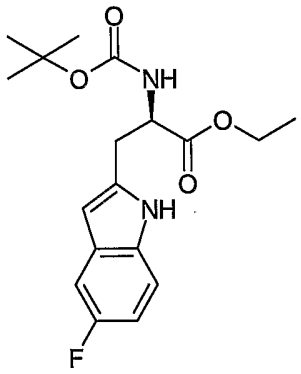
Example 141:



141

To a N, N-dimethyl-formamide solution (55 mL) of **103a** (4.82 g, 20 mmol) was added 4-fluoro-2-bromoaniline (4.18 g, 22 mmol), diisopropylamine (18 mL), dichlorobis(triphenylphosphine)-palladium (II) (618 mg, 0.88 mmol) and CuI (334 mg, 1.76 mmol). The mixture was stirred at 90°C for 2h after three circles of nitrogen/vacuum flush. DMF was removed by vacuum and the residue was diluted with dichloromethane (100 mL). It was then washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 26% yield (1.8g). ^{1}H NMR ($CDCl_3$): (a mixture of rotamers) δ 7.18-7.10 (1H, m), 6.40-6.30 (2H, m), 4.6-4.5 (1H, m), 4.38 (2H, br s), 4.30-4.18 (2H, m), 2.97 (2H, d, J=4.8Hz), 1.44 and 1.42 (9H, s), 1.29 (3H, t, J=7.1Hz).

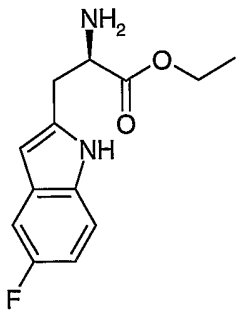
Example 142:



142

To a N, N-dimethyl-formamide solution (10 mL) of **141** (1.6 g, 4.57 mmol) was added CuI (0.869 g, 4.57 mmol). The mixture was stirred at 150°C for 3.5 hours after three circles of nitrogen/vacuum flush. It was filtered through a pad of celite. The filtrate was evaporated and the residue was diluted with dichloromethane (100 mL). It was then washed with water (2X50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 44% yield (0.7g). ^{1}H NMR ($CDCl_3$): δ 8.38 (1H, br s), 7.21 (1H, dd, J=8.8, 4.5Hz), 7.17 (1H, dd, J=9.6, 2.3Hz), 6.87 (1H, td, J=9.1, 2.6Hz), 6.23 (1H, br s), 5.15 (1H, br s), 4.61 (1H, m), 4.26-4.16 (2H, m), 3.26 (2H, br d, J=5.3Hz), 1.56 (9H, s), 1.24 (3H, t, J=7.3Hz).

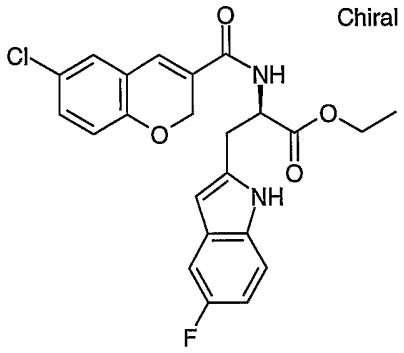
Example 143:



143

To a dichloromethane solution (8 mL) of **142** (660 mg, 1.89 mmol) was added trifluoroacetic acid (4 mL) at 0°C. The mixture was stirred at room temperature for 1 hour. It was then concentrated and the residue was diluted with ethyl acetate (40 mL). It was washed with cold 1M sodium bicarbonate (2X30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (3% methanol in dichloromethane), the title compound was obtained in 66% yield. ^{1}H NMR (DMSO-d_6): δ 11.01 (1H, br s), 7.27 (1H, dd, J=8.9, 4.9Hz), 7.16 (1H, dd, J=10.2, 2.5Hz), 6.83 (1H, td, J=9.4, 2.7Hz), 6.15 (1H, s), 4.05 (2H, q, J=7Hz), 3.69 (1H, t, J=7.3Hz), 3.30 (1H, dd, J=14.5, 6.2Hz), 2.90 (1H, dd, J=14.5, 7.3Hz), 1.11 (3H, t, J=7.2Hz). LCMS (APCI): 251.1 ($M+H^+$).

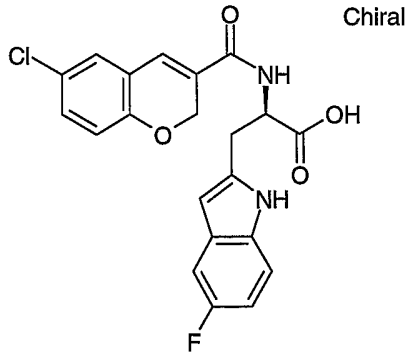
Example 144:



144

To a N, N-dimethyl-formamide solution (6 mL) of **143** (167 mg, 0.668 mmol) was added 6-Cl-2-H-1-benzopyran-3-carboxylic acid (281 mg, 1.34 mmol), EDC (320 mg, 1.67 mmol), triethylamine (338 mg, 3.34 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.17 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 71% yield. ^{1}H NMR (DMSO-d_6): δ 11.24 (1H, br s), 8.83 (1H, d, J=7.3Hz), 7.43 (1H, d, J=2.6Hz), 7.41-7.33 (3H, m), 7.29 (1H, dd, J=10.2, 2.6Hz), 6.98 (1H, d, J=8.5Hz), 6.95 (1H, td, J=9.6, 2.5Hz), 6.63 (1H, s), 4.98 (2H, s), 4.80 (2H, br q), 4.19 (2H, q, J=5.8Hz), 3.50-3.30 (3H, t, J=7Hz). LCMS (API-ES): 443.0 ($M+H^+$).

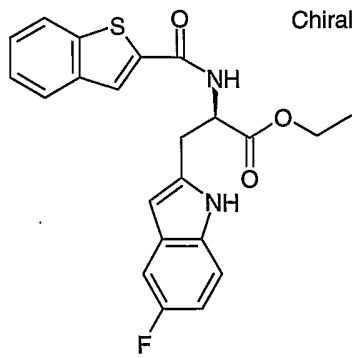
Example 145:



145

To a methanol solution (4 mL) of **144** (210 mg, 0.474 mmol) was added 5% sodium hydroxide (3 mL) at 0°C. The mixture was stirred at room temperature for 3 hours. It was then purified by prep. HPLC to give title compound in 30% yield. ^{1}H NMR (DMSO-d_6): δ 12.84 (1H, br s), 11.12 (1H, s), 8.60 (1H, d, J=7.9Hz), 7.33 (1H, d, J=2.6Hz), 7.30-7.24 (4H, m), 7.19 (1H, dd, J=10.1, 2.5Hz), 6.88 (1H, d, J=8.6Hz), 6.84 (1H, td, J=9.3, 2.5Hz), 6.23 (1H, d, J=1.2Hz), 4.88 (2H, s), 4.73-4.65 (1H, m), 3.29 (1H, dd, J=14.9, 4.8Hz), 3.19 (1H, dd, J=15.1, 10.1Hz). LCMS (APCI): 415.0 ($M+H^+$). Elemental Analysis for ($C_{21}H_{16}ClFN_2O_4 \bullet 0.85H_2O$) calc: C 58.64, H 4.15, N 6.51; found: C 58.93, H 4.18, N 6.19.

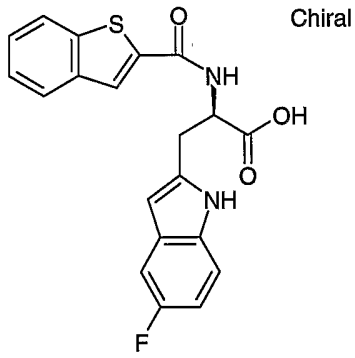
Example 146:



146

To a dichloromethane solution (5 mL) of **143** (145 mg, 0.580 mmol) was added benzo[B]thiophene-2-carbonyl chloride (171 mg, 0.870 mmol), triethylamine (176 mg, 1.74 mmol) and 4-(dimethylamino)pyridine (7 mg, 0.058 mmol). The mixture was stirred at room temperature for 3.5 hours. It was then evaporated. The residue was dissolved in ethyl acetate (30 mL). The ethyl acetate solution was washed with water (20 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 94% yield.
^{1}H NMR ($CDCl_3$): δ 7.66-7.56 (3H, m), 7.26-7.15 (1H, m), 7.03-6.95 (1H, m), 6.72-6.61 (2H, m), 4.89-4.80 (1H, m), 4.14-3.99 (2H, m), 3.27-3.18 (2H, m), 1.13-1.01 (3H, m).
LCMS (API-ES): 411.1 ($M+H^+$).

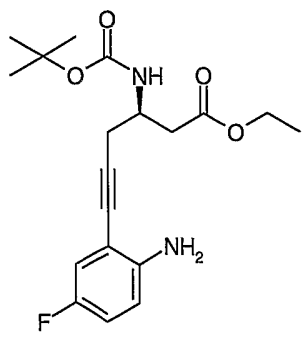
Example 147:



147

To a methanol solution (3 mL) of **146** (76 mg, 0.185 mmol) was added 5% sodium hydroxide (2 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. It was then purified by prep. HPLC to give title compound in 30% yield. ^{1}H NMR (DMSO-d_6): δ 11.21 (1H, br s), 8.46 (1H, br s), 8.01 (1H, s), 7.9-7.85 (1H, m), 7.80 (1H, d, J=6.9Hz), 7.30 (2H, m), 7.14 (1H, dd, J=8.6, 4.7Hz), 7.00 (1H, dd, J=10.1, 2.3Hz), 6.65 (1H, td, J=9.1, 2.2Hz), 6.10 (1H, s), 4.42 (1H, br s), 3.4-3.2 (2H, m). LCMS (APCI): 383.0 ($M+H^+$). HRMS (MALDI) calc for $C_{20}H_{16}N_2O_3FS(M+H^+)$ 383.0866; found 383.0874.

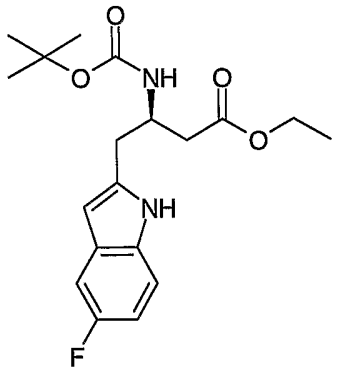
Example 148:



148

To a N, N-dimethyl-formamide solution (10 mL) of ethyl (3*R*)-3-[(*tert*-butoxycarbonyl)amino]hex-5-ynoate (1.26 g, 4.94 mmol) was added 4-fluoro-2-iodoaniline (1.29 g, 5.44 mmol), diisopropylamine (15 mL), dichlorobis(triphenylphosphine)-palladium (II) (76 mg, 0.109 mmol) and CuI (31 mg, 0.163 mmol). The mixture was stirred at 25°C for 15h after three circles of nitrogen/vacuum flush. DMF was removed by vacuum and the residue was diluted with EtOAc (75 mL). It was then washed with NH4Cl solution (1x50 mL) and brine (2x50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (12% ethyl acetate in hexane), the title compound was obtained in 88% yield (1.58g). ^{1}H NMR ($CDCl_3$): δ 6.95 (1H, m), 6.84 (1H, m), 6.64 (1H, m), 5.26 (1H, br s), 4.22-4.10 (3H, m), 2.82-2.60 (4H, m), 1.44 (9H, s), 1.27 (3H, t, J=7.1Hz).

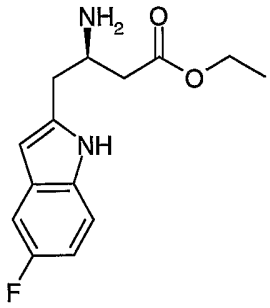
Example 149:



149

To a N, N-dimethyl-formamide solution (10 mL) of **148** (1.4 g, 3.85 mmol) was added CuI (0.877 g, 4.61 mmol). The mixture was stirred at 150°C for 2 hours after three circles of nitrogen/vacuum flush. It was filtered through a pad of celite. The filtrate was evaporated and the residue was diluted with dichloromethane (100 mL). It was then washed with water (2X50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 56% yield (0.788g). ^{1}H NMR ($CDCl_3$): δ 8.67 (1H, br s), 7.21 (1H, dd, J=8.8, 4.5Hz), 7.16 (1H, dd, J=9.6, 2.5Hz), 6.87 (1H, td, J=9.3, 2.5Hz), 6.24 (1H, s), 5.10 (1H, br s), 4.23 (1H, m), 4.18 (2H, q, J=7.1Hz), 3.10-2.95 (2H, m), 2.60-2.45 (2H, m), 1.41 (9H, s), 1.28 (3H, t, J=7.1Hz).

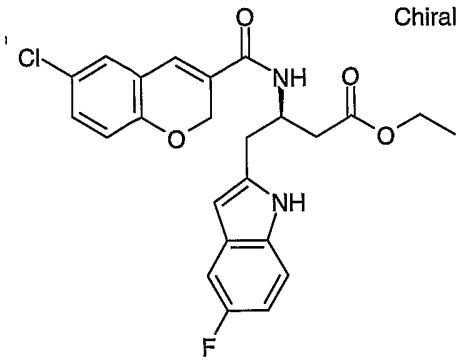
Compound 150a:



150a

To a dichloromethane solution (16 mL) of **149** (780 mg, 2.14 mmol) was added trifluoroacetic acid (4 mL) at 0°C. The mixture was stirred at room temperature for 1 hour and 45 minutes. It was then concentrated and the residue was diluted with ethyl acetate (40 mL). It was then washed with cold 1M sodium bicarbonate (2X50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated to give the crude title compound in 92% yield. ^{1}H NMR (CD_3OD): δ 11.05 (1H, s), 7.27 (1H, dd, J=8.8, 4.8Hz), 7.16 (1H, dd, J=10.1, 2.5Hz), 6.82 (1H, td, J=9.6, 2.5Hz), 6.17 (1H, s), 4.01 (2H, q, J=7.1Hz), 3.49-3.45 (1H, m), 2.79 (2H, d, J=6.8Hz), 2.43 (1H, dd, J=15.7, 4.8Hz), 2.29 (1H, dd, J=15.5, 8.1Hz), 1.14 (3H, t, J=7.1Hz).

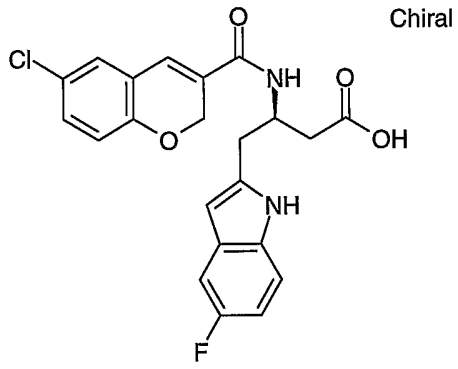
Example 151:



151

To a N, N-dimethyl-formamide solution (5 mL) of **150a** (130 mg, 0.492 mmol) was added 6-Cl-2-H-1-benzopyran-3-carboxylic acid (207 mg, 0.985 mmol), EDC (236 mg, 1.23 mmol), triethylamine (248 mg, 2.46 mmol) and 4-(dimethylamino)pyridine (15 mg, 0.12 mmol). The mixture was stirred at room temperature for 72h. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold 1M HCl (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (15-30% ethyl acetate in hexane), the title compound was obtained in 60% yield. ^1H NMR (CD_3OD): δ 10.99 (1H, br s), 8.15 (1H, d, J=8.1Hz), 7.23-7.13 (3H, m), 7.08 (1H, dd, J=10.2, 2.6Hz), 7.04 (1H, s), 6.77 (1H, d, J=8.6Hz), 6.73 (1H, td, J=9.4, 2.5Hz), 6.09 (1H, d, J=1Hz), 4.46 (1H, q, J=7Hz), 3.94-3.87 (2H, m), 2.90 (1H, dd, J=14.6, 7.1Hz), 2.82 (1H, dd, J=14.7, 6.6Hz), 2.45 (1H, d, J=7.1Hz), 2.40 (6H, m), 1.03 (3H, t, J=7.1Hz). LCMS (APCI): 457.1 ($M+H^+$).

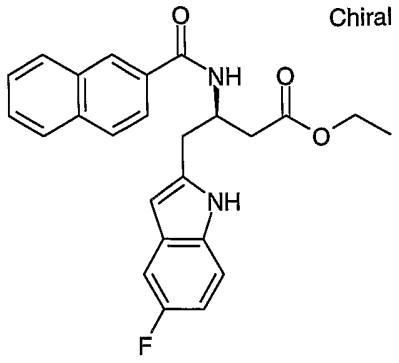
Example 152:



152

To a methanol solution (3 mL) of **151** (130 mg, 0.285 mmol) was added 5% sodium hydroxide (3 mL). The mixture was stirred at room temperature for 2 hours. It was then acidified with 1M HCl. Methanol was evaporated and the water phase was extracted with ethyl acetate (3 X 10 mL). The combined ethyl acetate extract was washed with brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane), the title compound was obtained in 82% yield. ^1H NMR (DMSO-d_6): δ 11.23 (1H, s), 8.44 (1H, d, J=7.5 Hz), 7.30-7.13 (4H, m), 7.15-7.05 (2H, m), 6.80 (1H, s), 6.78 (1H, s), 6.74 (1H, td, J=9.5, 2.5Hz), 6.10 (1H, s), 4.83 (2H, s), 4.43 (1H, q, J=7Hz), 2.92 (2H, m), 2.29 (2H, m). LCMS (APCI): 429.0 ($M+H^+$). Elemental Analysis for ($C_{22}H_{18}ClFN_2O_4 \bullet 1.2H_2O \bullet 0.2EtOAc$) calc: C 58.50, 4.74, N 5.98; found: C 58.78, H 4.51, N 5.69.

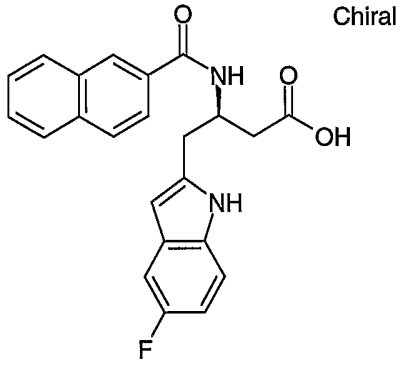
Example 153:



153

To an acetonitrile/water solution (2.5 mL/2.5 mL) of **150a** (130 mg, 0.492 mmol) were added 2-naphthoyl chloride (117 mg, 0.616 mmol) and sodium carbonate (261 mg, 2.46 mmol). The mixture was stirred at room temperature for 72h. It was then acidified with 1M HCl. Acetonitrile was evaporated and the water phase was extracted with ethyl acetate (3 X 10 mL). The combined ethyl acetate extract was washed with brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography purification (15-30% ethyl acetate in hexane), the title compound was obtained in 90% yield. ^{1}H NMR (DMSO-d_6): δ 11.13 (1H, br s), 8.60 (1H, m), 8.36 (1H, s), 8.14-7.90 (4H, m), 7.86 (1H, dd, J=8.6, 1.7Hz), 7.70-7.50 (3H, m), 7.26 (1H, dd, J=8.7, 4.7Hz), 7.15 (1H, dd, J=10, 2.5Hz), 6.81 (1H, td, J=9.4, 2.4Hz), 6.22 (1H, d, J=1.1Hz), 4.74 (1H, q, J=6.4Hz), 3.99 (1H, q, J=7.1Hz), 3.11 (1H, dd, J=14.8, 7.7Hz), 2.99 (1H, dd, J=14.5, 6.4 Hz), 2.71-2.57 (2H, m), 1.09 (3H, t, J=7.2Hz). LCMS (APCI): 419.1 ($M+H^+$).

Example 154:

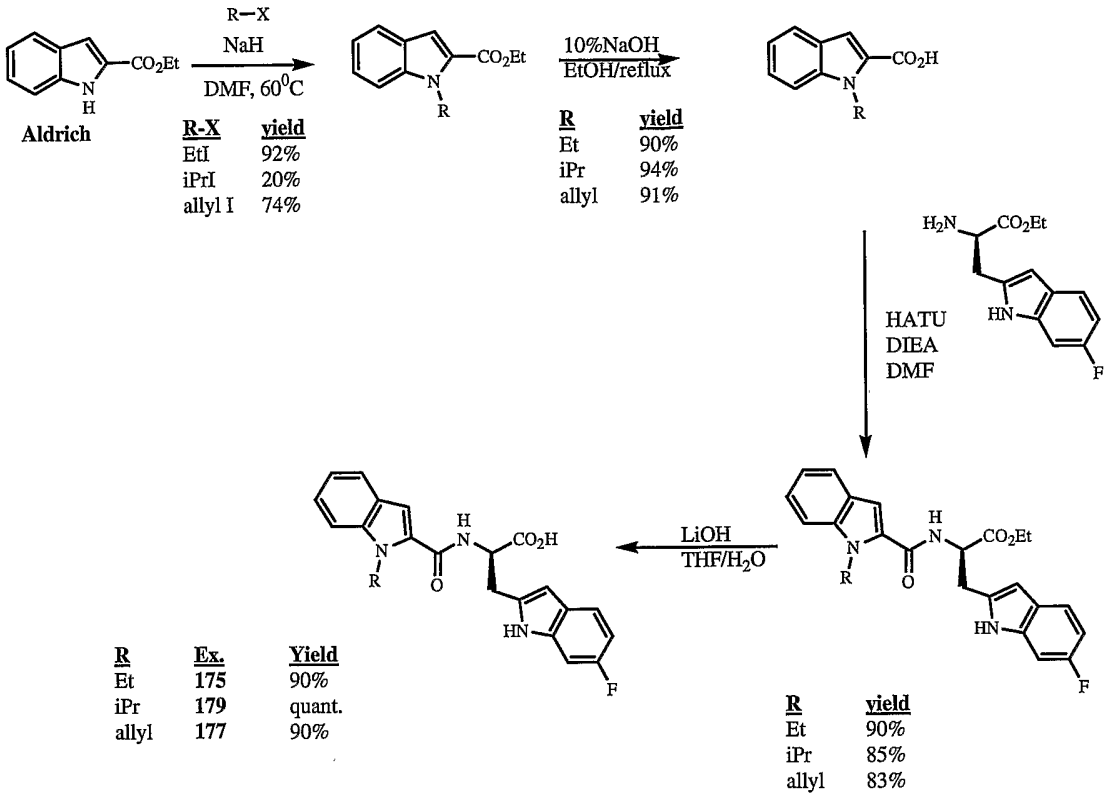


154

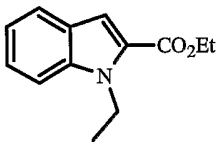
To a methanol solution (4 mL) of **153** (180 mg, 0.431 mmol) was added 5% sodium hydroxide (3 mL). The mixture was stirred at room temperature for 48h. It was then acidified with 1M HCl. Methanol was evaporated and the water phase was extracted with ethyl acetate (3 X 10 mL). The combined ethyl acetate extract was washed with brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane), the title compound was obtained in 52% yield. ^{1}H NMR (DMSO-d_6): δ 12.11 (1H, br s), 11.13 (1H, s), 8.58 (1H, d, J=8.3Hz), 8.39 (1H, s), 8.05-7.92 (3H, m), 7.89 (1H, dd, J=8.5, 1.5Hz), 7.60 (2H, m), 7.27 (1H, dd, J=8.6, 4.5Hz), 7.16 (1H, dd, J=10.2, 2.5Hz), 6.82 (1H, td, J=9.4, 2.7Hz), 6.23 (1H, dd, J=1.1Hz), 4.72 (1H, m), 3.19-2.97 (2H, m), 2.69-2.50 (2H, m). LCMS (APCI): 391.1 ($M+H^+$).

Elemental Analysis for ($C_{23}H_{19}FN_2O_3 \bullet 0.4H_2O \bullet 0.1$EtOAc) calc: C 69.15, 5.11, N 6.89; found: C 9.38, H 5.26, N 6.89.

Synthesis of Examples 155-191



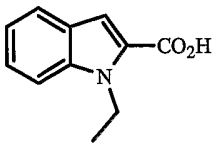
Compound 155a: Ethyl 1-ethyl-1*H*-indole-2-carboxylate



155a

Sodium hydride (60%, 0.12g, 2.93 mmol) was placed in the flask, washed with hexane, and dried. Dimethylformamide (9.0 mL) was added, and the flask placed in an ice bath. Ethyl indole-2-carboxylate (0.50g, 2.66 mmol) dissolved in DMF (6.0 mL) was added, and the reaction stirred at room temperature for 30 minutes. Iodoethane (0.30 mL, 3.73 mmol) dissolved in DMF (1.0 mL) was added, and the reaction heated to 100°C for one hour. The reaction was poured into ice water, and the product was extracted with diethyl ether. The organic phase was separated, washed with water and brine, dried ($MgSO_4$), and concentrated to give 0.53g (92%) of a clear oil: R_f = 0.31 (10% EtOAc/hexane); ^1H NMR ($CDCl_3$): 7.67 (1H, d, J = 8.1 Hz), 7.40 (1H, d, J = 7.6 Hz), 7.35-7.31 (1H, m), 7.30 (1H, s), 7.15-7.11 (1H, m), 4.62 (2H, q, J = 7.0 Hz), 4.37 (2H, q, J = 7.0 Hz), 1.42-1.37 (6H, m). See *J. Med. Chem.* 31, 944 (1988).

Compound 155b: 1-Ethyl-1*H*-indole-2-carboxylic acid

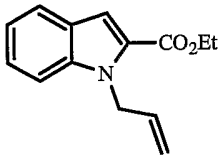


155b

Ester **155a** (0.53g, 2.42 mmol) was refluxed in 10% NaOH (4.0 mL) and ethanol (8.0 mL) for one hour. The ethanol was removed *in vacuo*, and the water acidified to pH = 2 with 10% HCl. The resulting solids were filtered, washed with water, and dried to give 0.41g (90%) of a white solid: ^1H

NMR ($CDCl_3$): δ 7.71 (1H, d, J = 8.1 Hz), 7.47 (1H, s), 7.43-7.35 (2H, m), 7.18-7.14 (1H, m), 4.64 (2H, q, J = 7.1 Hz), 1.42 (3H, t, J = 7.1 Hz). See *Tetrahedron* 45, 3351 (1989).

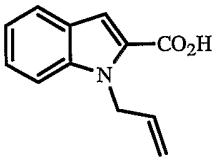
Compound 155c: Ethyl 1-allyl-1*H*-indole-2-carboxylate



155c

Following the procedure for making **155a**, **155c** was synthesized from ethyl indole-2-carboxylate (0.51g, 2.71 mmol) and allyl iodide. The product was purified by flash silica gel chromatography (3% EtOAc/hexane) to remove the unreacted starting material to afford 1.03g (74%) of a clear oil: R_f = 0.13 (3% EtOAc/hexane); ^1H NMR ($CDCl_3$): δ 7.68 (1H, d, J = 8.1 Hz), 7.37-7.30 (3H, m), 7.16-7.12 (1H, m), 6.05-5.95 (1H, m), 5.23-5.21 (2H, m), 5.09 (1H, dd, J = 10.4, 1.3 Hz), 4.89 (1H, dd, J = 17.1, 1.5 Hz), 4.36 (2H, q, J = 7.1 Hz), 1.39 (3H, t, J = 7.1 Hz). See *J. Org .Chem.* 59, 1418 (1994).

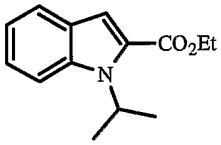
Compound 155d: 1-Allyl-1*H*-indole-2-carboxylic acid



155d

Ester **155c** (1.02g, 4.48 mmol) was refluxed in 10% NaOH (7.0 mL) and ethanol (14.0 mL) for one hour. The ethanol was removed *in vacuo*, and the water acidified to pH = 2 with 10% HCl. The resulting solids were filtered, washed with water, and dried to give 0.82g (91%) of a white solid: ^1H NMR ($CDCl_3$): δ 7.71 (1H, d, J = 8.1 Hz), 7.49 (1H, s), 7.39-7.34 (2H, m), 7.19-7.15 (1H, m), 6.06-5.96 (1H, m), 5.24-5.22 (2H, m), 5.11 (1H, dd, J = 10.4, 1.3 Hz), 4.91 (1H, dd, J = 17.1, 1.3 Hz). See *J. Org .Chem.* 59, 1418 (1994).

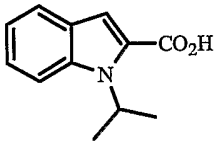
Compound 155e: Ethyl 1-isopropyl-1*H*-indole-2-carboxylate



173e

Following the procedure for making **155a**, **155e** was synthesized from ethyl indole-2-carboxylate (0.51g, 2.71 mmol) and 2-iodopropane. The product was purified by flash silica gel chromatography (3% EtOAc/hexane) to remove the unreacted starting material to afford 0.13g (20%) of a brown oil: R_f = 0.16 (3% EtOAc/hexane); ^1H NMR ($CDCl_3$): δ 7.66 (1H, d, J = 8.1 Hz), 7.61 (1H, d, J = 8.6 Hz), 7.29-7.24 (2H, m), 7.13-7.09 (1H, m), 5.80 (1H, hept, J = 7.1 Hz), 4.35 (2H, q, J = 7.1 Hz), 1.64 (6H, d, J = 7.0 Hz), 1.40 (3H, t, J = 7.1 Hz).

Compound 155f: 1-Isopropyl-1*H*-indole-2-carboxylic acid

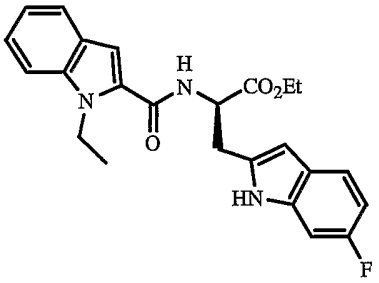


155f

Ester **155e** (0.12g, 0.53 mmol) was refluxed in 10% NaOH (1.0 mL) and ethanol (2.0 mL) for one hour. The ethanol was removed *in vacuo*, and the water acidified to pH = 2 with 10% HCl. The product was extracted into EtOAc in two portions. The organic layers were combined, washed successively with water and brine, dried ($MgSO_4$), and concentrated to give 0.10g (94%) of a white amorphous solid: mp = 117 °C ; ^1H NMR ($CDCl_3$): δ 7.70 (1H, d, J = 7.9 Hz), 7.63 (1H, d, J = 8.6

Hz), 7.44 (1H, s), 7.33-7.29 (1H, m), 7.15-7.11 (1H, m), 5.82 (1H, hept, J = 7.1 Hz), 1.66 (6H, d, J = 7.1 Hz). MS 204 (M+H). See *Chem. Pharm.Bull.(Japan)* 47, 1538 (1999).

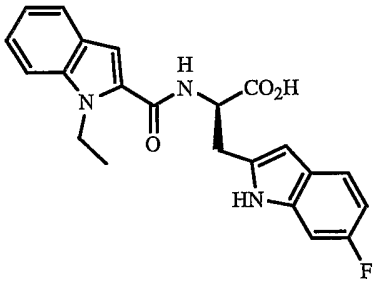
Example 155: Ethyl *N*-[(1-ethyl-1*H*-indol-2-yl)carbonyl]-3-(6-fluoro-1*H*-indol-2-yl)-D-alaninate



155

The amine **103d** (0.10g, 0.41 mmol) and acid **155b** (0.078g, 0.41 mmol) were dissolved in DMF (1.5 mL). Diisopropylamine (0.14 mL, 0.82 mmol) was added, and the reaction cooled to 0°C. HATU (0.16g, 0.41 mmol) was added, and the reaction stirred at 0°C two hours, then warmed to ambient temperature. The DMF was removed *in vacuo*, and the residue was dissolved in EtOAc/ sat. $NaHCO_3$. The organic layer was separated, washed successively with water and brine, dried ($MgSO_4$), and concentrated. The product was purified by flash silica gel chromatography (5-15% EtOAc/hexane) to afford 0.16g (90%) as a tan solid: mp = 128-130 °C; R_f = 0.18 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 11.15 (1H, s), 8.89 (1H, d, J = 7.8 Hz), 7.63 (1H, d, J = 8.0 Hz), 7.52 (1H, d, J = 8.3 Hz), 7.40-7.36 (1H, m), 7.26-7.23 (1H, m), 7.09-7.05 (3H, m), 6.78-6.73 (1H, m), 6.26 (1H, s), 4.83-4.77 (1H, m), 4.46 (2H, q, J = 7.1 Hz), 4.14-4.08 (2H, m), 3.30-3.24 (2H, m), 1.16-1.10 (6H, m). MS 422 (M+H); Elemental Analysis for ($C_{24}H_{24}N_3O_3F$) calc: C 68.39, H 5.74, N 9.97; found: C 68.16, H 5.81, N 9.84.

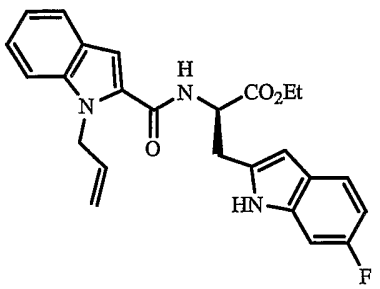
Example 156: *N*-[(1-Ethyl-1*H*-indol-2-yl)carbonyl]-3-(6-fluoro-1*H*-indol-2-yl)-D-alanine



156

Following the procedure to make **170, 156** was synthesized from **155** (0.11g, 0.27 mmol) to give 0.096 g (90%) of a white solid: mp = >120 °C (dec); ^{1}H NMR (DMSO-d_6): δ 11.16 (1H, s), 8.69 (1H, d, J = 7.5 Hz), 7.62 (1H, J = 7.8 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.38-7.34 (1H, m), 7.25-7.21 (1H, m), 7.08-7.04 (3H, m), 6.77-6.72 (1H, m), 6.24 (1H, s), 4.75-4.69 (1H, m), 4.48-4.43 (2H, m), 3.29-3.18 (2H, m), 1.14 (3H, t, J = 7.0 Hz). HRMS calcd for $C_{22}H_{21}N_3O_3F$ 394.1562 (M+H), found 394.1567. Elemental Analysis for ($C_{22}H_{20}N_3O_3F$•1.9H_2O) calc: C 61.79, H 5.61, N 9.83; found: C 61.79, H 5.27, N 9.74.

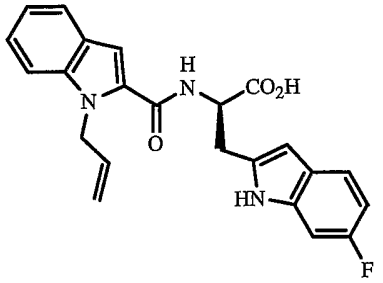
Example 157: Ethyl *N*-[(1-allyl-1*H*-indol-2-yl)carbonyl]-3-(6-fluoro-1*H*-indol-2-yl)-D-alaninate



157

Following the procedure used to make **155, 176** was synthesized using amine **103d** (0.098g, 0.39 mmol) and acid **173d** (0.079g, 0.39 mmol) to give 0.14g (83%) of a white flaky solid: mp = 108-110 °C; R_f = 0.18 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 11.14 (1H, s), 8.91 (1H, d, J = 7.9 Hz), 7.65 (1H, d, J = 8.1 Hz), 7.47 (1H, d, J = 8.4 Hz), 7.39-7.36 (1H, m), 7.26-7.22 (1H, m), 7.13 (1H, s), 7.05-7.10 (2H, m), 6.78-6.73 (1H, m), 6.25 (1H, s), 5.87-5.77 (1H, m), 5.12-5.11 (2H, m), 4.94-4.91 (1H, m), 4.81-4.76 (2H, m), 4.13-4.07 (2H, m), 3.30-3.20 (2H, m). MS 434 (M+H). Elemental Analysis for ($C_{25}H_{24}N_3O_3F$) calc: C 69.27, H 5.58, N 9.69; found: C 69.23, H 5.57, N 9.63.

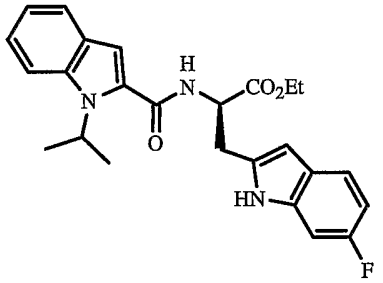
Example 158: *N*-[(1-Allyl-1*H*-indol-2-yl)carbonyl]-3-(6-fluoro-1*H*-indol-2-yl)-D-alanine



158

Following the procedure to make **170, 158** was synthesized from **157** (0.097g, 0.22 mmol) to give 0.081 g (90%) of a white solid: mp = >150 °C (dec); ^{1}H NMR (DMSO-d_6): δ 12.73 (1H, br), 11.12 (1H, s), 8.79 (1H, d, J = 8.1 Hz), 7.64 (1H, J = 7.8 Hz), 7.46 (1H, d, J = 8.4 Hz), 7.38-7.34 (1H, m), 7.25-7.21 (1H, m), 7.13 (1H, s), 7.10-7.04 (2H, m), 6.77-6.72 (1H, m), 6.24 (1H, s), 5.85-5.76 (1H, m), 5.11-5.10 (2H, m), 4.93-4.83 (2H, m), 4.79-4.73 (1H, m), 3.29-3.18 (2H, m). HRMS calcd for $C_{23}H_{21}N_3O_3F$ 406.1562 (M+H), found 406.1557. Elemental Analysis for ($C_{23}H_{20}N_3O_3F$) calc: C 66.65, H 5.11, N 10.14; found: C 66.49, H 5.02, N 10.02.

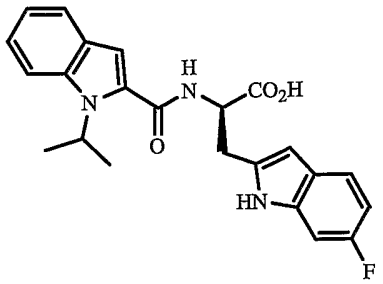
Example 159: Ethyl 3-(6-fluoro-1*H*-indol-2-yl)-*N*-[(1-isopropyl-1*H*-indol-2-yl)carbonyl]-D-alaninate



178

Following the procedure used to make **155, 178** was synthesized using amine **103d** (0.074g, 0.30 mmol) and acid **173f** (0.06g, 0.30 mmol) to give 0.11g (85%) of a white amorphous solid: mp = 70-74 °C; R_f = 0.18 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 11.14 (1H, s), 8.93 (1H, d, J = 7.9 Hz), 7.64-7.60 (2H, m), 7.41-7.38 (1H, m), 7.20-7.16 (1H, m), 7.09-7.03 (2H, m), 6.82 (1H, s), 6.79-6.74 (1H, m), 6.26 (1H, s), 5.22-5.19 (1H, m), 4.82-4.76 (1H, m), 4.15-4.09 (2H, m), 3.32-3.19 (2H, m), 1.46-1.43 (6H, m), 1.14 (3H, t, J = 7.1 Hz). MS 436 (M+H). Elemental Analysis for ($C_{25}H_{24}N_3O_3F$) calc: C 68.95, H 6.02, N 9.65; found: C 68.85, H 6.10, N 9.52.

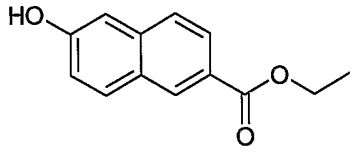
Example 160: 3-(6-Fluoro-1*H*-indol-2-yl)-*N*-[(1-isopropyl-1*H*-indol-2-yl)carbonyl]-D-alanine



179

Following the procedure to make **170, 160** was synthesized from **159** (0.10g, 0.22 mmol) to give 0.091 g (quant) of a white amorphous solid: mp = >70 °C (dec); ^{1}H NMR (DMSO-d_6): δ 11.12 (1H, s), 8.78 (1H, d, J = 8.1 Hz), 7.63-7.59 (2H, m), 7.40-7.36 (1H, m), 7.19-7.15 (1H, m), 7.08-7.02 (2H, m), 6.81 (1H, s), 6.78-6.73 (1H, m), 6.25 (1H, s), 5.20 (1H, hept, J = 7.1 Hz), 4.80-4.73 (1H, m), 3.32-3.16 (2H, m), 1.43 (6H, d, J = 7.1 Hz). HRMS calcd for $C_{23}H_{23}N_3O_3F$ 408.1718 (M+H), found 408.1710. Elemental Analysis for ($C_{23}H_{22}N_3O_3F$•0.15H_2O•0.3Et_2O) calc: C 67.22, H 5.90, N 9.72; found: C 67.28, H 5.87, N 9.55.

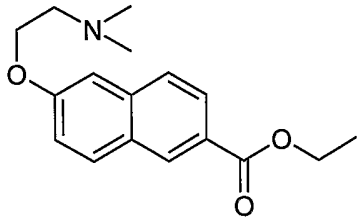
Compound 161a:



161a

To an ethanol solution (50 mL) of 6-hydroxy-naphthalene-2-carboxylic acid (5.29 g, 28.0 mmol) was added thionyl chloride (6 mL) at 0°C. The mixture was stirred at room temperature for 72h. Excess reagents were evaporated. The residue was dissolved in ethyl acetate (100 mL). The ethyl acetate solution was washed with water (80 mL), cold 1M sodium bicarbonate (80 mL) and brine (80 mL). It was dried over Na_2SO_4 and concentrated to give the crude title compound in 99% yield. ^{1}H NMR ($CDCl_3$): δ 8.53 (1H, br s), 8.01 (1H, dd, J=8.5, 1.7Hz), 7.86 (1H, d, J=8.5Hz), 7.20-7.13 (2H, m), 4.43 (2H, q, J=7.3Hz), 1.43 (3H, t, J=7.1Hz).
LCMS (APCI): 217.1 ($M+H^+$).

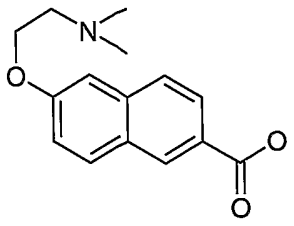
Compound 162b:



162b

To a toluene solution (70 mL) of **161a** (2.01 g, 9.30 mmol) were added N,N-dimethylaminoethanol (4.14 g, 46.7 mmol), triphenylphosphine (9.75 g, 37.3 mmol) and diisopropylazodicarboxlate (7.54 g, 37.3 mmol). The mixture was stirred at room temperature overnight. It was then diluted with ether (70 mL), washed with saturated ammonium chloride (100 mL) and brine (100 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane), the title compound was obtained in 38% yield. ^{1}H NMR ($CDCl_3$): δ 8.52 (1H, s), 8.06-8.00 (1H, m), 7.83 (1H, d, J=8.5Hz), 7.75 (1H, d, J=8.7Hz), 7.25-7.15 (2H, m), 4.48-4.35 (4H, m), 3.17 (2H, m), 2.65 (6H, s), 1.42 (3H, t, J=7.1Hz). LCMS (APCI): 288.1 ($M+H^+$).

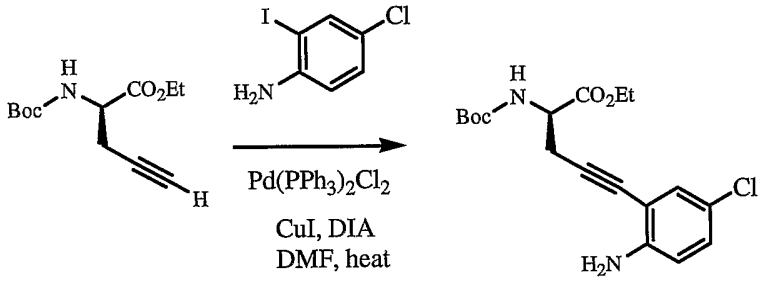
Compound 162c:



162c

To a methanol solution (15 mL) of **162b** (984 mg, 3.43 mmol) was added 5% sodium hydroxide (10 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. Methanol was evaporated. The residue was acidified with 1M HCl to pH 6. The solids were filtered and washed with water (20 mL) to give the title compound in 55% yield. ^{1}H NMR (DMSO-d_6): δ 8.49 (1H, s), 7.99 (1H, d, J=9.1Hz), 7.92 (1H, dd, J=8.5, 1.5Hz), 7.84 (1H, d, J=8.6Hz), 7.41 (1H, d, J=2.2Hz), 7.22 (1H, dd, J=8.9, 2.3Hz), 4.20 (2H, t, J=5.8Hz), 2.71 (2H, d, J=5.8Hz), 2.25 (6H, s). LCMS (APCI): 260.1 ($M+H^+$).

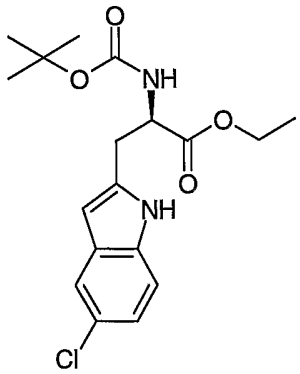
Example 162: Ethyl (2*R*)-5-(2-amino-5-chlorophenyl)-2-[(*tert*-butoxycarbonyl)amino]pent-4-ynoate



162

Following the procedure used to make **92, 162** was synthesized from alkyne **174e** (6.27g, 26.0 mmol) and 4-Chloro-2-iodoaniline (7.25g, 28.6 mmol) to give 9.90 g (96%) of a brown oil: R_f = 0.21 (1% MeOH/$CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 7.50 (1H, d, J = 7.7 Hz), 7.05-7.01 (2H, m), 6.65 (1H, d, J = 8.7 Hz), 5.51 (2H, s), 4.30-4.19 (1H, m), 4.15-4.05 (2H, m), 2.85-2.82 (2H, m), 1.38 (9H, s), 1.20-1.14 (3H, m). MS 267 (M+H-Boc).

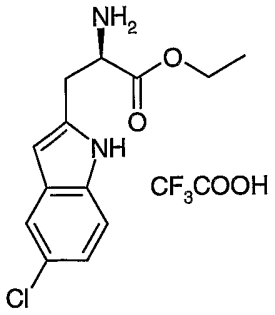
Example 163:



163

To a N, N-dimethyl-formamide solution (10 mL) of **162** (9.5 g, 25.7 mmol) was added CuI (4.92 g, 25.9 mmol). The mixture was stirred at 150°C for 2h after three circles of nitrogen/vacuum flush. It was filtered through a pad of celite. The filtrate was evaporated and the residue was diluted with dichloromethane (150 mL). It was then washed with water (2X100 mL) and brine (100 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 47% yield (4.5g). ^{1}H NMR ($CDCl_3$): δ 8.47 (1H, br s), 7.49 (1H, d, J=2Hz), 7.22 (1H, d, J=8.6Hz), 7.09 (1H, dd, J=8.6, 2Hz), 6.22 (1H, s), 5.18 (1H, d, J=8.1Hz), 4.61 (1H, br s), 4.26-4.18 (2H, m), 3.30-3.24 (2H, m), 1.43 (9H, s), 1.25 (3H, t, J=7Hz).

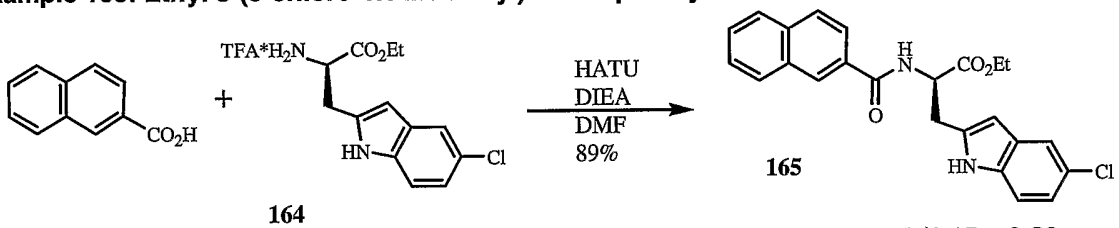
Example 164:



164

To a dichloromethane solution (25 mL) of **163** (4.5g, 12.3 mmol) was added trifluoroacetic acid (5 mL) at 0°C. The mixture was stirred at room temperature for 1 hour. It was then concentrated and the residue was diluted with ethyl acetate (100 mL). It was washed with brine (50 mL), dried with Na_2SO_4 and concentrated. The residue was triturated with warm hexanes to afford 4.2g (71% yield) of the title compound as a solid. ^{1}H NMR (DMSO-d_6): δ 11.28 (1H, br s), 8.46 (3H, br s), 7.51 (1H, s), 7.34 (1H, d, J=8.6Hz), 7.04 (1H, dd, J=8.6, 2Hz), 6.28 (1H, d, J=1.3Hz), 4.36 (1H, t, J=7Hz), 4.18-4.09 (2H, m), 3.25 (2H, d, J=6.8Hz), 1.07 (3H, t, J=7.1Hz).

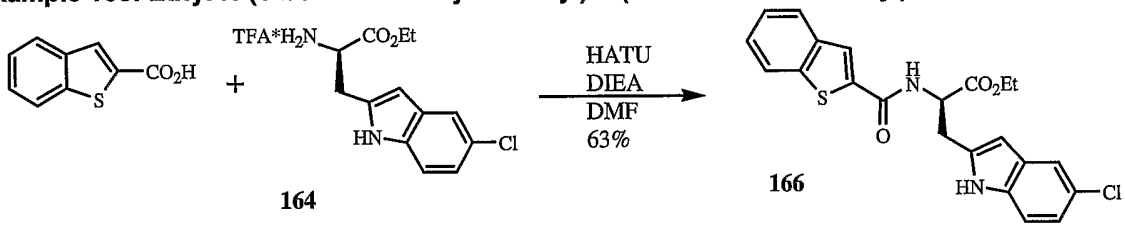
Example 165: Ethyl 3-(5-chloro-1*H*-indol-2-yl)-*N*-2-naphthoyl-D-alaninate



164 **165**

Following the procedure used to make **155, 165** was synthesized from amine **164** (0.15g, 0.39 mmol) to give 0.14g (89%) of an off-white solid: mp = 188-190 °C; R_f = 0.13 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 11.30 (1H, s), 9.06 (1H, d, J = 7.7 Hz), 8.43 (1H, s), 8.02-7.95 (3H, m), 7.89 (1H, dd, J = 8.7, 1.5 Hz), 7.64-7.56 (2H, m), 7.45 (1H, d, J = 1.9 Hz), 7.30 (1H, d, J = 8.7 Hz), 6.98 (1H, dd, J = 8.7, 1.9 Hz), 6.27 (1H, s), 4.91-4.84 (1H, m), 4.10 (2H, q, J = 7.0 Hz), 3.36-3.30 (2H, m), 1.10 (3H, t, J = 7.0 Hz). MS 421 (M+H). Elemental Analysis for ($C_{24}H_{21}N_2O_3Cl$•0.4H_2O) calc: C 67.33, H 5.13, N 6.54; found: C 67.51, H 4.88, N 6.46.

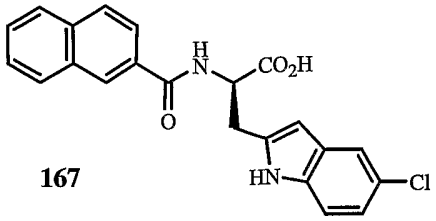
Example 166: Ethyl *N*-(1-benzothien-2-ylcarbonyl)-3-(5-chloro-1*H*-indol-2-yl)-D-alaninate



164 **166**

Following the procedure used to make **155, 166** was synthesized from amine **164** (0.16g, 0.41 mmol) and thianapthene-2-carboxylic acid to give 0.11g (63%) of a white solid: mp = 178-180 °C; R_f = 0.11 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 11.28 (1H, s), 9.20 (1H, d, J = 7.6 Hz), 8.15 (1H, s), 8.01-7.95 (2H, m), 7.48-7.41 (3H, m), 7.29 (1H, d, J = 8.6 Hz), 6.98 (1H, dd, J = 8.6, 2.0 Hz), 6.25 (1H, s), 4.85-4.79 (1H, m), 4.12-4.07 (2H, m), 3.30-3.24 (2H, m), 1.10 (3H, t, J = 7.1 Hz). MS 427 (M+H). Elemental Analysis for ($C_{22}H_{19}N_2O_3SCl$) calc: C 61.89, H 4.49, N 6.56; found: C 61.82, H 4.37, N 6.61.

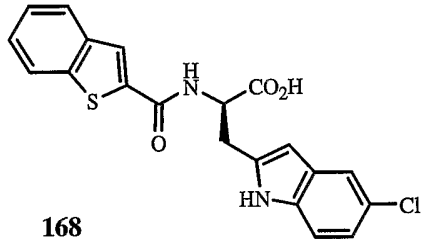
Example 167: 3-(5-Chloro-1*H*-indol-2-yl)-*N*-2-naphthoyl-D-alanine



167

Ester **165** (0.10g, 0.25 mmol) was dissolved in THF (1.0 mL) and water (0.5 mL). Solid LiOH (0.024g, 1.00 mmol) was added, and the reaction stirred at ambient temperature overnight. The solvent was removed *in vacuo*, and the residuewas diluted with water and acidified to pH = 2 with 10% HCl. The resulting precipitated solids were filtered and washed with water before drying to afford 0.058g (59%) of a white solid: mp = >110 °C (dec); ^{1}H NMR (DMSO-d_6): δ 11.39 (1H, s), 8.72 (1H, d, J = 7.7 Hz), 8.41 (1H, s), 8.02-7.94 (3H, m), 7.88 (1H, dd, J = 8.6, 1.5 Hz), 7.62-7.55 (2H, m), 7.42 (1H, d, J = 2.0 Hz), 7.28 (1H, d, J = 8.6 Hz), 6.95 (1H, dd, J = 8.6, 2.0 Hz), 6.23 (1H, s), 4.73-4.70 (1H, m), 3.33-3.24 (2H, m). HRMS calcd for $C_{22}H_{18}N_2O_3Cl$ 393.1001 (M+H), found 393.1009. Elemental Analysis for ($C_{22}H_{17}N_2O_3Cl$•0.4H_2O) calc: C 66.05, H 4.49, N 7.00; found: C 66.08, H 4.27, N 6.91.

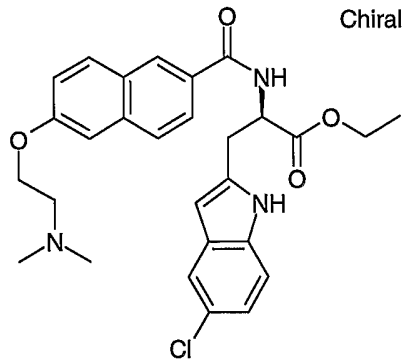
Example 168: *N*-(1-Benzothien-2-ylcarbonyl)-3-(5-chloro-1*H*-indol-2-yl)-D-alanine



168

Following the procedure used to make **155, 168** was synthesized from ester **166** (0.097g, 0.23 mmol) to give 0.088g (97%) of a white solid: mp = >200 °C (dec); ^{1}H NMR (DMSO-d_6): δ 11.48 (1H, s), 8.73 (1H, br), 8.10 (1H, s), 7.99-7.97 (1H, m), 7.93-7.91 (1H, m), 7.45-7.38 (3H, m), 7.27 (1H, d, J = 8.6 Hz), 6.93 (1H, dd, J = 8.6, 2.0 Hz), 6.19 (1H, s), 4.52-4.45 (1H, m), 3.31-3.18 (2H, m). HRMS calcd for $C_{20}H_{16}N_2O_3SCl$ 399.0565 (M+H), found 399.0561. Elemental Analysis for ($C_{20}H_{15}N_2O_3SCl$•0.8H_2O) calc: C 58.12, H 4.05, N 6.78; found: C 58.08, H 4.11, N 6.64.

Example 169:

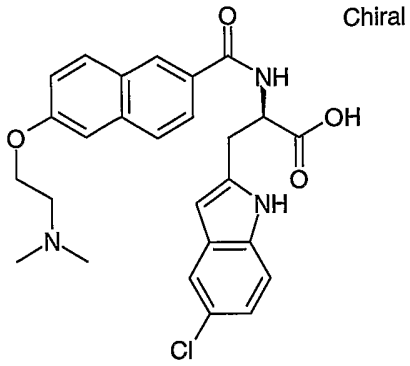


187

To a N, N-dimethyl-formamide solution (5 mL) of **162c** (140 mg, 0.474 mmol) was added **164** (180 mg, 0.474 mmol), EDC (272 mg, 1.42 mmol), triethylamine (431 mg, 4.27 mmol) and 4-(dimethylamino)pyridine (14 mg, 0.12 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold saturated ammonium chloride (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane), the title compound was obtained in 38% yield. ^{1}H NMR ($CDCl_3$): δ 12.59 (1H, br s), 9.52 (1H, s), 8.11 (1H, s), 7.68 (1H, dd, J=8.6, 1.5Hz), 7.61 (1H, d, J=9.1Hz), 7.53-7.48 (2H, m), 7.30-7.25 (2H, m), 7.09-6.98 (2H, m), 6.93 (1H, s), 6.26 (1H, s), 5.09

(1H, q, J=6Hz), 4.46 (2H, m), 4.30-4.20 (2H, m), 3.55-3.43 (4H, m), 2.94-2.89 (6H, m), 12.8 (3H, t, J=7.1Hz). LCMS (APCI): 508.1 ($M+H^+$).

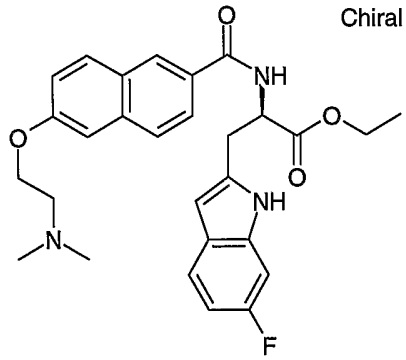
Example 170:



170

To a methanol solution (2 mL) of **169** (87 mg, 0.171 mmol) was added 5% sodium hydroxide (2 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. It was then purified by prep. HPLC to give title compound in 40% yield. ^1H NMR (DMSO-d_6): δ 11.38 (1H, s), 8.95 (1H, d, J=8Hz), 8.48 91H, s), 8.06 (1H, d, J=8.9Hz), 7.97 (2H, m), 7.53 (2H, m), 7.41-7.34 (1H, m), 7.07 (1H, dd, J=8.6, 2.1Hz), 6.36 (1H, s), 4.95 (1H, m), 4.52 (2H, m), 3.57 (2H, br s), 2.90 (6H, s).
LCMS (APCI): 480.1 ($M+H^+$). Elemental Analysis for ($C_{26}H_{26}ClN_3O_4$•1TFA•0.5H_2O) calc: C 55.77, H 4.68, N 6.97; found: C 55.82, H 4.66, N 6.87.

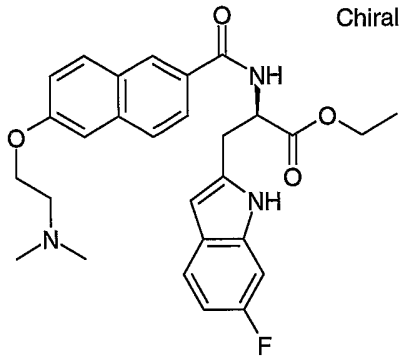
Example 171:



171

To a N, N-dimethyl-formamide solution (5 mL) of **162c** (130 mg, 0.440 mmol) was added **103d** (110 mg, 0.440 mmol), EDC (253 mg, 1.32 mmol), triethylamine (400 mg, 3.96 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.11 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (40 mL), cold saturated ammonium chloride (20 mL), cold 5% sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane), the title compound was obtained in 17% yield. ^1H NMR (CD_3OD): δ 8.14 (1H, s), 7.74 (1H, d, J=9.3Hz), 7.73-7.65 (2H, m), 7.26 (1H, dd, J=8.6, 5.6Hz), 7.21 (1H, d, J=2.3Hz), 7.13 (1H, dd, J=8.8, 2.5Hz), 6.88 (1H, dd, J=9.8, 2Hz), 6.65-6.58 (1H, m), 6.17 (1H, s), 4.93-4.80 (1H, m), 4.17-4.13 (2H, m), 4.09 (2H, q, J=7.2Hz), 3.35-3.22 (2H, m), 2.76 (2H, t, J=5.3Hz), 2.28 (6H, s), 1.09 (3H, t, J=7.4Hz). LCMS (APCI): 492.2 ($M+H^+$).

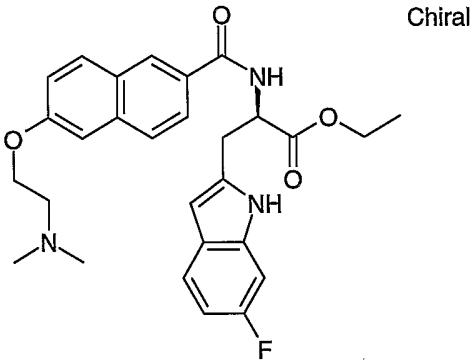
Example 172:



172

To a methanol solution (2 mL) of **171** (34 mg, 0.0692 mmol) was added 5% sodium hydroxide (1 mL). The mixture was stirred at room temperature overnight. It was then adjusted to pH 6 with 1M HCl. Solids were filtered and purified by prep HPLC to give the title compound in 13% yield. ^{1}H NMR (DMSO-d_6): δ 11.28 (1H, s), 8.94 (1H, d, J=7.6Hz), 8.50 (1H, s), 8.10-7.95 (3H, m), 7.55 (1H, s), 7.50 (1H, dd, J=8.3, 5.5Hz), 7.38 (1H, d, J=9Hz), 7.19 (1H, d, J=8.5Hz), 6.88 (1H, t, J=8.5Hz), 6.39 (1H, s), 4.96 (1H, m), 4.47 (2H, m), 2.74 (6H, s). HRMS (MALDI) calc for $C_{26}H_{27}N_3O_4F(M+H^+)$ 464.1986; found 464.2005.

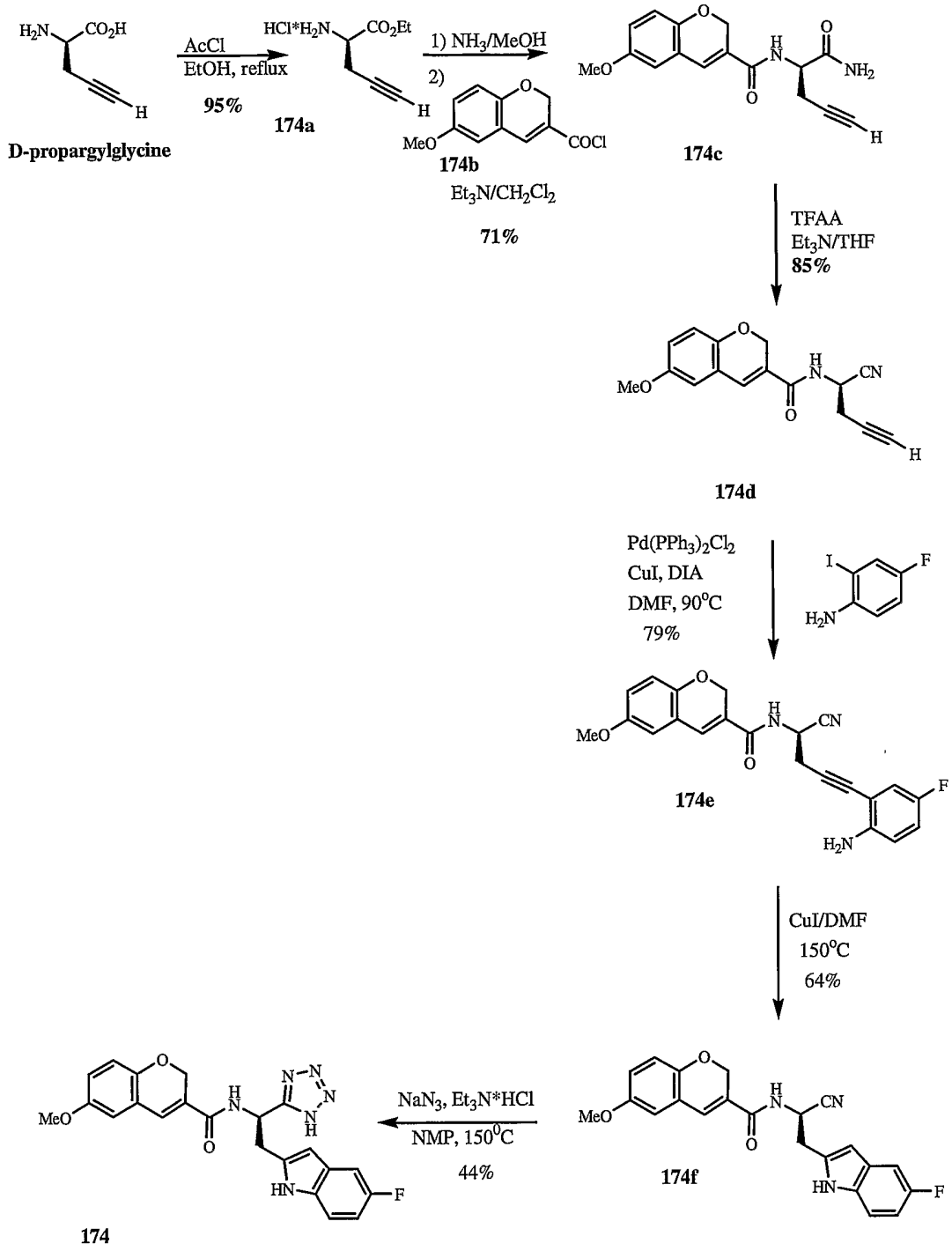
Example 173:



173

To a N, N-dimethyl-formamide solution (5 mL) of **162c** (192 mg, 0.515 mmol) were added **103d** (129 mg, 0.515 mmol), EDC (247 mg, 1.29 mmol), triethylamine (312 mg, 3.09 mmol) and 4-(dimethylamino)pyridine (16 mg, 0.129 mmol). The mixture was stirred at room temperature overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (20 mL), saturated ammonium chloride (20 mL), saturated cold sodium carbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane), the title compound was obtained in 25% yield. ^{1}H NMR (CD_3OD): δ 8.21 (1H, s), 7.84-7.70 (3H, m), 7.33 (1H, dd, J=8.6, 5.3Hz), 7.28 (1H, d, J=2.3Hz), 7.20 (1H, dd, J=8.8, 2.5Hz), 6.95 (1H, dd, J=9.9, 2Hz), 6.74-6.65 (1H, m), 6.25 (1H, s), 4.96 (1H, dd, J=8.8, 6.1Hz), 4.22 (2H, t, J=5.4Hz), 4.16 (1H, q, J=7.1Hz), 3.46-3.25 (2H, m), 2.83 (2H, t, J=5.3Hz), 2.35 (6H, s), 1.16 (3H, t, J=7.1Hz). LCMS (APCI): 492.2 ($M+H^+$). HRMS (MALDI) calc for $C_{28}H_{31}N_3O_4F(M+H^+)$ 492.2299; found 492.2291.

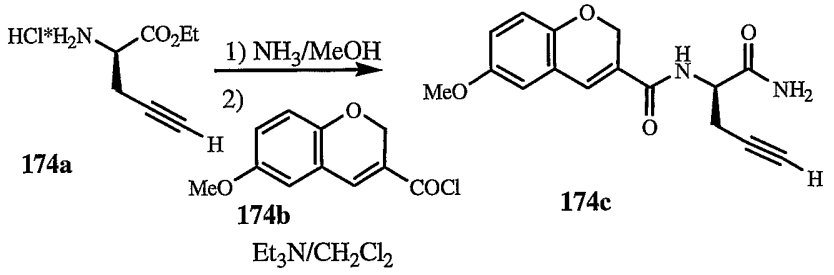
Synthesis of 174



Compound 174b: 6-Methoxy-2H-chromene-3-carbonyl chloride

6-Methoxy-2H-chromene-3-carboxylic acid (2.82g, 13.70 mmol) was dissolved in CH_2Cl_2 (70 mL). Oxalyl chloride (1.35 mL, 15.07 mmol) was added followed by a drop of DMF. The reaction stirred overnight at room temperature, and the solvent was removed *in vacuo* to give 3.08g (quant.) of a yellow solid: ^{1}H NMR ($CDCl_3$): δ 7.75 (1H, s), 6.91 (1H, dd, J = 9.0, 3.0 Hz), 6.83 (1H, d, J = 9.0 Hz), 6.77 (1H, d, J = 3.0 Hz), 4.95 (1H, s), 3.78 (3H, s).

Compound 174c: *N*-[(1*R*)-1-(Aminocarbonyl)but-3-ynyl]-6-methoxy-2*H*-chromene-3-carboxamide



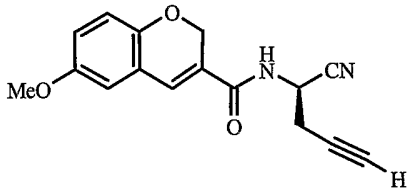
174a 174b 174c

Et_3N/CH_2Cl_2

71%

Amine salt **174a** (2.03g, 11.42 mmol) was dissolved in MeOH (30 mL) and cooled to 0°C. Dry ammonia gas was bubbled through the solution for 1 hour. The flask was capped with a rubber suba-seal septa and secured with copper wire. The reaction warmed to room temperature and stirred overnight. A second charge of ammonia gas was performed as before, and the reaction stirred an additional 2 days. The solvent was removed *in vacuo*, and the material used without further purification. The resulting amide was suspended in CH_2Cl_2 (75 mL) and treated with triethylamine (1.91 mL, 13.70 mmol) and **174b** (6-methoxy-2H-chromene-3-carbonyl chloride, 3.08g, 13.70 mmol), stirring overnight. The reaction was poured into saturated $NaHCO_3$ solution, and the organic phase was separated, washed successively with water and brine, dried ($MgSO_4$), and concentrated. The product was purified by flash silica gel chromatography (10-75% EtOAc/hexane) to give 2.43g (71%) of a yellow solid: mp = 158-159 °C (dec); R_f = 0.08 (50% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 8.30 (1H, d, J = 8.1 Hz), 7.49 (1H, s), 7.32 (1H, s), 7.19 (1H, s), 6.83-6.78 (3H, m), 4.82 (2H, s), 4.46-4.41 (1H, m), 3.71 (3H, s), 2.84 (1H, s), 2.68-2.62 (1H, m), 2.57-2.52 (1H, m). MS 299 (M-H). Elemental Analysis for ($C_{16}H_{16}N_2O_4$) calc: C 63.99, H 5.37, N 9.33; found: C 63.99, H 5.35, N 9.40.

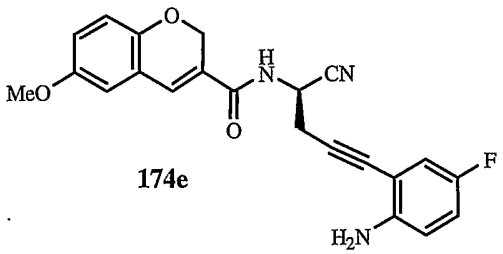
Compound 174d: *N*-[(1*R*)-1-Cyanobut-3-ynyl]-6-methoxy-2*H*-chromene-3-carboxamide



174d

Amide **174c** (2.35g, 7.84 mmol) was dissolved in THF (75 mL) and triethylamine (2.41 mL, 17.26 mmol) and cooled in an ice bath. Trifluoroacetic anhydride (1.22 mL, 8.63 mmol) was added slowly dropwise, and the ice bath was removed. The reaction warmed to room temperature and stirred 3 hours. The solvent was removed *in vacuo*, and the residue subjected to flash silica gel chromatography (10-30% EtOAc/hexane) to give 1.88g (85%) of a yellow amorphous solid: mp = 98-100 °C; R_f = 0.16 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 9.08 (1H, d, J = 7.7 Hz), 7.33 (1H, s), 6.86-6.80 (3H, m), 5.01-4.95 (1H, m), 4.82 (2H, s), 3.71 (3H, s), 3.14-3.12 (1H, m), 2.83-2.79 (2H, m). MS 283 (M+H). Elemental Analysis for ($C_{16}H_{14}N_2O_3$) calc: C 68.07, H 5.00, N 9.92; found: C 67.86, H 5.18, N 9.80.

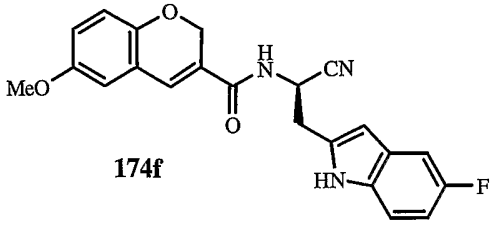
Compound 174e: *N*-[(1*R*)-4-(2-Amino-5-fluorophenyl)-1-cyanobut-3-ynyl]-6-methoxy-2*H*-chromene-3-carboxamide



174e

Following the procedure used to make **162, 174e** was synthesized from alkyne **174d** (0.26g, 0.92 mmol) and 4-fluoro-2-iodoaniline to give 0.29g (79%) of an olive-colored solid: mp = >150 °C (dec); R_f = 0.08 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 9.16 (1H, d, J = 7.6 Hz), 7.34 (1H, s), 6.94-6.89 (2H, m), 6.85-6.79 (3H, m), 6.66-6.63 (1H, m), 5.31 (2H, s), 5.19 (1H, q, J = 7.4 Hz), 4.84 (2H, s), 3.71 (3H, s), 3.16-3.03 (2H, m). MS 392 (M+H).

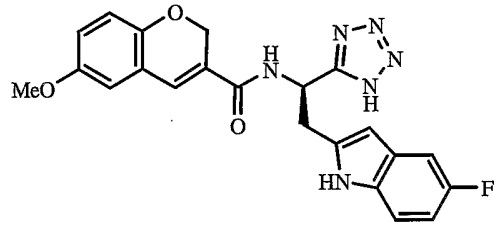
Compound 174f: *N*-[(1*R*)-1-Cyano-2-(5-fluoro-1*H*-indol-2-yl)ethyl]-6-methoxy-2*H*-chromene-3-carboxamide



174f

Aniline **174e** (0.24g, 0.62 mmol) was dissolved in DMF (6.0 mL). Copper(I)iodide (0.12g, 0.62 mmol) was added. The reaction was degassed and placed under an argon atmosphere, then placed in a preheated 150 °C oil bath for 2.5 hours. The DMF was removed *in vacuo*, and the residue was dissolved in EtOAc/water. The organic phase was separated, washed successively with water and brine, dried ($MgSO_4$), and concentrated. The product was purified by flash silica gel chromatography (10-20% EtOAc/hexane) to give 0.16g (64%) of a yellow solid: mp = 192-193 °C; R_f = 0.16 (30% EtOAc/hexane); ^{1}H NMR (DMSO-d_6): δ 11.20 (1H, s), 9.09 (1H, d, J = 7.6 Hz), 7.33-7.32 (1H, m), 7.30 (1H, s), 7.23 (1H, dd, J = 10.1, 2.5 Hz), 6.90-6.79 (4H, m), 6.35 (1H, s), 5.23 (1H, q, J = 7.8 Hz), 4.82 (2H, s), 3.71 (3H, s), 3.37-3.27 (2H, m). MS 392 (M+H). Elemental Analysis for ($C_{22}H_{18}N_3O_3F$•0.1H_2O) calc: C 67.2, H 4.67, N 10.69; found: C 67.10, H 4.69, N 10.57.

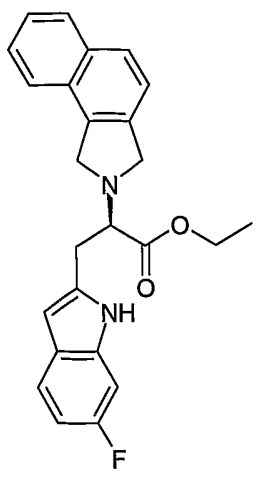
Example 174: *N*-[(1*R*)-2-(5-Fluoro-1*H*-indol-2-yl)-1-(1*H*-tetrazol-5-yl)ethyl]-6-methoxy-2*H*-chromene-3-carboxamide



174

Nitrile **174f** (0.12g, 0.31 mmol), sodium azide (0.06g, 0.93 mmol), and triethylamine hydrochloride (0.064g, 0.47 mmol) were suspended in N-methylpyrrolidinone and heated to 150 °C for 5 hours. A few drops of conc. HCl were added to the reaction, and the solvent evacuated to dryness. The crude product was purified by preparative HPLC (acetonitrile/water). The oily material was then triturated with Et_2O to produce 0.058g (44%) of a brown amorphous solid: mp = >100 °C (dec); ^{1}H NMR (DMSO-d_6): δ 11.16 (1H, s), 8.95 (1H, d, J = 7.8 Hz), 7.29-7.25 (2H, m), 7.18-7.14 (1H, m), 6.85-6.77 (4H, m), 6.15 (1H, s), 5.68-5.66 (1H, m), 4.77 (2H, s), 3.70 (3H, s), 3.57-3.36 (2H, m). HRMS calcd for $C_{22}H_{20}N_6O_3F$ 435.1576 (M+H), found 435.1575. Elemental Analysis for ($C_{22}H_{19}N_6O_3F$•0.3H_2O•0.35EtOAc) calc: C 59.71, H 4.80, N 17.86; found: C 59.75, H 4.84, N 17.66.

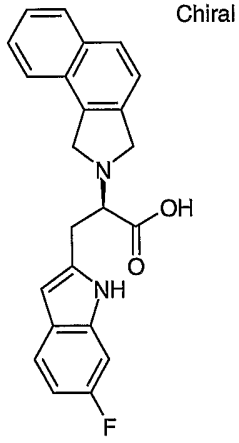
Example 175:



175

To an acetonitrile solution (30 mL) of **103d** (245 mg, 0.980 mmol) were added 1,2-bis(bromomethyl)naphthalene (282 mg, 0.898 mmol) and potassium bicarbonate (245 mg, 2.45 mmol). The mixture was refluxed for 6 hours. It was then filtered and the filtrate was concentrated. After column chromatography (30% ethyl acetate in hexane), the title compound was obtained in 48% yield. ^{1}H NMR (DMSO-d_6): δ 10.92 (1H, s), 7.74 (1H, d, J=8.1Hz), 7.61 (1H, d, J=8.0Hz), 7.53 (1H, d, J=7.9Hz), 7.34 (1H, t, J=6.8Hz), 7.29 (1H, t, J=7Hz), 7.23 (1H, d, J=8.4Hz), 7.18 (1H, dd, J=8.6, 5.6Hz), 6.87 (1H, dd, J=9.9, 1.8Hz), 6.07 (1H, s), 4.35 (2H, q, J=10.1Hz), 4.15 (2H, m), 3.90 (1H, q, J=9.1Hz), 3.06 (2H, m), 0.85 (3H, t, 7.1Hz). LCMS (APCI): 403.1 (M+H$^+$). HRMS (MALDI) calc for $C_{25}H_{24}N_2O_2F$(M+H$^+$) 403.1822; found 403.1834.

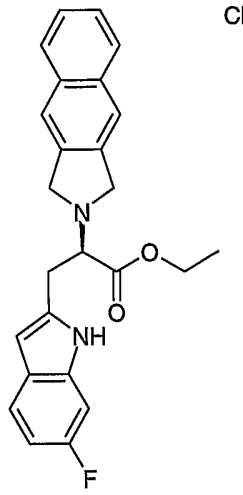
Example 176:



176

To a methanol solution (6 mL) of **175** (152 mg, 0.387 mmol) was added 5% sodium hydroxide (2 mL). The mixture was stirred at room temperature overnight. It was then diluted with ethyl acetate (10 mL) and adjusted to pH 6 with 1M HCl. Solid was collected by filtration and washed with water (2X10 mL) and ethyl acetate (2X10 mL) to give the title compound in 71% yield. ^{1}H NMR (DMSO-d_6): δ 12.5 (1H, br s), 7.88 (1H, d, J=7.8Hz), 7.75 (1H, d, J=8.3Hz), 7.67 (1H, d, J=7.8Hz), 7.51-7.40 (2H, m), 7.37 (1H, d, J=8.3Hz), 7.31 (1H, dd, J=8.6, 5.6Hz), 7.00 (1H, dd, J=10.1, 2.1Hz), 6.75-6.65 (1H, m), 6.23 (1H, s), 4.51 (2H, m), 4.31 (2H, m), 3.97 (1H, t, J=8.1Hz), 3.25-3.10 (2H, m). LCMS (APCI): 375.1 (M+H$^+$). Elemental Analysis for ($C_{23}H_{19}FN_2O_2$•0.3H_2O) calc: C 72.73, H 5.20, N 7.38; found: C 72.66, H 5.14, N 7.31.

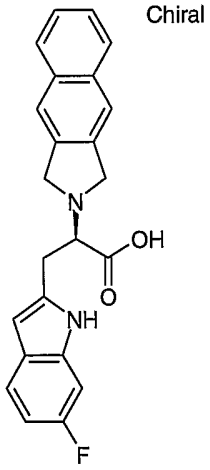
Example 177:



177

To an acetonitrile solution (25 mL) of **103d** (187 mg, 0.748 mmol) was added 2,3-bis(bromomethyl)naphthalene (235 mg, 0.748 mmol) and potassium bicarbonate (187 mg, 1.87 mmol). The mixture was refluxed for 6 hours. It was then filtered and the filtrate was concentrated. After column chromatography (15% ethyl acetate in hexane), the title compound was obtained in 39% yield. ^{1}H NMR (DMSO-d_6): δ 11.04 (1H, s), 7.80-7.75 (2H, m), 7.68 (2H, s), 7.42-7.35 (2H, m), 7.31 (1H, dd, J=8.6, 5.6Hz), 7.00 (1H, dd, J=10.1, 2.3Hz), 6.75-6.65 (1H, m), 6.17 (1H, s), 4.18 (4H, m), 4.05-3.92 (3H, m), 3.20-3.14 (2H, m), 1.01 (3H, t, J=7.1Hz). LCMS (APCI): 403.1 (M+H$^+$). HRMS (MALDI) calc for $C_{25}H_{24}N_2O_2F$(M+H$^+$) 403.1822; found 403.1810.

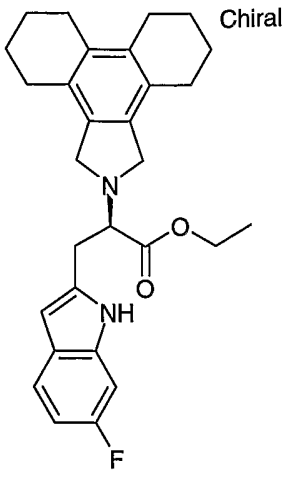
Example 178:



178

To a methanol solution (5 mL) of **177** (59 mg, 0.147 mmol) was added 5% sodium hydroxide (2 mL). The mixture was stirred at room temperature for overweekend. It was then diluted with ethyl acetate (10 mL) and adjusted to pH 1.5 with 1M HCl. Solids were filtered and washed with water (2X10 mL) and ethyl acetate (2X10 mL) to give the title compound in 55% yield. ^{1}H NMR (DMSO-d_6): δ 11.06 (1H, s), 7.85-7.75 (2H, m), 7.71 (2H, s), 7.45-7.35 (2H, m), 7.33 (1H, dd, J=8.35, 5.3Hz), 7.01 (1H, dd, J=10.1, 1.7Hz), 6.76-6.66 (1H, m), 6.21 (1H, s), 4.30 (4H, br s), 3.98 (1H, s), 3.21 (2H, m). LCMS (APCI): 375.1 (M+H$^+$). Elemental Analysis for ($C_{23}H_{19}FN_2O_2$•0.4HCl•0.2H_2O) calc: C 70.36, H 5.08, N 7.14; found: C 70.63, H 5.10, N 7.05.

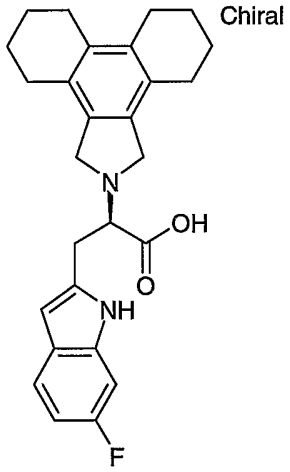
Example 179:



179

To an acetonitrile solution (17 mL) of **103d** (125 mg, 0.500 mmol) was added 9,10-bis-chloromethyl-1,2,3,4,5,6,7,8-octahydro-phenanthrene (142 mg, 0.500 mmol) and sodium bicarbonate (125 mg, 1.25 mmol). The mixture was refluxed overnight. It was filtered and the filtrate was concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 39% yield. ^{1}H NMR (DMSO-d_6): δ 11.05 (1H, s), 7.37 (1H, dd, J=8.5, 5.5Hz), 7.05 (1H, dd, J=9.9, 2Hz), 6.80-6.72 (1H, m), 6.21 (1H, d, J=1Hz), 4.09-3.90 (6H, m), 3.21-3.10 (2H, m), 2.55-2.48 (8H, m), 2.47 (2H, m), 1.72-1.63 (8H, m), 1.06 (3H, t, J=7.1Hz).
LCMS (APCI): 461.2 ($M+H^+$).

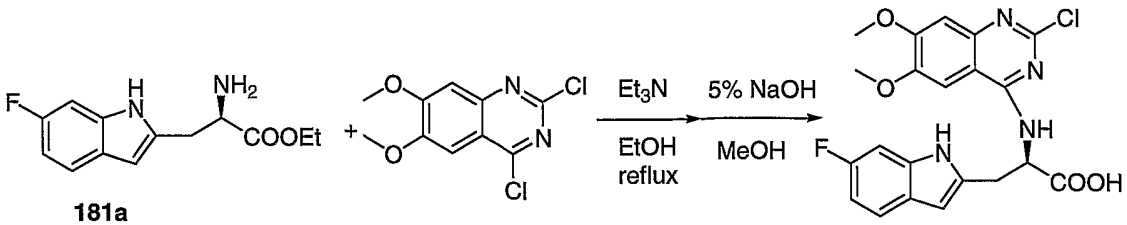
Example 180:



180

To a methanol solution (2 mL) of **179** (87 mg, 0.189 mmol) was added 5% sodium hydroxide (1 mL). The mixture was stirred at 80°C for 3 hours. It was then diluted with ethyl acetate (10 mL) and acidified with 1M HCl. Solid was collected by filtration and washed with water (2X10 mL) and ethyl acetate (2X10 mL) to give the title compound in 55% yield. ^{1}H NMR (DMSO-d_6): δ 11.23 (1H, s), 7.55 (1H, dd, J=8.3, 5.5Hz), 7.24 (1H, dd, J=10.1, 2Hz), 6.98-6.90 (1H, m), 6.41 (1H, s), 4.26 (4H, s), 4.11 (1H, br s), 3.39 (1H, dd, J=14.7, 6.8Hz), 3.29 (1H, dd, J=15.1, 8Hz), 2.64 (8H, m), 1.95-1.80 (8H, m).
LCMS (APCI): 433.2 ($M+H^+$). Elemental Analysis for ($C_{23}H_{19}FN_2O_2 \bullet 0.4HCl \bullet 0.2H_2O$) calc: C 71.95, H 6.66, N 6.22; found: C 72.18, H 6.79, N 6.14.

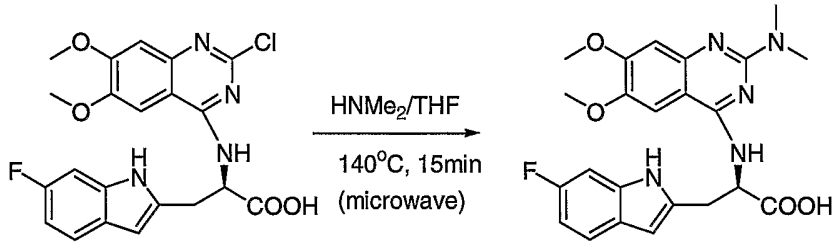
Example 181:



181a **181**

To an ethanol solution (3mL) of triethylamine (0.2mL) was added the amino ester **181a** (93mg, 0.372mmol) and 2,4-Dichloro-6,7-dimethoxyquinazoline (97mg, 0.375mmol). The mixture was heated at reflux for 15h. The resulted solution was concentrated. The residue was dissolved in EtOAc (30mL). The solution was then washed with ice-cooled 5% HCl (2x15mL) and water (1x20mL), dried ($MgSO_4$) and concentrated. The crude solid (180mg) was re-dissolved in MeOH (5mL). At 0°C, 10% NaOH solution (5mL) was added. After stirred at 25°C for 1.5h, the solution was concentrated and acidified by addition of ice-cooled 5% HCl solution (pH~2). The precipitate was collected by filtration. After being dried *in vacuo*, the title compound (160mg, 97% yield) was obtained as a yellow solid. ^{1}H NMR (DMSO-*d6*): δ 13.0 (1H, br s), 11.24 (1H, s), 8.61 (1H, d, J=7.8Hz), 7.75 (1H, s), 7.38 (1H, dd, J=8.6, 5.6Hz), 7.10 (1H, s), 7.07 (1H, dd, J=10.1, 2Hz), 6.8-6.73 (1H, m), 6.28 (1H, s), 5.09-5.02 (1H, m), 3.92 (3H, s), 3.90 (3H, s), 3.44-3.40 (2H, m). LCMS (APCI positive): 445 ($M+H^+$). Elemental Analysis for ($C_{21}H_{18}N_4O_4Cl \bullet 2.05H_2O \bullet 1.04HCl$) calc: C 48.50, H 4.49, N 10.77, Cl 13.98; found: C 48.36, H 4.30, N 10.57, Cl 13.72.

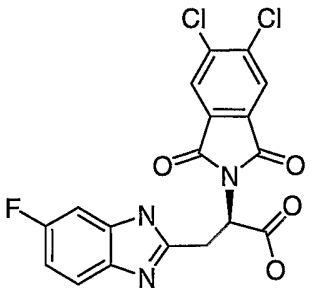
Example 182:



181 **182**

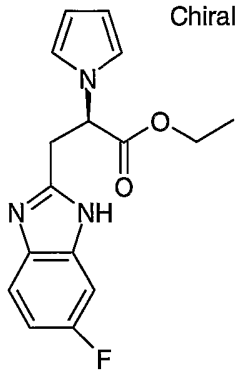
To a THF solution (1.5mL) of dimethylamine (0.2mL) in a sealed tube was added the chloride **181** (75.5mg, 0.17mmol). The solution heated at 140°C for 15min. Preparative HPLC purification provided 50mg (65% yield) of the title compound as a solid. ^{1}H NMR (DMSO-*d6*): δ 12.99 (1H, br s), 11.42 (1H, s), 11.07 (1H, s), 9.19 (1H, d, J=7.6Hz), 7.64 (1H, s), 7.25 (1H, dd, J=8.4, 5.1Hz), 7.13 (1H, s), 6.95 (1H, m), 6.65 (1H, m), 6.13 (1H, s), 4.92-4.88 (1H, m), 3.78 (3H, s), 3.75 (3H, s), 3.33 (2H, m), 3.09 (6H, s). Elemental Analysis for ($C_{23}H_{24}FN_5O_4 \bullet 0.85H_2O \bullet 1.25CF_3COOH$) calc: C 50.10, H 4.44, N 11.46; found: C 50.13, H 4.42, N 11.35.

Example 183



3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine trifluoroacetate **18a** was dissolved in anhydrous NMP, and *N,O*-bis(trimethylsilyl)acetamide (2.2 equivalents) and diisopropylethylamine were added. The reaction mixture was allowed to stir for 16h at room temperature. 4,5-Dichlorophthalic anhydride was added, and the reaction was allowed to stir at room temperature. Water (20 mL) and aqueous HCl solution (4.0 M, 400□L) were added. The reaction was filtered, and the crude material was dried in a vacuum oven. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.47 (dd, *J*=15.30, 8.88 Hz, 1 H) 3.70 (dd, *J*=15.49, 6.04 Hz, 1 H) 5.38 (dd, *J*=8.88, 5.85 Hz, 1 H) 6.89 - 7.01 (m, 1 H) 7.22 (dd, *J*=9.44, 2.64 Hz, 1 H) 7.39 (dd, *J*=8.88, 4.72 Hz, 1 H) 8.23 (s, 2 H) 13.08 (none, 1 H). Anal. Calcd. For $C_{18}H_{10}Cl_2FN_3O_4$: C, 51.21; H, 2.39; N, 9.95. Found: C, 51.35; H, 2.42; N, 9.73. LC/MS: 423 (M + H).

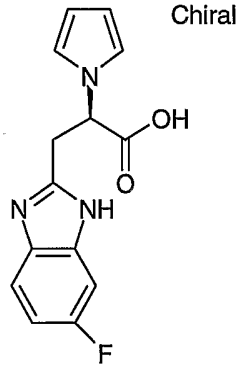
Compound 184a:



184a

To a dichloroethane/water solution (2 mL/2 mL) of **103d** (110 mg, 0.383 mmol) was added 2,5-dimethoxytetrahydrofuran (118 mg, 0.893 mmol). The mixture was stirred vigorously at 80°C for 45 minutes. It was diluted with dichloromethane (30 mL), washed with cold saturated sodium bicarbonate (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (30% ethyl acetate in hexane), the title compound was obtained in 44% yield. ^{1}H NMR ($CDCl_3$): δ 7.52-7.40 (1H, m), 7.26-7.20 (1H, m), 7.00-6.90 (1H, m), 6.61 (2H, m), 5.81 (2H, m), 5.75 (1H, m), 4.05-3.85 (4H, m), 0.89 (1H, t, J=7Hz). LCMS (APCI): 302.1 ($M+H^+$).

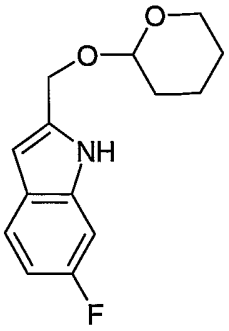
Example 184:



184

To a methanol solution (1 mL) of **184a** (49 mg, 0.163 mmol) was added 5% sodium hydroxide (1 mL) at 0°C. The mixture was stirred at room temperature for overnight. It was then purified by prep. HPLC to give title compound in 68% yield. ^{1}H NMR (CD_3OD): δ 7.55 (1H, dd, J=8.97, 4.42 Hz), 7.32 (1H, dd, J=8.34, 2.27 Hz), 7.21-7.15 (1H, m), 6.61 (2H, t, J=2.02 Hz), 5.95 (2H, t, J=2.15 Hz), 5.24 (1H, dd, J=9.09, 6.32 Hz), 3.87-3.79 (1H, m), 3.65 (1H, dd, J=15.28, 9.22 Hz), 3.39 (1H, q, J=6.99 Hz). LCMS (APCI): 274.1 ($M+H^+$). HRMS (MALDI) calc for $C_{14}H_{13}N_3O_2F(M+H^+)$ 274.0992; found 274.0995.

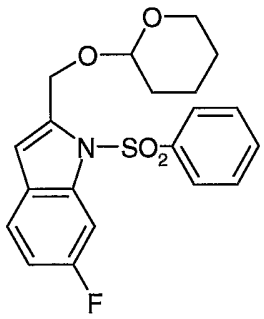
Compound 185a:



185a

To a N, N-dimethyl-formamide/dioxane solution (12 mL/48 mL) of (6-Fluoro-1H-indol-2-yl)-methanol (4.00 g, 17.2 mmol) were added tetrahydro-2-(2-propynyloxy)-2H-pyran (4.83 g, 34.5 mmol), 1,1,3,3-tetramethylguanidine (19.8 g, 172 mmol), dichlorobis(triphenylphosphine)-palladium (II) (605 mg, 0.862 mmol) and CuI (164 mg, 0.862 mmol). The mixture was stirred at 90°C for 16 hours after three circles of nitrogen/vacuum flush. CuI (3.28 g, 17.2 mmol) was introduced to the reaction mixture and stirred at 90°C for 18 hours. DMF was removed by vacuum and the residue was diluted with ethyl acetate (100 mL). It was then washed with water (50 mL) cold 1M HCl (50 mL), cold saturated sodium bicarbonate (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 71% yield. ^1H NMR (DMSO-d_6): δ 8.53 (1H, br s), 7.46 (1H, dd, J=8.6, 5.3Hz), 7.03 (1H, dt, J=9.9, 2.5Hz), 6.87-6.80 (1H, m), 6.39 (1H, s), 4.88-4.78 (2H, m), 4.22-4.65 (1H, m), 4.00-3.90 (1H, m), 3.62-3.50 (1H, m), 1.90-1.50 (6H, m).

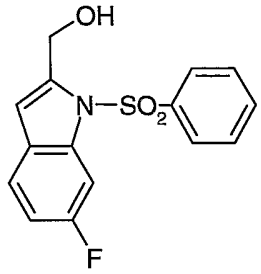
Compound 185b:



185b

To a tetrahydrofuran solution (40 mL) of **185a** (3.04 g, 12.2 mmol) at 0°C was added sodium hydride (364 mg, 14.4 mmol). The mixture was stirred at 0°C for 40 minutes. Benzenesulfonyl chloride (2.26 g, 12.8 mmol) was introduced to the reaction mixture and stirred at room temperature for overnight. THF was removed by vacuum and the residue was diluted with ethyl acetate (100 mL). It was then washed with water (50 mL), saturated ammonium chloride (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 85% yield. ^1H NMR (DMSO-d_6): δ 8.10-8.05 (2H, m), 7.82 (1H, dd, J=10.3, 2.3Hz), 7.70 (1H, t, J=7.3Hz), 7.58 (2H, t, J=8.4Hz), 7.43 (1H, dd, J=8.6, 4.6Hz), 7.27 (1H, td, J=9.1, 2.5Hz), 5.11 (1H, d, J=2.1Hz), 4.88 (1H, d, J=12.1Hz), 4.75 (1H, t, J=3Hz), 3.93-3.86 (1H, m), 3.57-3.50 (1H, m), 1.60-1.38 (6H, m). LCMS (API-ES): 412.1 ($M+Na^+$).

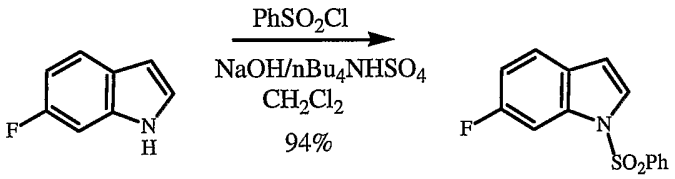
Compound 185c:



185c

To a methanol solution (40 mL) of **185b** (1.75 g, 4.50 mmol) was added toluene-4-sulfonic acid (4.76 g, 25.0 mmol). The mixture was stirred for 15 minutes. Sodium bicarbonate (4.95 g, 59.0 mmol) was introduced to the reaction mixture and stirred at room temperature for 15 minutes. Methanol was removed by vacuum and the residue was diluted with dichloromethane (40 mL). It was then filtered. The filtrate was dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 63% yield. ^{1}H NMR (DMSO-d_6): δ 8.00-7.95 (2H, m), 7.76 (1H, dd, J=9.1, 2.3Hz), 7.70 (1H, t, J=7.4Hz), 7.65-7.50 (3H, m), 7.12 (1H, td, J=9.4, 2.3Hz), 6.75 (1H, s), 5.55 (1H, t, J=5.8Hz), 4.83 (2H, d, J=5.6Hz). LCMS (API-ES): 328.1 ($M+Na^+$).

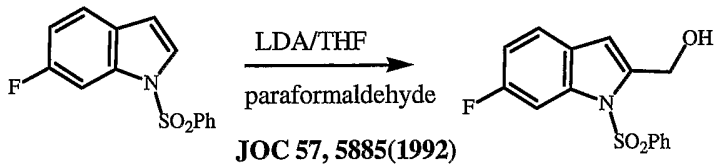
Compound 185d: 6-Fluoro-1-(phenylsulfonyl)-1*H*-indole



185d

Powdered NaOH (18.92g, 473 mmol) was suspended in CH_2Cl_2 (250 mL) and cooled to 0°C. Tetrabutylammonium hydrogensulfate (1.60g, 4.73 mmol) was added to the flask followed by the addition of solid 6-fluoroindole (21.31g, 157.7 mmol). Benzenesulfonyl chloride (25.16 mL, 197 mmol) dissolved in CH_2Cl_2 (115 mL) was added via an addition funnel at a rate such that the reaction temperature was maintained below 20°C. The mixture was stirred vigorously at room temperature for three hours. The reaction was filtered through filter paper and concentrated. The resulting solids were recrystallized with MeOH to give 41.02g (94%) of a white crystalline solid: mp = 100-101°C;); R_f = 0.66 ($CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 8.02 (2H, d, J = 8.3 Hz), 7.83 (1H, d, J = 3.8 Hz), 7.72-7.69 (2H, m), 7.64-7.58 (3H, m), 7.17-7.12 (1H, m), 6.85-6.84 (1H, m).

Compound 185e:

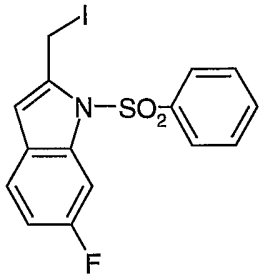


185e

n-Butyllithium (2.87M/hexane, 41.44 mL, 119 mmol) was added to a solution of diisopropylamine (17.95 mL, 128 mmol) in THF (150 mL) at 0°C, and the reaction was stirred at 0°C for 30 minutes. The flask was then cooled to –30°C, and indole **185d** (25.18g, 91.48 mmol) dissolved in THF (75 mL) was added dropwise. The reaction was warmed to 0°C over 1 hour and stirred at that temperature for an additional 4.5 hours. The reaction was again cooled to –30°C, and solid paraformaldehyde (8.25g, 274 mmol) which had been dried under vacuum (> 0.5 mm Hg) was added in one portion. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with 10% $NaHCO_3$ (10 mL), and the solvent removed *in vacuo*. The residue was dissolved in EtOAc/10%

$NaHCO_3$. The organic phase was separated, washed sequentially with water and brine, dried ($MgSO_4$), and the solvent removed. The product was purified by flash silica gel chromatography (3-20% EtOAc/hexane) to give 16.12g (58%) of an off-white solid: R_f = 0.11 (30% EtOAc/hexane); ^1H NMR (DMSO-d_6): δ 7.98-7.96 (2H, m), 7.77-7.74 (1H, m), 7.72-7.68 (1H, m), 7.61-7.55 (3H, m), 7.15-7.09 (1H, m), 6.75 (1H, s), 5.53 (1H, t, J = 5.8 Hz), 4.83 (2H, d, J = 5.3 Hz).

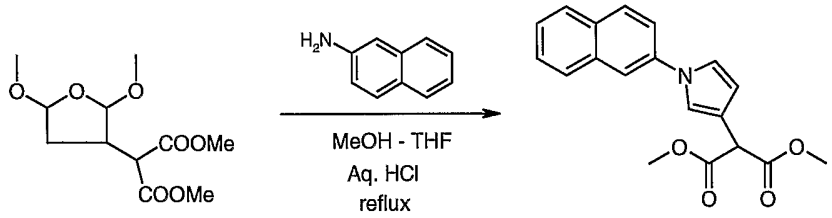
Compound 185f:



185f

To a dichloromethane solution (28 mL) of triphenylphosphine (polymer-supported, 3 mmol/g, 1.46 g, 4.37 mmol) was added I_2 (1.11 g, 4.37 mmol). The mixture was stirred for 15 minutes. Imidazole (320 mg, 4.98 mmol) was introduced and stirred gently at room temperature for another 15 minutes. **185c** (606 mg, 1.99 mmole) was also introduced into the reaction mixture and refluxed for 1 hour. It was filtered through a pad of celite. The filtrate was diluted with dichloromethane (30 mL), washed with saturated $Na_2S_2O_3$ (30 mL), water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated to give the crude title compound in 71% yield. ^1H NMR (DMSO-d_6): δ 8.05-7.55 (7H, m), 7.11 (1H, s), 7.25-7.20 (1H, m), 5.07 (2H, m). LCMS (APCI): 415.9 ($M+H^+$).

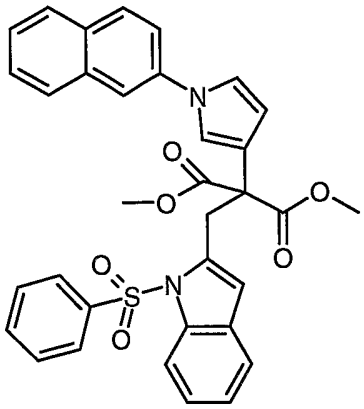
Compound 185g:



185g

To a tetrahydrofuran/methanol solution (5 mL/5 mL) of tetrahydrofuran derivative (avaibable from BASF, Ludwigscheifen, Germany, 1.00 g, 3.82 mmol) were added naphthalen-2-ylamine (273 mg, 1.91 mmol) and 1M HCl (2.1 mL, 0.55 mmol). The mixture was refluxed for 45 minutes. It was then evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 44% yield. ^1H NMR (DMSO-d_6): δ 8.09 (1H, d, J=2Hz), 8.04 (1H, d, J=8.9Hz), 7.96 (1H, d, J=8.6Hz), 7.80 (1H, dd, J=8.9, 2.3Hz), 7.65-7.46 (4H, m),.7.28 (1H, td, J=6.8, 1.3Hz), 7.09 (1H, m), 6.94 (1H, dd, J=8.6, 2.1Hz), 6.82 (1H, d, J=2Hz), 6.34 (2H, m), 5.38 (1H, br s), 3.71 (6H, s), 3.70-3.65 (2H, m). LCMS (APCI): 324.1 ($M+H^+$).

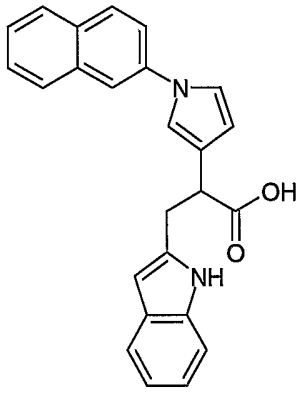
Compound 185h:



185h

To a N, N-dimethyl-formamide solution (5 mL) of **185g** (263 mg, 0.814 mmol) at 0°C was added sodium hydride (49 mg, 60% dispersion in mineral oil, 1.22 mmol). The mixture was stirred at room temperature for 1 hour. 2-(Bromomethyl)-1-(phenylsulfonyl)-1H indole (356 mg, 1.02 mmol) was introduced and stirred for overnight. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-15% ethyl acetate in hexane), the title compound was obtained in 39% yield. ^{1}H NMR ($CDCl_3$): δ 8.26 (1H, d, J=8.4Hz), 8.00-7.15 (9H, m), 6.38 (2H, m), 4.28 (2H, s), 3.80 (6H, s). LCMS (APCI): 593.1 ($M+H^+$).

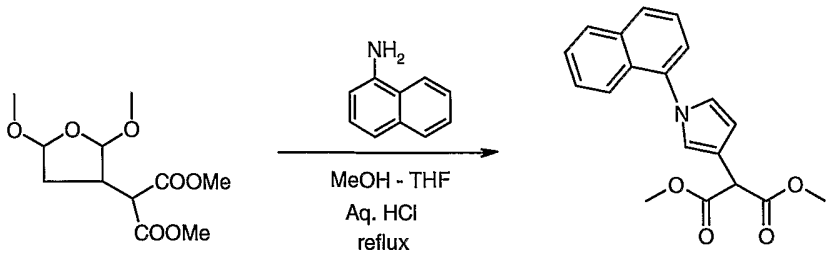
Example 185:



185

To a methanol solution (5 mL) of **185h** (183 mg, 0.309 mmol) was added 5% sodium hydroxide (5 mL). The mixture was refluxed for overnight. It was then acidified with 1M HCl. Methanol was evaporated and the water phase was extracted with ethyl acetate (3 X 10 mL). The combined ethyl acetate extract was washed with brine (20 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% methanol in dichloromethane) and further purification by prep. HPLC, the title compound was obtained in 21% yield. ^{1}H NMR (DMSO-d_6): δ 12.23 (1H, br s), 10.98 (1H, s), 8.06 (1H, d, J=2.1Hz), 8.02 (1H, d, J=8.7Hz), 7.95 (1H, s0, 7.92 (1H, s), 7.80 (1H, dd, J=9.1, 2.3Hz), 7.59-7.44 (4H, m), 7.40 (1H, d, J=7.1Hz), 7.28 (1H, d, J=8.1Hz), 6.99 (1H, td, J=7.2, 1.2Hz), 6.91 (1H, m), 6.33 (1H, t, J=2.1Hz), 6.18 (1H, s), 4.00 (1H, dd, J=8, 9.6Hz), 3.47-3.35 (1H, m), 3.24 (1H, dd, J=15.1, 6.6Hz). LCMS (APCI): 381.1 ($M+H^+$). Elemental Analysis for ($C_{25}H_{20}N_2O_2 \bullet 0.4H_2O \bullet 0.5CH_3CN$) calc: C 76.51, 5.51, N 8.58; found: C 76.44, H 5.38, N 8.67.

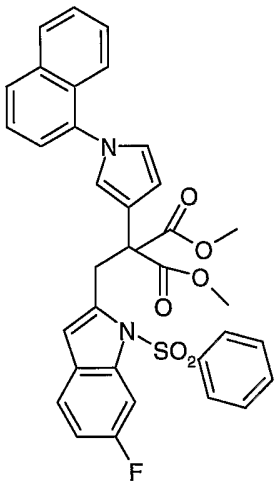
Compound 186a:



186a

To a tetrahydrofuran/methanol solution (30 mL/30 mL) of tetrahydrofuran derivative (avaibable from BASF, Ludwigscheifen, Germany, 8.00 g, 30.56 mmol) were added naphthalen-1-ylamine (2.18 g, 15.3 mmol) and 1M HCl (15 mL). The mixture was refluxed for 50 minutes. It was then evaporated. The residue was dissolved in ethyl acetate (150 mL). The ethyl acetate solution was washed with brine (2x80 mL), dried with Na_2SO_4 and concentrated. After column chromatography (15-25% EtOAc in hexane), the title compound was obtained as an oil in 50% yield (2.5g). LCMS (APCI): 324 ($M+H^+$).

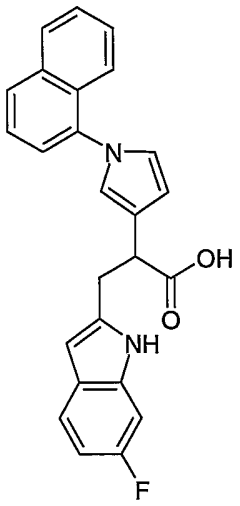
Compound 186b:



186b

To a N, N-dimethyl-formamide solution (4 mL) of **186a** (199 mg, 0.616 mmol) at 0°C was added sodium hydride (20 mg, 0.77 mmol). The mixture was stirred at 0°C for 1.5 hour. 3484-179 (128 mg, 0.308 mmol) was introduced and stirred for 2 hours. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 46% yield. ^1H NMR (DMSO-d_6): δ 8.00 (1H, dd, J=12.7, 8.1Hz), 7.81-7.72 (2H, m), 7.58-7.50 (3H, m), 7.48-7.42 (2H, m), 7.33 (1H, d, J=8.3Hz), 7.28-7.23 (1H, m), 7.13 (1H, td, J=9.3, 2.5Hz), 7.01 (1H, t, J=2.5Hz), 6.92 (1H, d, J=2Hz), 6.35 (1H, s), 6.30 (1H, dd, J=2.8, 1.8Hz), 3.68 (2H, s), 3.32 (6H, s). LCMS (APCI): 611.1 ($M+H^+$).

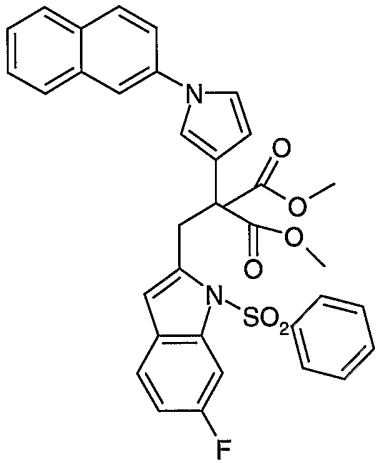
Example 186:



186

To a methanol solution (3 mL) of **186b** (84 mg, 0.138 mmol) was added 5% sodium hydroxide (1 mL). The mixture was refluxed for overnight. It was then diluted with ethyl acetate and acidified with 1M HCl. The ethyl acetate phase was separated and concentrated. After column chromatography (30-50% ethyl acetate in hexane), the title compound was obtained in 55% yield.
^{1}H NMR (DMSO-d_6): δ 12.4 (1H, br s), 11.21 (1H, s), 8.18 (1H, d, J=8.4Hz), 8.13 (1H, d, J=8Hz), 7.76-7.70 (2H, m), 7.65 (1H, s), 7.63 (1H, s), 7.61-7.54 (2H, m), 7.21 (1H, dd, J=9.8, 2Hz), 7.20-7.10 (2H, m), 6.70-6.85 (1H, m), 6.47 (1H, t, J=2.3Hz), 6.33 (1H, s), 4.14 (1H, m), 3.54 (1H, m), 3.28 (1H, dd, J=6.3Hz). LCMS (APCI): 399.1 ($M+H^+$). HRMS (MALDI) calc for $C_{25}H_{20}N_2O_2F(M+H^+)$ 399.1509; found 399.1523.

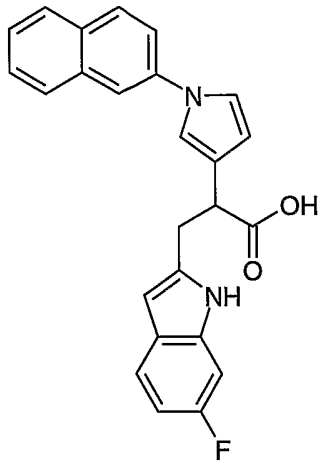
Compound 187a:



187a

To a N, N-dimethyl-formamide solution (4 mL) of **185g** (149 mg, 0.462 mmol) at 0°C was added sodium hydride (14 mg, 0.54 mmol). The mixture was stirred at 0°C for 1.5 hour. 3484-179 (128 mg, 0.308 mmol) was introduced and stirred for 2 hours. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 57% yield. ^{1}H NMR (DMSO-d_6): δ 8.1-7.4 (10H, m), 7.08-7.03 (2H, m), 6.30 (2H, s), 4.10 (2H, s), 3.64 (6H, s). LCMS (APCI): 611.1 ($M+H^+$).

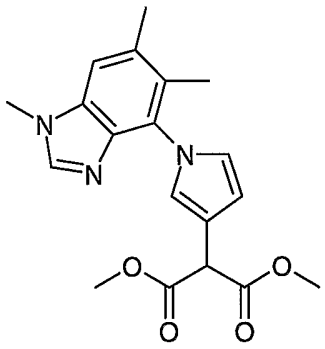
Example 187:



187

To a methanol solution (4 mL) of **187a** (101 mg, 0.166 mmol) was added 5% sodium hydroxide (3 mL). The mixture was refluxed for overnight. Methanol was evaporated. The residue was then diluted with ethyl acetate and acidified with 1M HCl. The ethyl acetate phase was separated and concentrated. After column chromatography (20-30% ethyl acetate in hexane), the title compound was obtained in 50% yield. ^{1}H NMR (DMSO-d_6): δ 12.09 (1H, br s), 10.93 (1H, s), 7.92 91H, d, J=2.0Hz), 7.87 (1H, d, J=8.9Hz), 7.80 (1H, s), 7.65 (1H, dd, J=8.9, 2.3Hz), 7.40 (1H, t, J=7.3Hz), 7.38-7.30 (3H, m), 7.24 (1H, dd, J=8.3, 5.3Hz), 6.91 (1H, dd, J=10.1, 2.3Hz), 6.68-6.58 (1H, m), 6.17 (1H, t, J=2.3Hz), 6.04 (1H, s), 3.84 (1H, dd, J=9.3, 6.3Hz), 3.24 91H, dd, J=15.1, 9.3Hz), 2.98 (1H, dd, J=14.9, 6.3Hz). LCMS (APCI): 399.1 ($M+H^+$). Elemental Analysis for ($C_{25}H_{19}FN_2O_2$•0.35H_2O•0.15EtOAc) calc: C 73.57, H 5.04, N 6.70; found: C 73.84, H 5.18, N 6.46.

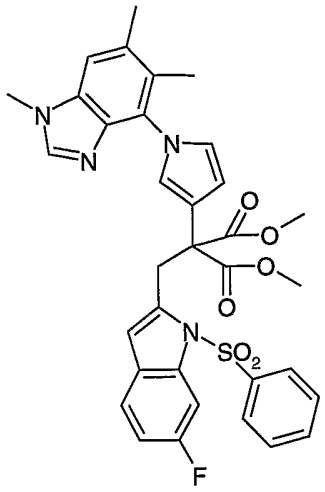
Compound 188a:



188a

To a tetrahydrofuran/methanol solution (10 mL/10 mL) of tetrahydrofuran derivative (avaibable from BASF, Ludwigscheifen, Germany, 1.50 g, 5.71 mmol) were added 1,5,6-trimethyl-1H-benzoimidazol-4-ylamine (500 mg, 2.86 mmol) and 1M HCl (2.89 mL, 2.89 mmol). The mixture was refluxed for overnight. It was then evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with cold saturated sodium bicarbonate (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (75-100% ethyl acetate in hexane), the title compound was obtained in 17% yield. ^{1}H NMR (DMSO-d_6): δ 8.04 (1H, s), 7.44 (1H, s), 6.90 (1H, t, J=2.1Hz), 6.87 (1H, t, J=2.5Hz), 6.23 (1H, m), 4.84 (1H, s), 3.81 (3H, s), 3.68 (6H, s), 2.40 (3H, s), 2.04 (3H, s). LCMS (APCI): 356.1 ($M+H^+$).

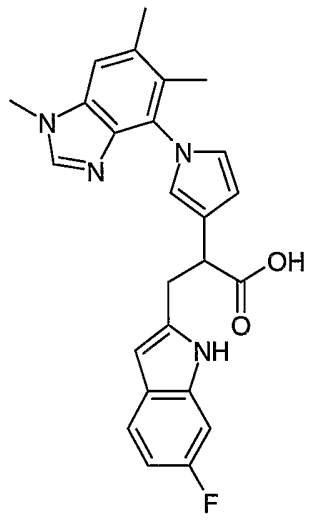
Compound 188b:



188b

To a N, N-dimethyl-formamide solution (5 mL) of **188a** (170 mg, 0.479 mmol) at 0°C was added sodium hydride (18 mg, 0.72 mmol). The mixture was stirred at 0°C for 1.5 hour. **185b** (248 mg, 0.599 mmol) was introduced and stirred for 3 hours. DMF was evaporated. The residue was dissolved in ethyl acetate (40 mL). The ethyl acetate solution was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (50-100% ethyl acetate in hexane), the title compound was obtained in 78% yield. ^{1}H NMR (DMSO-d_6): δ 8.04 (1H, s), 7.82-7.75 (2H, m), 7.62-7.50 (2H, m), 7.48-7.40 (2H, m), 7.09 (1H, td, J=9.1, 2.3Hz), 6.88 (1H, t, J=1.7Hz), 6.80 (1H, t, J=2.2Hz), 6.33 (1H, s), 6.20 (1H, m), 4.1-4.0 (2H, m), 3.80 (3H, s), 3.65 (6H, s), 2.36 (3H, s), 1.98 (3H, s). LCMS (APCI): 643.1 ($M+H^+$).

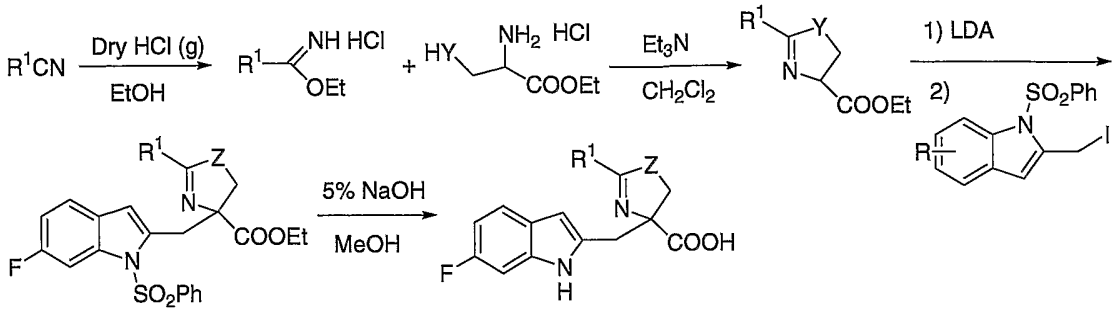
Example 189:



189

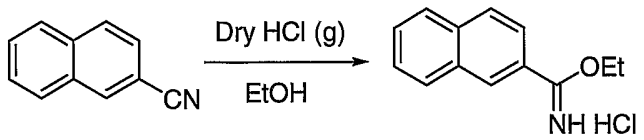
To a methanol solution (3 mL) of **189b** (235 mg, 0.366 mmol) was added 5% sodium hydroxide (2 mL). The mixture was stirred at 65°C overnight. It was then purified by prep. HPLC to give the title compound in 31% yield. ^{1}H NMR (DMSO-d_6): δ 12.0 (1H, br s), 11.01 (1H, s), 8.8 (1H, br s), 7.66 (1H, s), 7.35 (1H, dd, J=8.6, 5.6Hz), 7.02 (1H, dd, J=10.1, 2.2Hz), 6.85-6.80 (2H, m), 6.78-6.70 (1H, m), 6.29 (1H, br t, J=2.2Hz), 6.13 (1H, s), 3.95 (1H, s), 3.95 (1H, dd, J=9.4,6.1Hz), 3.91 (3H, s), 3.34 (1H, dd, J=14.9, 9.6Hz), 3.07 (1H, dd, J=14.9, 6.0Hz), 2.40 (3H, s), 1.93 (3H, s). LCMS (APCI): 431.1 ($M+H^+$). Elemental Analysis for ($C_{25}H_{23}FN_4O_2$•0.7H_2O•1TFA) calc: C 58.21, H 4.60, N 10.06; found: C 58.19, H 4.60, N 10.08.

Synthesis of Spiro-thiazoline and Spiro-oxazoline:



Z=O or S

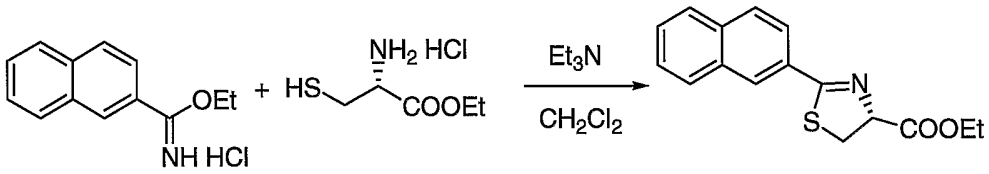
Compound 190a:



190a

At 0°C, dry HCl gas was bubbled through an ethanol solution (28mL) of 2-Naphthonitrile (3.8g, 24.8mmol) for 1h. The solution was stirred at 25°C for 10h. The precipitate was collected by filtration (2.9g). The filtrate was evaporated *in vacuo* to dryness giving 2.9g of an oil. Both crops were confirmed to be the title compound.

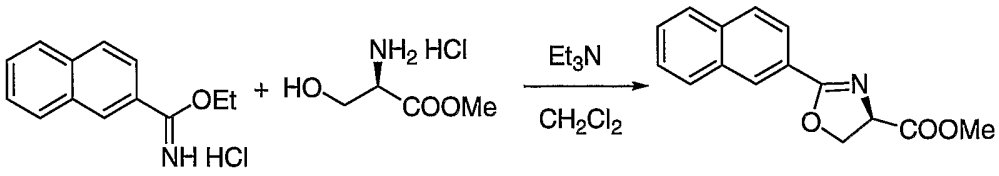
Compound 190b:



190a **190b**

To a methylene chloride suspension (15mL) of Ethyl L-cysteinate hydrochloride (3.07g, 16.5mmol) at 0°C was added triethylamine (1.7mL, 12.2mmol) and the imidate **190c** (2.9g, 12.3mmol). After stirred at 25°C for 12h, the mixture was diluted with methylene chloride (20mL), washed with brined (2x30mL), dried ($MgSO_4$) and concentrated. The residue was purified with column chromatography (15-30% EtOAc in hexanes) affording the title compound (3g, 86% yield) as a white solid. ^1H NMR ($CDCl_3$): δ 8.31 (1H, s), 8.03 (1H, dd, J=8.6, 1.8Hz), 7.93-7.83 (3H, m), 7.58-7.50 (2H, m), 5.32 (1H, t, J=9.4Hz), 4.32 (2H, q, J=7.1Hz), 3.76 (1H, dd, J=11.1, 8.8Hz), 3.68 (1H, dd, J=11.1, 9.3Hz), 1.35 (3H, t, J=7.3Hz). LCMS (APCI positive): 286 ($M+H^+$).

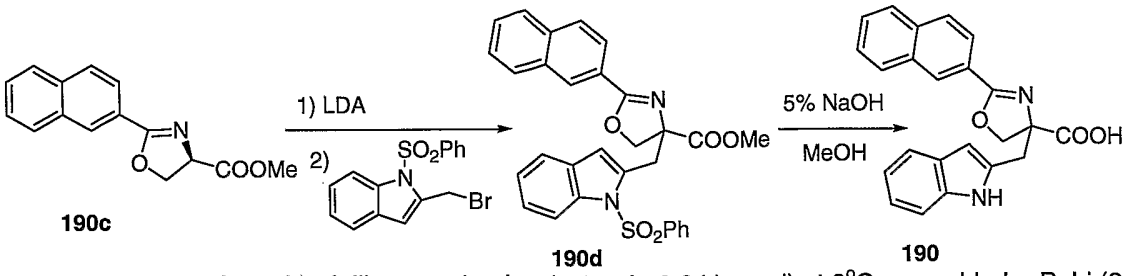
Compound 207c:



190a **190c**

To a methylene chloride suspension (15mL) of methyl D-serinate hydrochloride (2.56g, 16.5mmol) at 0°C was added triethylamine (1.7mL, 12.2mmol) and the imidate **190a** (2.9g, 12.3mmol). After stirred at 25°C for 12h, the mixture was diluted with methylene chloride (20mL), washed with brined (2x30mL), dried ($MgSO_4$) and concentrated. The residue was purified with column chromatography (20-40% EtOAc in hexanes) affording the title compound (2g, 64% yield) as a white solid. LCMS (APCI positive): 256 ($M+H^+$).

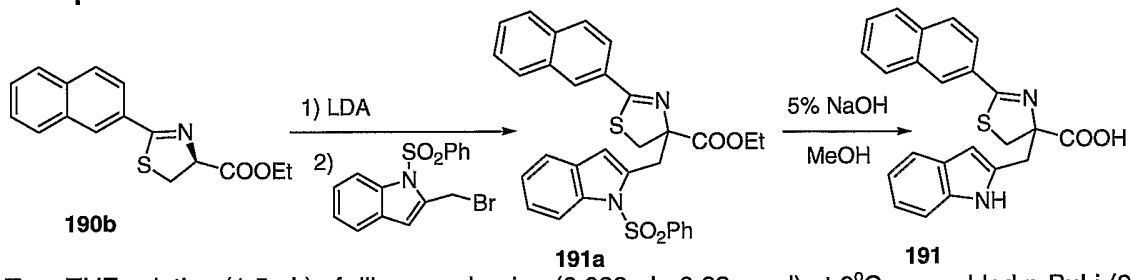
Example 190:



190c **190d** **190**

To a THF solution (1.5mL) of diisopropylamine (0.13mL, 0.941mmol) at 0°C was added n-BuLi (2.5M, 0.38mL, 0.941mmol). The solution was stirred for 15min at 0°C and then cooled to –78°C. A THF solution (1mL) of the oxazoline **190c** (200mg, 0.784mmol) was added. The solution turned dark red and was stirred for 25min at –78°C. 2-(Bromomethyl)-1-(phenylsulfonyl)-1*H*-indole (329mg, 0.941mmol) was added in one portion. The mixture was stirred at 25°C for 2h. The resulted suspension was added MeOH (1mL) and 10% NaOH solution (1mL), heated at reflux for 12h. Ice-cooled 5% HCl was adjusted the pH to 5-6. The mixture was extracted with EtOAc (3x25mL). Combined organic layers were washed with brine (1x20mL), dried (Na_2SO_4) and concentrated. The residue was purified with column chromatography (EtOAc) to give the title compound (40mg, 13% yield) as a pale tan solid. ^{1}H NMR (CD_3OD): δ 10.11 (1H, br s), 8.32 (1H, s), 7.91 (1H, d, J=8.9Hz), 7.83-7.77 (3H, m), 7.45 (2H, m), 7.27 (1H, d, J=7.8Hz), 7.14 (1H, d, J=8Hz), 6.88 (1H, td, J=8.1, 1Hz), 6.80 (1H, m), 6.16 (1H, s), 4.79 (1H, d), 4.47 (1H, d, J=9.1Hz), 3.42 (1H, d, J=14.6Hz), 3.28 (1H, d, J=14.6Hz). Elemental Analysis for ($C_{23}H_{18}N_2O_3$•0.75H_2O) calc: C 71.95, H 5.12, N 7.30; found: C 71.96, H 4.96, N 7.24.

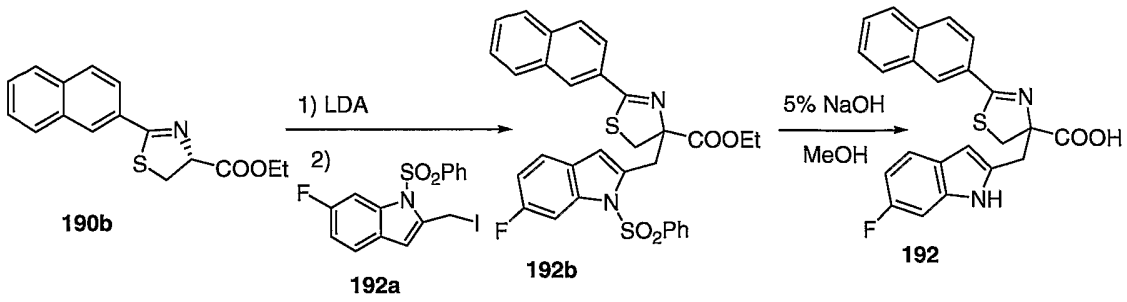
Example 191:



190b **191a** **191**

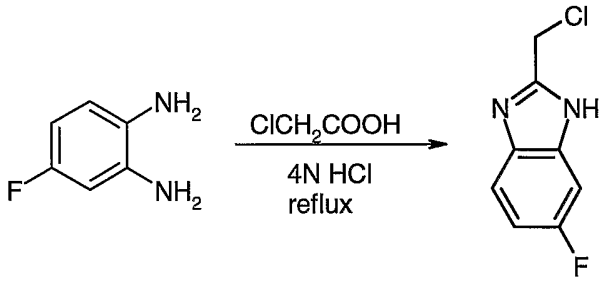
To a THF solution (1.5mL) of diisopropylamine (0.089mL, 0.63mmol) at 0°C was added n-BuLi (2.5M, 0.25mL, 0.63mmol). The solution was stirred for 15min at 0°C and then cooled to –78°C. A THF solution (1mL) of the thiazoline **190b** (150mg, 0.526mmol) was added. The solution turned dark red and was stirred for 25min at –78°C. 2-(Bromomethyl)-1-(phenylsulfonyl)-1*H*-indole (220mg, 0.63mmol) was added in one portion. The mixture was stirred at 25°C for 2h. The resulted suspension was added MeOH (1mL) and 10% NaOH solution (1mL), heated at reflux for 12h. Ice-cooled 5% HCl was adjusted the pH to 5-6. The mixture was extracted with EtOAc (3x25mL). Combined organic layers were washed with brine (1x20mL), dried (Na_2SO_4) and concentrated. The residue was purified with column chromatography (EtOAc to 1% MeOH in EtOAc) to give the title compound (6mg, 3% yield) as a pale tan solid. ^{1}H NMR (CD_3OD): δ 8.23 (1H, br s), 7.95-7.80 (4H, m), 7.46 (2H, m), 7.30 (1H, d, J=7.5Hz), 7.17 (1H, d, J=7.9Hz), 6.90 (1H, t, J=7.1Hz), 6.82 (1H, t, J=7.6Hz), 6.20 (1H, s), 3.88 (1H, br s), 3.55-3.35 (3H, br s). (poor resolution due to low solubility); LCMS (APCI positive): 387 ($M+H^+$). HRMS (MALDI) calc for $C_{23}H_{19}N_2O_2S$ ($M+H^+$) 387.1167; found 387.1165.

Example 192:



To a THF solution (1mL) of diisopropylamine (0.059mL, 0.42mmol) at 0°C was added n-BuLi (2.5M, 0.17mL, 0.42mmol). The solution was stirred for 15min at 0°C and then cooled to –78°C. A THF solution (1mL) of the thiazoline **190b** (100mg, 0.351mmol) was added. The solution turned dark red and was stirred for 25min at –78°C. **192a** (174mg, 0.42mmol) was added in one portion. The mixture was stirred at 25°C for 2h. The resulted suspension was added MeOH (1mL) and 10% NaOH solution (1mL), heated at reflux for 12h. Ice-cooled 5% HCl was adjusted the pH to 5-6. The mixture was extracted with EtOAc (3x25mL). Combined organic layers were washed with brine (1x20mL), dried (Na_2SO_4) and concentrated. The residue was purified with column chromatography (EtOAc to 1% MeOH in EtOAc) to give the title compound (60mg, 42% yield) as a pale tan solid. ^{1}H NMR (CD_3OD): δ 8.12 (1H, s), 7.86 (1H, dd, J=8.6, 1.5Hz), 7.8-7.73 (3H, m), 7.43 (2H, m), 7.19 (1H, dd, J=8.6, 5.3Hz), 6.86 (1H, dd, J=10.1, 2.3Hz), 6.6-6.54 (1H, m), 6.14 (1H, s), 3.86 (1H, d, J=11.1Hz), 3.41 (1H, d, J=11.2Hz), 3.39-3.24 (2H, m). LCMS (APCI positive): 405 ($M+H^+$). Elemental Analysis for ($C_{23}H_{17}FN_2O_2S\bullet0.3H_2O\bullet0.55MeOH\bullet0.4CH_2Cl_2$) calc: C 62.33, H 4.50, N 6.07, S 6.95; found: C 62.48, H 4.42, N 6.20, S 6.56.

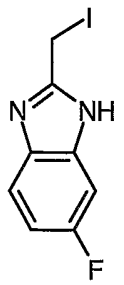
Compound 193a:



193a

A suspension of 4-Fluoro-benzene-1,2-diamine (2.52g, 20mmol) and Chloroacetic acid (2.27g, 24mmol) in 4N HCl solution (20mL) was heated at reflux for 2h. The solution was cooled to 25°C and neutralized by addition of Na_2CO_3. The resulted precipitate (3.3g, 90% yield) was collected by filtration, washed with water and dried in vacumm oven. LCMS: 185 ($M+H^+$).

Compound 193b:

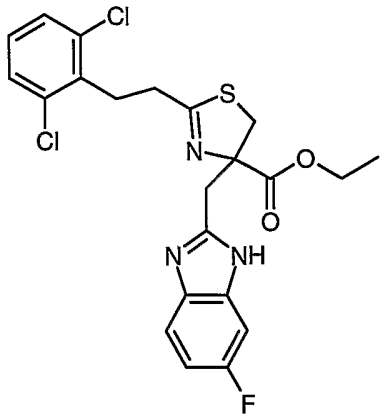


193b

To an acetone solution (90 mL) of **193a** (3.30 g, 17.9 mmol) at 0°C was added KI (2.97 g, 17.9 mmol). The mixture was refluxed for 1.5 hour. It was then filtered and the filtrate was concentrated. After column chromatography (30-50% ethyl acetate in hexane), the title compound was obtained in 51%

yield. ^{1}H NMR (DMSO-d_6): δ 12.79 (1H, br s), 7.50 (1H, dd, J=8.6, 4.8Hz), 7.30 (1H, dd, J=9.6, 2.6Hz), 7.07-7.00 (1H, m), 4.59 (2H, s). LCMS (APCI): 276.9 (M+H$^+$).

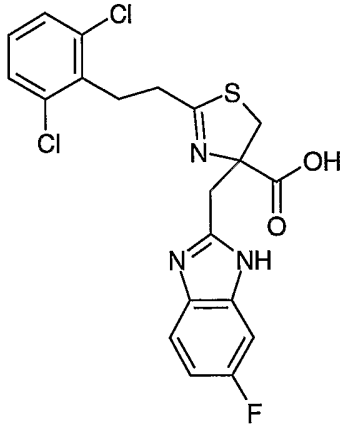
Example 193:



193

To a tetrahydrofuran solution (1.5 mL) of diisopropylamine (89 mg, 0.877 mmol) at 0°C was added *n*-butyllithium (0.28 mL, 2.5 M in hexane, 0.80 mmol) dropwise. The mixture was stirred at 0°C for 15 minutes. A tetrahydrofuran solution (2 mL) of **203b** (242 mg, 0.731 mmol) was introduced at -78°C and stirred at -78°C for 30 minutes. Iodide **193b** (242 mg, 0.732 mmol) was added at -78°C and stirred at room temperature for 2 hours. The reaction was quenched with cold saturated ammonium chloride. Tetrahydrofuran was evaporated. The residue was extracted with ethyl acetate (2X10 mL). The ethyl acetate solution was washed with brine (10 mL), dried with Na_2SO_4 and concentrated. After column chromatography (30-50% ethyl acetate in hexane), the title compound was obtained in 83% yield. LCMS (APCI): 480.0 (M+H$^+$).

Example 194:

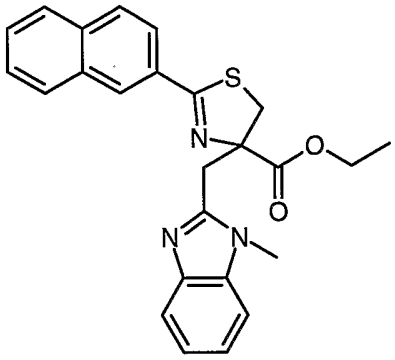


194

To a methanol solution (4 mL) of **193** (292 mg, 0.608 mmol) was added 5% sodium hydroxide (2 mL). The mixture was stirred at room temperature for 4 hours. It was then purified by prep. HPLC to give the title compound in 7% yield. ^{1}H NMR (DMSO-d_6): δ 12.7 (1H, br s), 7.59-7.45 (3H, m), 7.33 (2H, m), 7.07-7.0 (1H, m), 3.92 (2H, m), 3.14-3.08 (2H, m), 2.7-2.6 (4H, m).

LCMS (APCI): 452.0 (M+H$^+$). Elemental Analysis for ($C_{20}H_{16}Cl_2FN_3O_2S$•0.7H_2O•0.4TFA) calc: C 48.93, H 3.51, N 8.23; found: C 48.88, H 3.42, N 8.42.

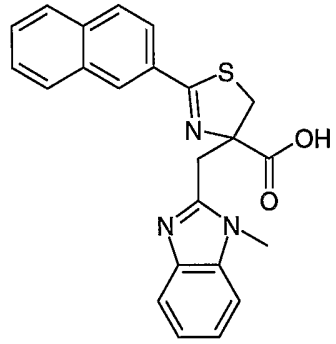
Example 195:



195

To a tetrahydrofuran solution (1.5 mL) of diisopropylamine (92 mg, 0.907 mmol) at 0°C was added *n*-butyllithium (0.29 mL, 2.5 M in hexane, 0.83 mmol) dropwise. The mixture was stirred at 0°C for 15 minutes. A tetrahydrofuran solution (2 mL) of **190b** (215 mg, 0.755 mmol) was introduced at -78°C and stirred at -78°C for 30 minutes. 2-(BROMOMETHYL)-1-METHYL-1H-BENZIMIDAZOLE (MFCD05664649, 150 mg, 0.831 mmol) was added at -78°C and stirred at room temperature for 2 hours. The reaction was quenched with cold saturated ammonium chloride. Tetrahydrofuran was evaporated. The residue was extracted with ethyl acetate (2X10 mL). The ethyl acetate solution was washed with brine (10 mL), dried with Na_2SO_4 and concentrated. After column chromatography (20-30% ethyl acetate in hexane), the title compound was obtained in 60% yield. ^{1}H NMR ($CDCl_3$): δ 8.18 (1H, s), 7.97 (1H, dd, J=8.6, 1.5Hz), 7.89-7.80 (3H, m), 7.75-7.70 (1H, m), 7.58-7.49 (2H, m), 7.26-7.20 (2H, m), 4.31-4.23 (3H, m), 4.12 (1H, d, J=11.9Hz), 3.77 (3H, s), 3.70 (2H, s), 1.25 (3H, t, J=7.1Hz). LCMS (APCI): 430.1 ($M+H^+$).

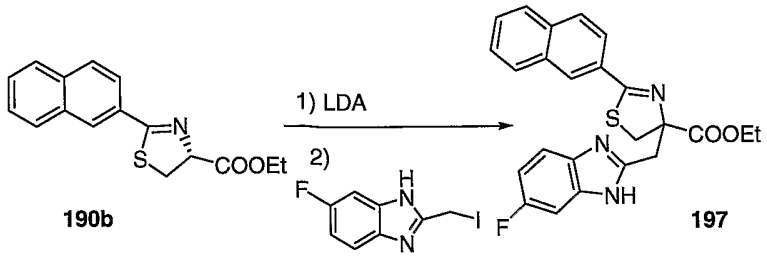
Example 196:



196

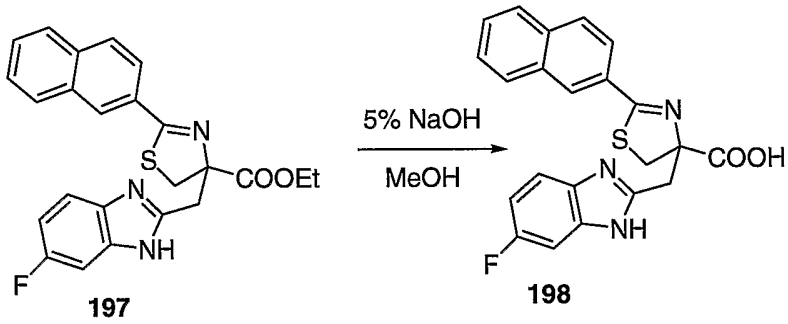
To a methanol solution (4 mL) of **195** (175 mg, 0.408 mmol) was added 5% sodium hydroxide (3 mL). The mixture was stirred at room temperature for 3.5 hours. Methanol was evaporated. The residue was neutralized with saturated ammonium chloride. It was then extracted with ethyl acetate (3X10 mL). The ethyl acetate solution was concentrated and the solids were washed with ethyl ether (2X10 mL) to give the title compound in 100% yield. ^{1}H NMR (DMSO-d_6): δ 8.31 (1H, s), 8.18 (1H, d, J=7.6Hz), 8.12-8.04 (3H, m), 7.76-7.64 (4H, m), 7.54-7.50 (1H, m), 7.28-7.20 (2H, m), 3.91 (3H, s), 3.65 (1H, d, J=14.4Hz), 3.59 (1H, d, J=14.7Hz), 3.51 (2H, AB). LCMS (APCI): 402.0 ($M+H^+$). Elemental Analysis for ($C_{23}H_{19}N_3O_2S \bullet 0.7NH_3 \bullet 2.3H_2O \bullet 0.1$EtOAc) calc: C 60.62, H 5.76, N 11.18; found: C 60.58, H 5.60, N 11.16.

Example 197:



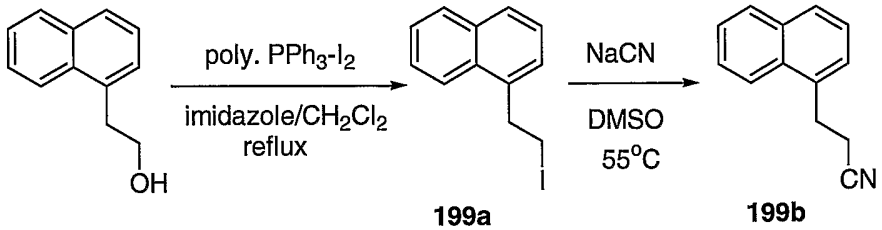
To a THF solution (2mL) of diisopropylamine (0.16mL, 1.16 mmol) at 0°C was added n-BuLi (2.87M, 0.40mL, 0.1.16mmol). The solution was stirred for 15min at 0°C and then cooled to –78°C. A THF solution (1mL) of the thiazoline **190b** (300mg, 1.05mmol) was added. The solution turned dark red and was stirred for 25min at –78°C. Iodide **193b** (500mg, 1.81mmol) was added in one portion. The mixture was stirred at 25°C for 15h. A concentrated ammonium chloride solution (2.5mL) was added. The aqueous solution was extracted with EtOAc (3x20mL). Combined organic layers were washed with brine (1x50mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified with column chromatography (30-40% EtOAc in hexanes) to give the title compound (400mg, 88% yield) as a solid. ^{1}H NMR (DMSO-*d6*): δ 10.12 (1H, br s), 8.31 (1H, s), 8.03 (1H, dd, J=8.6, 1.8Hz), 7.97-7.88 (3H, m), 7.66-7.52 (3H, m), 7.42-7.30 (1H, m), 6.98 (1H, tt, J=9.4, 2.5Hz), 4.24-4.17 (2H, m), 3.97 (1H, d, J=11.6Hz), 3.74-3.58 (3H, m), 1.15 (3H, t, J=7.1Hz). LCMS (APCI positive): 454 ($M+H^+$).

Example 198:



To a methanol solution (4mL) of the ester **197** (400mg, 0.923mmol) was added 10% NaOH solution (2mL). After stirred at 25°C for 15h, the solution was concentrated and added ammonium chloride solution (5mL). The suspension was extracted with EtOAc (3x15mL). The combined organic layers were washed (brine, 1x25mL), dried (Na_2SO_4) and concentrated. The residue was triturated with warm ether and dried in vacuum oven, affording the title compound (280mg, 75% yield) as pale yellow solid. ^{1}H NMR (DMSO-*d6*): δ 12.94 (1H, br s), 8.39 (1H, s), 8.25-8.21 (1H, m), 8.15-8.04 (3H, m), 7.76 (2H, m), 7.64 (1H, dd, J=8.8, 5.0Hz), 7.46 (1H, dd, J=9.8, 2.5Hz), 7.12-7.05 (1H, m), 4.17 (1H, d, J=10.7Hz), 3.68-3.61 (2H, m), 3.34 (1H, d, J=13.9Hz). LCMS (APCI positive): 406 ($M+H^+$). Elemental Analysis for ($C_{22}H_{16}FN_3O_2S$•0.20H_2O•0.85HCl) calc: C 60.00, H 3.96, N 9.54, S 7.28; found: C 60.37, H 4.16, N 9.40, S 6.90.

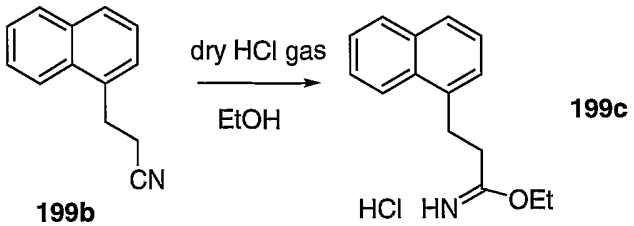
Compound 199b:



To a methylene chloride suspension (100mL) of polymer-supported PPh_3 (6.66g, 20mmol) was added iodine (5.07g, 20mmol). After 15min, imidazole was added (1.7g, 25mmol) and the mixture was stirred for another 15min. 2-Naphthalen-1-yl-ethanol (1.72, 10mmol) was added. The suspension was heated at reflux for 30min, cooled to 25°C and filtered. The filtrate was washed with sat'd

$Na_2S_2O_3$ solution (2x25mL) and water (1x30mL), dried ($MgSO_4$) and evaporated *in vacuo* to dryness. The resulted iodide **199a** (2.3g) was dissolved in DMSO (20mL). Sodium cyanide (0.735g, 15mmol) was added. The solution was heated at 55°C for 2.5h and then concentrated *in vacuo*. The residue was re-dissolved in a co-solvent EtOAc/CH_2Cl_2/Et_2O (10mL/10mL/10mL). The solution was washed with brine (4x20mL), dried ($MgSO_4$) and evaporated *in vacuo* to dryness. The title compound (1.7g) was obtained as an oil. **199a:** ^{1}H NMR ($CDCl_3$): δ 7.97 (1H, d, J=8.5Hz), 7.98-7.85 (1H, m), 7.79 (1H, d, J=8.1Hz), 7.58-7.46 (2H, m), 7.42 (1H, t, J=7Hz), 7.36 (1H, d, J=6.1Hz), 3.65 (2H, t, J=7.8Hz), 3.47 (2H, t, J=8.4Hz). **199b:** ^{1}H NMR ($CDCl_3$): δ 7.92 –7.86 (2H, m), 7.78 (1H, d, J=8.1Hz), 7.58-7.36 (4H, m), 3.41 (2H, t, J=7.3Hz), 2.73 (2H, t, J=7.5Hz)

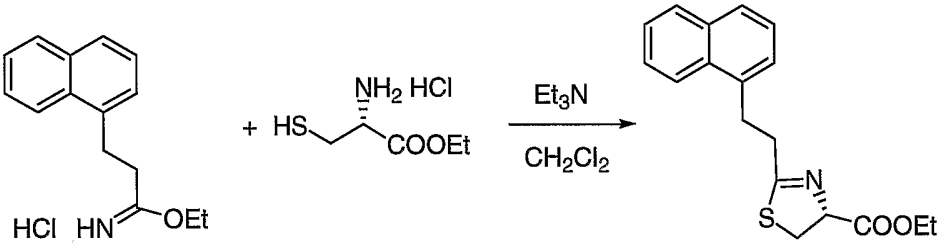
Compound 199c:



199b **199c**

At 0°C, dry HCl gas was bubbled through an ethanol solution (14mL) of the nitrile **199b** (1.1g) for 1h. The solution was stirred at 25°C for 10h. The solution was concentrated *in vacuo*. The residue was triturated with Et_2O. The title compound **199c** (1.4g) was obtained as an off-white solid. ^{1}H NMR (DMSO-*d6*): δ 8.16 (1H, d, J=8.3Hz), 7.99 (1H, m), 7.87 (1H, d, J=8Hz), 7.68-7.55 (2H, m), 7.50 (1H, t, J=7Hz), 7.44 (1H, d, J=6.3Hz), 4.40 (2H, q, J=7.1Hz), 3.05 (2H, t, J=8.4Hz), 1.33 (3H, t, J=6.8Hz).

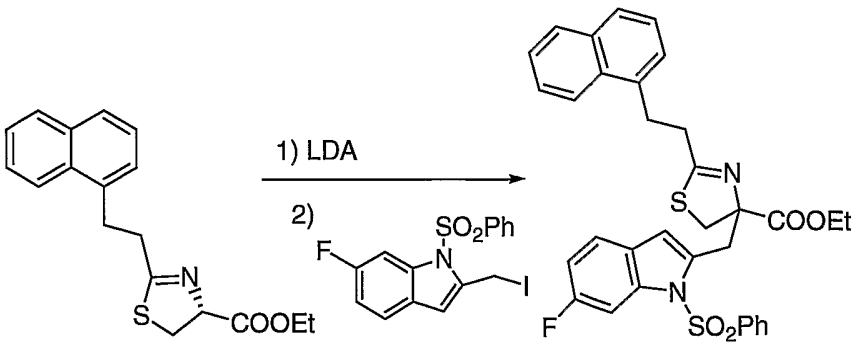
Compound 199d:



199c **199d**

To a methylene chloride suspension (15mL) of Ethyl L-cysteinate hydrochloride (1.5g, 8.1mmol) at 0°C was added triethylamine (1.5mL) and the imidate **199c** (1.4g, 5.32mmol). After stirred at 25°C for 12h, the mixture was diluted with methylene chloride (20mL), washed with brined (2x30mL), dried ($MgSO_4$) and concentrated. The residue was purified with column chromatography (15-30% EtOAc in hexanes) affording the title compound (1.4g, 84% yield) as a white solid. ^{1}H NMR (DMSO-*d6*): δ 8.11 (1H, d, J=8.4Hz), 8.01 (1H, m), 7.87 (1H, t, J=4.3Hz), 7.69-7.55 (2H, m), 7.53-7.48 (2H, m), 5.19 (1H, t, J=8.3Hz), 4.28-4.29 (2H, m), 3.68 (1H, dd, J=11.3, 9.8Hz), 3.56 (1H, dd, J=11.1, 8.3Hz), 3.48-3.40 (2H, m), 2.98 (2H, m), 1.30 (3H, t, J=7.1Hz).

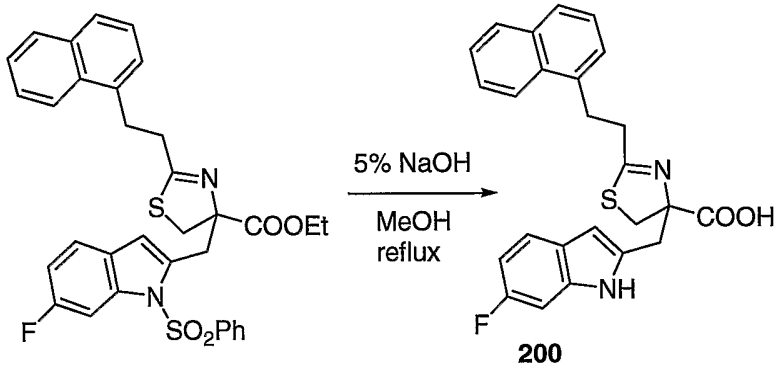
Example 199:



199d **199**

To a THF solution (1.5mL) of diisopropylamine (0.11mL, 0.767mmol) at 0°C was added n-BuLi (2.5M, 0.31mL, 0.767mmol). The solution was stirred for 15min at 0°C and then cooled to –78°C. A THF solution (1mL) of the thiazoline **199d** (200mg, 0.639mmol) was added. The solution turned brown and was stirred for 25min at –78°C. **192a** (317.6mg, 0.767mmol) was added in one portion. The mixture was stirred at 25°C for 2h and added sat'd ammonium chloride solution (5mL). The suspension was extracted with EtOAc (2x15mL). The combined organic layers were washed brine (2x20mL), dried and concentrated. The residue was purified with column chromatography (20-30% EtOAc in hexanes) providing the title compound (225.8mg, 59% yield) as an oil. ^{1}H NMR ($CDCl_3$): δ 8.2-7.2 (9H, m), 6.96 (1H, td, J=8.8, 2.3Hz), 6.48 (1H, s), 4.27-4.16 (2H, m), 3.88-3.80 (2H, m), 3.67-3.53 (2H, m), 3.41 (2H, t, J=8.1Hz), 3.03-2.92 (2H, m), 1.18 (3H, t, J=7Hz). LCMS (ESI positive): 601 ($M+H^+$), 6.23 ($M+Na^+$).

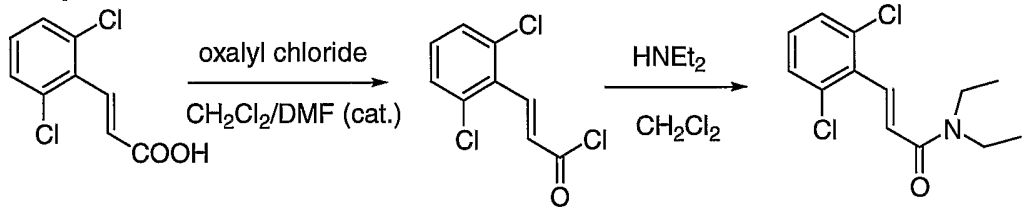
Example 200:



199 **200**

To a MeOH solution (1.5mL) of **199** (70mg, 0.117mmol) was added 10% NaOH solution (1.5mL). The mixture was heated at reflux for 14h. Preparative HPLC purification provided the title compound (13.5mg, 27% yield) as a brown solid. ^{1}H NMR (CD_3OD): δ 7.94 (1H, d, J=8.6Hz), 7.76-7.70 (2H, m), 7.63-7.59 (2H, m), 7.54 (1H, dd, J=8.5, 4.8Hz), 7.20-7.14 (2H, m), 6.94 (1H, td, J=9.4, 2.3Hz), 6.83 (1H, dd, J=10.1, 2.6Hz), 6.67-6.60 (1H, m), 6.11 (1H, s), 3.77-3.31 (4H, m), 3.0-2.86 (4H, m). LCMS (ESI positive): 433 ($M+H^+$). HRMS (MALDI) calc for $C_{21}H_{15}N_2Cl_2FO_2S$ ($M+H^+$) 433.1381; found 433.1390.

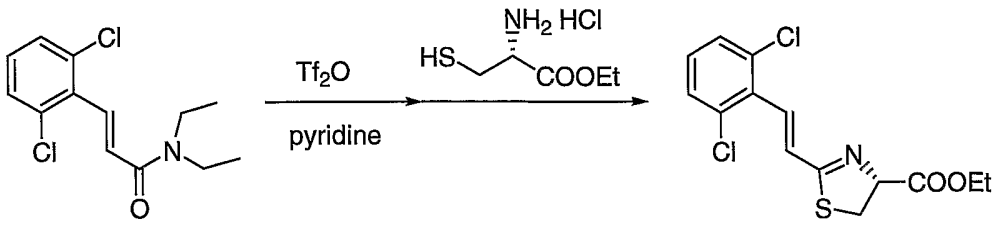
Compound 201b:



201a **201b**

To a methylene chloride suspension (20mL) of 3-(2,6-Dichloro-phenyl)-acrylic acid (1.5g, 6.91mmol) at 0°C was added oxalyl chloride (0.9mL, 10.4mmol) and DMF (1 drop). The solution was stirred at 25°C for 2h and evaporated *in vacuo* to dryness. The solid **201a** was dissolved in methylene chloride (20mL) and cooled to 0°C. The solution was added diethylamine (3mL). After stirred at 25°C for 2h, the mixture was diluted with methylene chloride (30mL), washed with $NaHCO_3$ solution (2x25mL), dried and concentrated *in vacuo* to dryness. The title compound (1.75g, 93% yield) was obtained as a solid. ^{1}H NMR ($CDCl_3$): δ 7.73 (1H, d, J=15.9Hz), 7.35 (2H, d, J=8.1Hz), 7.16 (1H, t, J=8.3Hz), 6.97 (1H, d, J=15.7Hz), 3.55-3.40 (4H, m), 1.28-1.18 (6H, m).

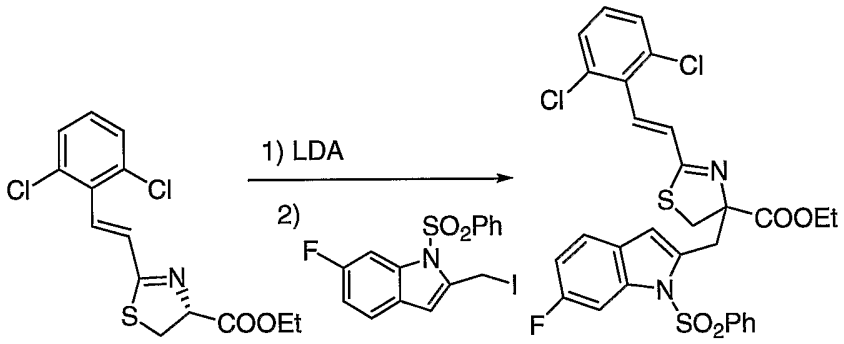
Compound 201c:



201b **201c**

To a methylene chloride solution (30mL) of the amide **201b** (500mg, 1.84mmol) at –78°C was added pyridine (1.49mL, 18.4mmol) and Tf_2O (0.55mL, 3.31mmol). The mixture was slowly warmed to 0°C over a 3h period and then cooled to –78°C. Ethyl L-cysteinate hydrochloride (1.03g, 5.5mmol) was added. The mixture was stirred for 18h at 25°C and diluted with methylene chloride (25mL). The solution was washed with ice-cooled 5% HCl solution (1x20mL), sat'd $NaHCO_3$ solution (1x20mL) and brine (1x20mL), dried and concentrated. The residue was purified with column chromatography (15-25% EtOAc in hexanes) providing the title compound (46mg, 7.6% yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.35 (2H, J=8.1Hz), 7.24 (2H, s), 7.18 (1H, t, J=8.6Hz), 5.21 (1H, t, J=9.4Hz), 4.35-4.26 (2H, m), 3.66 (1H, dd, J=11.2, 9.6Hz), 3.60 (1H, dd, J=11.1, 9.3Hz), 1.35 (3H, t, J=7.4Hz). LCMS (APCI positive): 330 ($M+H^+$)

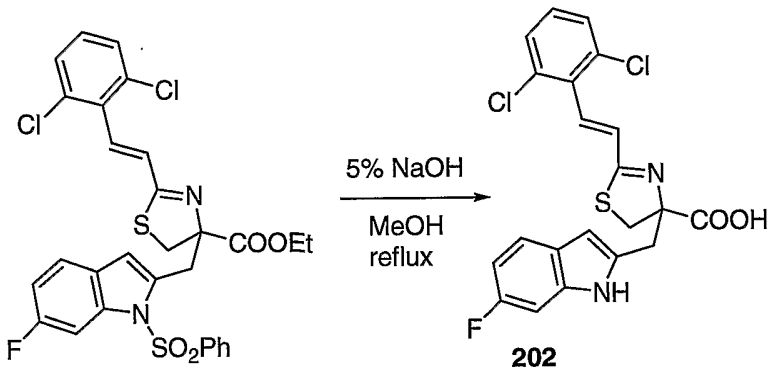
Example 201:



201c **201**

To a THF solution (1.5mL) of diisopropylamine (0.039mL, 0.277mmol) at 0°C was added n-BuLi (2.5M, 0.11mL, 0.277mmol). The solution was stirred for 15min at 0°C and then cooled to –78°C. A THF solution (1mL) of the thiazoline **201c** (76mg, 0.231mmol) was added. The solution turned deep purple and was stirred for 25min at –78°C. **192a** (143mg, 0.346mmol) was added in one portion. The mixture was stirred at 25°C for 12h and added sat'd ammonium chloride solution (5mL). The suspension was extracted with EtOAc (2x15mL). The combined organic layers were washed brine (2x20mL), dried and concentrated. The residue was purified with column chromatography (15-20% EtOAc in hexanes) providing the title compound (68mg, 48% yield) as an oil . ^{1}H NMR ($CDCl_3$): δ 7.93 (1H, dd, J=10.3, 2.3Hz), 7.75-7.1 (11H, m), 6.97 (1H, td, J=8.8, 2.3Hz), 6.54 (1H, s), 4.26 (2H, m), 3.94 (1H, d, J=15.9Hz), 3.92 (1H, d, J=11.6Hz), 3.69 (1H, d, J=15.9Hz), 3.64 (1H, d, J=11.6Hz), 1.21 (3H, t, J=7.1Hz).. LCMS (APCI positive): 617 ($M+H^+$).

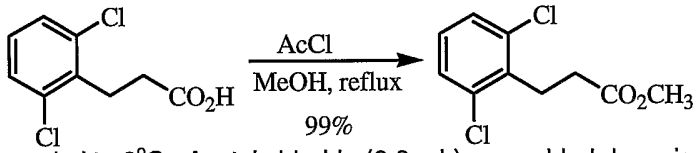
Example 202:



201 **202**

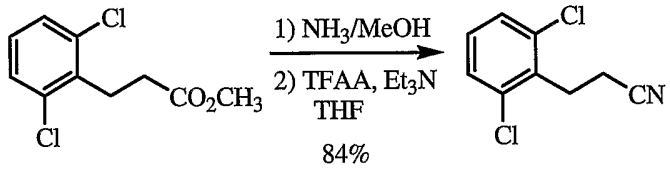
To a MeOH solution (1.5mL) of **201** (68mg, 0.11mmol) was added 10% NaOH solution (1.5mL). The mixture was heated at reflux for 14h. Preparative HPLC purification provided the title compound (2.5mg, 5% yield) as a brown solid. ^{1}H NMR (CD_3OD): δ 7.89 (1H, s), 7.39 (1H, s), 7.37 (1H, s), 7.30-7.21 (2H, m), 7.17 (1H, s), 7.12 (1H, s), 6.90 (1H, dd, J=10.1, 2.6Hz), 6.68-6.6 (1H, m), 6.19 (1H, s), 3.82 (1H, d, J=11.6Hz), 3.50 (1H, d, J=11.6Hz), 3.35-3.32 (2H, m). LCMS (APCI negative): 447 (M-H); HRMS (MALDI) calc for $C_{21}H_{16}N_2Cl_2FO_2S$ ($M+H^+$) 449.0288; found 449.0292.

Compound 203a':



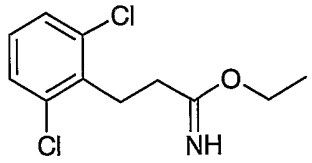
MeOH (120 mL) was cooled to 0°C. Acetyl chloride (6.0 mL) was added dropwise. The ice bath was removed, and the reaction allowed to warm to room temperature over 30 minutes. 3-(2,6-Dichlorophenyl)propionic acid (5.21g, 23.82 mmol) was added, and the reaction was refluxed for three hours. The solvent was removed *in vacuo* to give 5.51g (99 %) of a clear liquid: ^{1}H NMR ($CDCl_3$) δ 7.28-7.25 (2H, m), 7.10-7.06 (m, 1H), 3.71 (s, 3H), 3.27-3.24 (2H, m), 2.59-2.55 (2H, m).

Compound 203b'



Ester **203a'** (5.51g, 23.65 mmol) was dissolved in MeOH (60 mL) and cooled to 0°C. Dry ammonia gas was bubbled into the solution for 1 hour. The reaction flask was wired shut with a rubber suba-seal septum. The reaction was allowed to warm to room temperature and stirred three days. The solvent was removed *in vacuo* to give 5.11g (quant.) of a white crystalline solid which was used without further purification: ^{1}H NMR ($CDCl_3$) □ 7.29-7.27 (2H, m), 7.11-7.07 (1H, m), 5.38 (2H, br), 3.30-3.24 (2H, m), 2.50-2.46 (2H, m). The amide was dissolved in THF (100 mL) and triethylamine (7.25 mL, 52.04 mmol) and cooled to 0°C. Trifluoroacetic anhydride (3.67 mL, 26.02 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for four hours. The solvent was removed, and the crude product was subjected to flash silica gel chromatrography (3% EtOAc/hexane) to give 3.99g (84%) of a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.32 (2H, d, J = 7.8 Hz), 7.17-7.14 (1H, m), 3.35-3.31 (2H, m), 2.66-2.62 (2H, m).

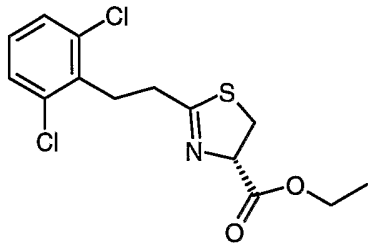
Compound 203a:



203a

Into an ethanol solution (40 mL) of **203b'** (1.72 g, 8.6 mmol) at 0°C was bubbled HCl gas for 1.5 hours. The mixture was stirred at room temperature for overnight. It was then concentrated to give the crude title compound as a HCl salt in 100% yield. ^{1}H NMR (DMSO-d_6): δ 7.50 (2H, d, J=8.3Hz), 7.33 (1H, t, J=7.8Hz), 4.36 (2H, q, J=7.1Hz), 3.23 (1H, t, J=7.3Hz), 2.85 (1H, t, J=7.6Hz), 1.30 (3H, t, J=7Hz). LCMS (APCI): 246.0 (M+H$^+$).

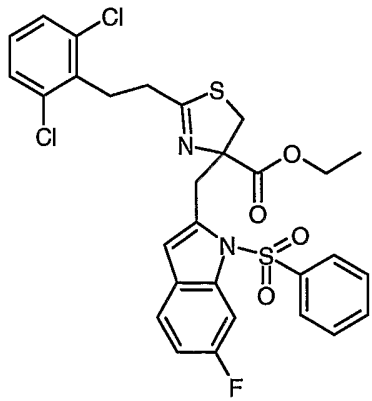
Compound 203b:



203b

To a dichloromethane solution (30 mL) of L-cysteine ethyl ester hydrochloride (2.15 g, 11.6 mmol) at 0°C was added triethylamine (1.55 g, 11.6 mmol). The mixture was stirred at 0°C for 20 minutes. **203a** (2.46 g, 8.71 mmol) was introduced at 0°C and stirred for overnight. It was diluted with dichloromethane (40 mL). The dichloromethane solution was washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5-10% ethyl acetate in hexane), the title compound was obtained in 83% yield. ^{1}H NMR (DMSO-d_6): δ 7.46 (2H, d, J=8Hz), 7.29 (1H, dd, J=8.6, 7.6Hz), 5.12 (1H, m), 4.20-4.10 (2H, m), 3.62 (1H, dd, J=11.1, 9.6Hz), 3.50 (1H, dd, J=11.4, 8.6Hz), 3.17 (2H, t, J=7.8Hz), 2.71-2.64 (2H, m), 1.22 (3H, t, J=7.4Hz). LCMS (APCI): 332.0 (M+H$^+$).

Compound 203c:

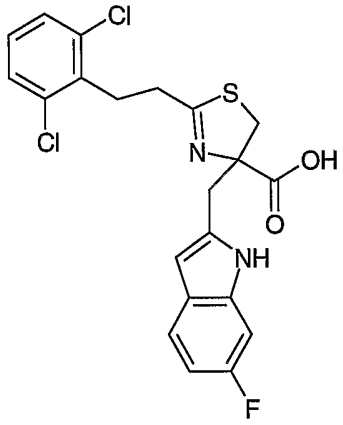


203c

To a tetrahydrofuran solution (2 mL) of diisopropylamine (88 mg, 0.868 mmol) at 0°C was added *n*-butyllithium (0.318 mL, 2.5 M in hexane, 0.795 mmol) dropwise. The mixture was stirred at 0°C for 15 minutes. A tetrahydrofuran solution (2 mL) of **203b** (239 mg, 0.723 mmol) was introduced at -78°C and stirred at -78°C for 30 minutes. **192a** (300 mg, 0.723 mmol) was added at -78°C and stirred at room temperature for 2 hours. The reaction was quenched with cold saturated ammonium chloride.

Tetrahydrofuran was evaporated. The residue was extracted with ethyl acetate (2X10 mL). The ethyl acetate solution was washed with brine (10 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 71% yield. ^{1}H NMR (DMSO-d_6): δ 7.85-7.75 (3H, m), 7.68 (1H, t, J=7.3Hz), 7.60-7.50 (3H, m), 7.43 (2H, d, J=8Hz), 7.25 (1H, t, J=7.6Hz), 7.12 (1H, td, J=9.4, 2.3Hz), 6.65 (1H, s), 4.09 (2H, q, J=6.1Hz), 3.81 (1H, d, J=11.6Hz), 3.75 (1H, d, J=16.2Hz), 3.61 (2H, br d), 3.14 (2H, t, J=8.8Hz), 2.72-2.64 (2H, m), 1.03 (3H, t, J=7.1Hz). LCMS (APCI): 619.0 ($M+H^+$).

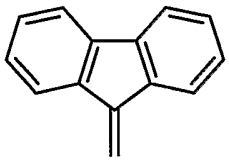
Example 203:



203

To a methanol solution (6 mL) of **203c** (310 mg, 0.502 mmol) was added 5% sodium hydroxide (3 mL). The mixture was stirred at 70°C for overnight. It was then purified by prep. HPLC. Further purification by column chromatography (5% methanol in dichloromethane) gave the title compound in 4% yield. ^{1}H NMR (DMSO-d_6): δ 10.95 (1H, s), 7.48 (1H, s), 7.46 (1H, s), 7.37 (1H, dd, J=8.6, 5.5Hz), 7.29 (1H, t, J=8.1Hz), 7.12 (1H, br d, J=2Hz), 7.80-7.72 (1H, m), 6.21 (1H, s), 3.81 (1H, d, J=11.1Hz), 3.12 (2H, m), 2.70-2.58 (2H, m). LCMS (APCI): 451.0 ($M+H^+$). HRMS (MALDI) calc for $C_{21}H_{18}N_2O_2FSCl_2$($M+H^+$) 451.0450; found 451.0462.

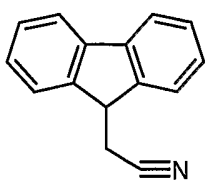
Compound 204a:



204a

To a dichloromethane solution (35 mL) of triphenylphosphine (polymer-supported, 3 mmol/g, 1.87 g, 5.61 mmol) was added I_2 (1.42 g, 5.61 mmol). The mixture was stirred for 15 minutes. Imidazole (410 mg, 6.38 mmol) was introduced and stirred gently at room temperature for another 15 minutes. 9-Fluorenyl methanol (500 mg, 2.55 mmole) was then introduced into the reaction mixture and refluxed for 30 minutes. It was filtered through a pad of celite. The filtrate was diluted with dichloromethane (30 mL), washed with saturated $Na_2S_2O_3$ (30 mL), water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated to give the title compound in 100% yield. ^{1}H NMR (DMSO-d_6): δ 7.88 (2H, d, J=7.3Hz), 7.83 (2H, d, J=7.6Hz), 7.41 (2H, td, J=7.6, 1.1Hz), 7.33 (2H, td, J=7.6, 1.3Hz), 6.27 (2H, s). LCMS (APCI): 179.0 ($M+H^+$).

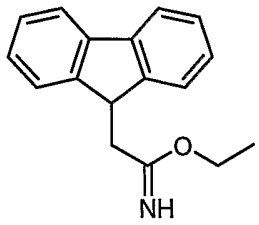
Compound 204b:



204b

To a methanol solution (15 mL) of **204a** (400 mg, 3.60 mmol) was added sodium cyanide (220 mg, 4.49 mmol). The mixture was stirred at 0°C for 20 minutes. **204a** (2.46 g, 8.71 mmol) was introduced and refluxed for 2 days. Methanol was evaporated. The residue was dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated. After column chromatography (5% ethyl acetate in hexane), the title compound was obtained in 46% yield. ^{1}H NMR ($CDCl_3$): δ 7.77 (2H, d, J=7.5Hz), 7.67 (2H, d, J=7.6Hz), 7.43 (2H, t, J=7.5Hz), 7.35 (2H, t, J=7.6Hz), 4.17 (1H, t, J=7.4Hz), 2.81 (2H, d, J=7.1Hz). LCMS (APCI): 206.1 ($M+H^+$).

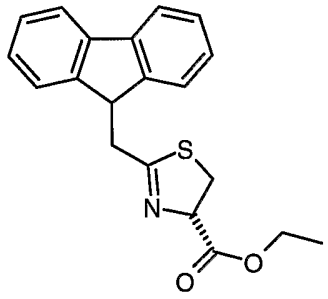
Compound 204c:



204c

Into an ethanol solution (30 mL) of **204b** (800 mg, 3.90 mmol) at 0°C was bubbled HCl gas for 1.5 hours. The mixture was stirred at room temperature for overnight. It was then concentrated to give the crude title compound as a HCl salt in 100% yield. ^{1}H NMR (DMSO-d_6): δ 7.90 (2H, d, J=7.6Hz), 7.59 (2H, d, J=7.3Hz), 7.43 (2H, t, J=7.3Hz), 7.36 (2H, td, J=7.4, 0.8Hz), 4.41 (1H, t, J=6.5Hz), 4.26 (2H, q, J=6.8Hz), 3.27 (2H, d, J=6.6Hz), 1.07 (3H, t, J=6.8Hz). LCMS (APCI): 252.1 ($M+H^+$).

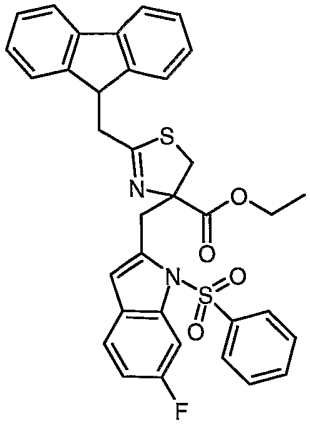
Compound 204d:



204d

To a dichloromethane solution (20 mL) of L-cysteine ethyl ester hydrochloride (1.44 g, 7.76 mmol) at 0°C was added triethylamine (784 mg, 7.76 mmol). The mixture was stirred at 0°C for 20 minutes. **204c** (2.23 g, 7.76 mmol) was introduced at 0°C and stirred for overnight. It was diluted with dichloromethane (30 mL). The dichloromethane solution was washed with water (40 mL) and brine (40 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 59% yield. ^{1}H NMR ($CDCl_3$): δ 7.78-7.63 (4H, m), 7.43-7.25 (4H, m), 5.05 (1H, m), 4.45 (1H, t, J=5.8Hz), 4.28-4.18 (2H, m), 3.55-3.45 (4H, m), 1.32 (3H, t, J=7Hz). LCMS (APCI): 338.1 ($M+H^+$).

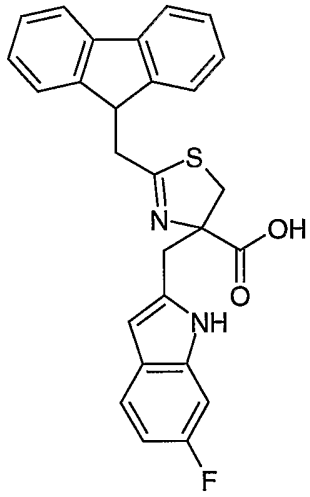
Compound 204e:



204e

To a tetrahydrofuran solution (1.5 mL) of diisopropylamine (111 mg, 1.10 mmol) at 0°C was added *n*-butyllithium (0.403 mL, 2.5 M in hexane, 1.01 mmol) dropwise. The mixture was stirred at 0°C for 15 minutes. A tetrahydrofuran solution (2 mL) of **204d** (154 mg, 0.458 mmol) was introduced at -78°C and stirred at -78°C for 30 minutes. **192a** (190 mg, 0.458 mmol) was added at -78°C and stirred at room temperature for 2 hours. The reaction was quenched with cold saturated ammonium chloride. Tetrahydrofuran was evaporated. The residue was extracted with ethyl acetate (2X10 mL). The ethyl acetate solution was washed with brine (10 mL), dried with Na_2SO_4 and concentrated. After column chromatography (10-20% ethyl acetate in hexane), the title compound was obtained in 58% yield. ^{1}H NMR (DMSO-d_6): δ 7.86-7.76 (5H, m), 7.73-7.66 (2H, m), 7.63-7.50 (4H, m), 7.37 (1H, t, J=7.3Hz), 7.32 (1H, t, J=7.6Hz), 7.26 (1H, td, J=7.6, 1.1Hz), 7.18-7.07 (2H, m), 6.65 (1H, s), 4.39 (1H, t, J=6.6Hz), 4.08 (2H, q, J=7.1Hz), 3.78 (1H, d, J=11.9Hz), 3.59-3.50 (3H, m), 3.12 (1H, dd, J=15.7, 6.3Hz), 3.02 (1H, dd, J=15.7, 7.3Hz), 1.00 (3H, t, J=7.1Hz). LCMS (APCI): 625.1($M+H^+$).

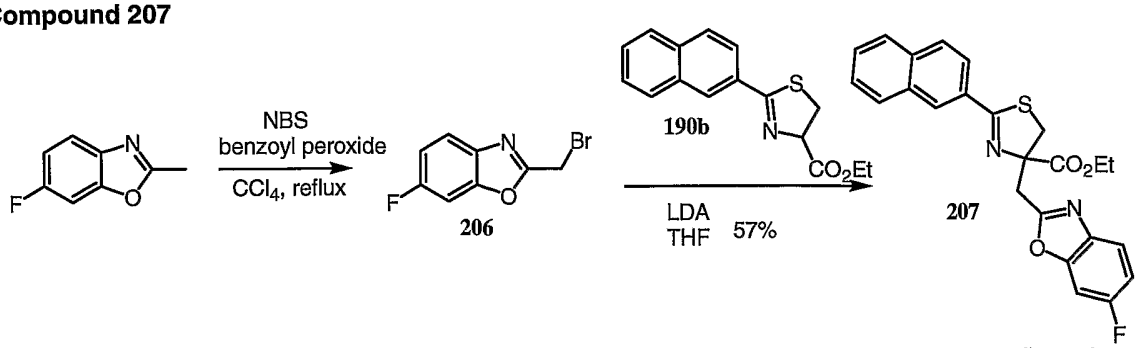
Example 205:



205

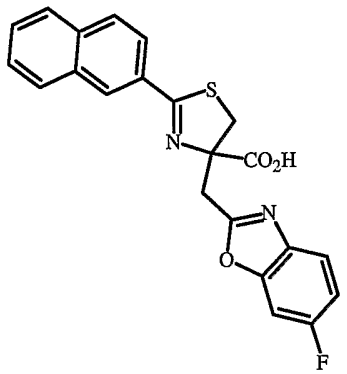
To a methanol solution (3 mL) of **204e** (162 mg, 0.260 mmol) was added 5% sodium hydroxide (2 mL). The mixture was stirred at 70°C for overnight. It was then acidified with 1M HCl. Methanol was evaporated. The residue was extracted with ethyl acetate (2X10 mL). The ethyl acetate extract was concentrated and purified by column chromatography (5% methanol in dichloromethane) to give the title compound in 47% yield. ^{1}H NMR (DMSO-d_6): δ 11.19 (1H, s), 8.09 (1H, d, J=7.6Hz), 8.03 (1H, s), 8.01 (1H, s), 7.91 (1H, d, J=7.3Hz), 7.86 (1H, m), 7.75 (1H, d, J=6.3Hz), 7.62 (1H, t, J=7.3Hz), 7.58-7.48 (3H, m), 7.43-7.28 (3H, m), 6.94 (1H, t, J=8.1Hz), 4.56 (1H, s), 4.02 (1H, d, J=10Hz), 3.42 (1H, d, J=11.1Hz), 3.21-3.00 (3H, m). LCMS (APCI): 457.1 ($M+H^+$). Elemental Analysis for ($C_{27}H_{21}FN_2O_2S$•0.65H_2O•0.3CH_2Cl_2) calc: C 66.41, H 4.68, N 5.67; found: C 66.36, H 4.57, N 5.76.

Compound 207



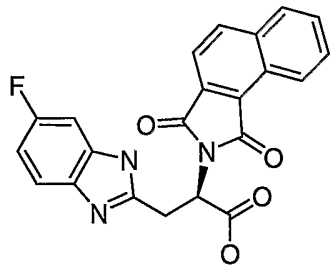
6-Fluoro-2-methylbenzoxazole (6.01g, 39.8 mmol), N-bromosuccimide (14.17g, 79.6 mmol), and benzoyl peroxide (0.19g, 0.8 mmol) were refluxed overnight in CCl_4 (50 mL). The succinimide was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated to dryness to give 11.6g of crude liquid. Approximately 1 gram of the crude was purified by flash silica gel chromatography (EtOAc/hexane) to yield 0.41g of 2-(bromomethyl)-6-fluoro-1,3-benzoxazole **206**: R_f = 0.18 (10% EtOAc/hexane); ^{1}H NMR (DMSO-d_6) □ 7.81-7.77 (2H, m), 7.32-7.27 (1H, m), 4.91 (2H, s). Diisopropylamine (0.25 mL, 1.82 mmol) was dissolved in THF (5mL) at 0°C. n-Butyllithium (2.87M/hexane, 0.61 mL, 1.74 mmol) was added dropwise, and the reaction was stirred for 20 minutes. The reaction was then cooled to –78°C, and thiazoline **190b** (0.41g, 1.45 mmol) was added as a THF (3 mL) solution. The reaction was stirred at –78°C for 30 minutes producing a deep red color. The bromide (0.40g, 1.74 mmol) dissolved in THF (2 mL) was added. The ice bath was removed, and the reaction was warmed to room temperature overnight. A solution of saturated ammonium chloride (1 mL) was added to quench the reaction, and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc/water. The organic phase was separated, washed sequentially with water and brine, and dried ($MgSO_4$). The crude product was purified by flash silica gel chromatography (3-12% EtOAc/hexane) to give 0.36g (57%) of the title compound as an off-white solid: R_f = 0.18 (20% EtOAc/hexane); ^{1}H NMR (DMSO-d_6) δ 8.31 (1H, s), 8.11 (1H, d, J = 7.5 Hz), 8.01-7.97 (2H, m), 7.90-7.88 (1H, m), 7.74-7.58 (4H, m), 7.24-7.19 (1H, m), 4.24-4.15 (2H, m), 4.08 (1H, d, J = 11.9 Hz), 3.91 (1H, d, J = 11.9 Hz), 3.69 (1H, d, J = 15.4 Hz), 3.66 (1H, d, J = 15.4 Hz), 1.13 (3H, t, J = 7.1 Hz). MS 435 (M+H).

Example 208:



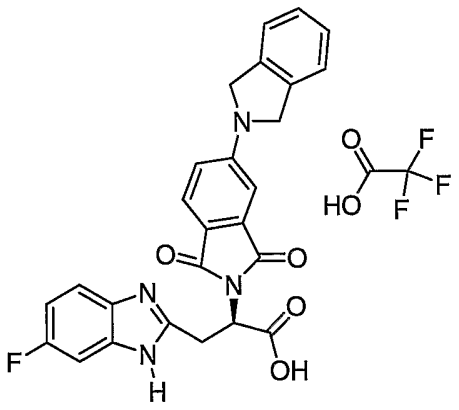
Ester **207**(0.32g, 0.728 mmol) was dissolved in THF (2.0 mL) and water (1.0 mL). Solid LiOH (0.07g, 2.91 mmol) was added, and the reaction stirred at room temperature for 5 hours. The solvent was removed *in vacuo*, and the residue treated with saturated ammonium chloride solution. The product was extracted into EtOAc, and the organic phase separated and washed with brine. After drying ($MgSO_4$) the solvent was evaporated to give 0.29g (97%) of a white solid: ^{1}H NMR (DMSO-d_6) δ 8.18 (1H, s), 8.02-8.01 (1H, m), 7.94-7.88 (3H, m), 7.66-7.47 (4H, m), 7.15-7.10 (1H, m), 3.99-3.96 (1H, m), 3.74-3.72 (1H, m). MS 407 (M+H). Elemental Analysis for ($C_{22}H_{15}N_2O_3SF$•0.55HCl) calc:C 61.95, H 3.68, N 6.57; found: C 65.02, H 3.51, 6.36.

Example 209



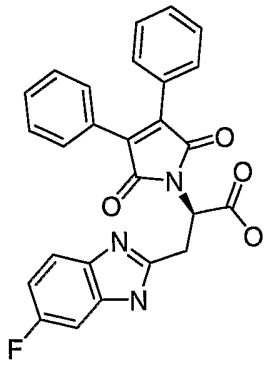
3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine trifluoroacetate **18a** was dissolved in anhydrous NMP, and *N,O*-bis(trimethylsilyl)acetamide (2.2 equivalents) and diisopropylethylamine were added. The reaction mixture was allowed to stir for 16h at room temperature. 1,2-Naphthalic anhydride was added, and the reaction was allowed to stir at room temperature. Water (20 mL) and aqueous HCl solution (4.0 M, 400□L) were added. The reaction was filtered, and the crude material was dried in a vacuum oven. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.57 (dd, *J*=15.11, 9.07 Hz, 1 H) 3.76 (dd, *J*=15.11, 6.04 Hz, 1 H) 5.44 (dd, *J*=8.69, 6.04 Hz, 1 H) 6.87 - 6.98 (m, 1 H) 7.21 (dd, *J*=9.44, 2.27 Hz, 1 H) 7.38 (dd, *J*=8.69, 4.91 Hz, 1 H) 7.73 - 7.86 (m, 2 H) 7.89 (d, *J*=8.31 Hz, 1 H) 8.18 (d, *J*=7.93 Hz, 1 H) 8.42 (d, *J*=8.31 Hz, 1 H) 8.74 (d, *J*=7.93 Hz, 1 H) 12.65 - 13.39 (m, 1 H). Anal. Calcd. For $C_{22}H_{14}FN_3O_4 \cdot 0.5H_2O$: C, 64.02; H, 3.64; N, 10.18. Found: C, 63.93; H, 3.48; N, 9.96. LC/MS: 404 (M + H).

Example 210



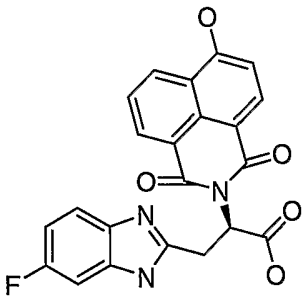
3-(6-Fluoro-1H-benzoimidazol-2-yl)-2-(5-fluoro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid; compound with trifluoro-acetic acid (0.049 ; 0.099 mmole) was dissolved in NMP, and isoindoline (0.017 g; 0.14 mmole) and triethylamine (0.03 g; 0.30 mmole) were added. The reaction mixture was heated in an oven (65-70 °C) for three days. Purification by HPLC provided the desired product. Anal. Calcd. For $C_{28}H_{20}F_4N_4O_6$: C, 57.5; H, 3.42; N, 9.58. Found: C, 58.13; H, 3.77; N, 9.18. LC/MS: 471 (M + H).

Example 211



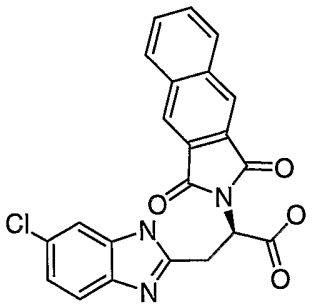
3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine trifluoroacetate **18a** (0.084g; 0.25 mmole) was dissolved in anhydrous NMP (1 mL), and *N,O*-bis(trimethylsilyl)acetamide (0.111 g; 0.55 mmole) and diisopropylethylamine (0.032 g; 0.25 mmole) were added. The reaction mixture was allowed to stir for 16h at room temperature. Diphenylmaleic anhydride (0.063 g; 0.25 mmole) was added. Purification by HPLC afforded the final product. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.60 (dd, *J*=15.11, 8.31 Hz, 1 H) 3.82 (dd, *J*=15.30, 6.61 Hz, 1 H) 5.39 (t, *J*=7.18 Hz, 1 H) 7.19 (td, *J*=9.25, 2.27 Hz, 1 H) 7.32 - 7.46 (m, 11 H) 7.51 (dd, *J*=9.07, 2.27 Hz, 1 H) 7.65 (dd, *J*=8.88, 4.72 Hz, 1 H). Anal. Calcd. For $C_{22}H_{14}FN_3O_4 \cdot CF_3CO_2H$: C, 59.0; H, 3.33; N, 7.38. Found: C, 59.61; H, 3.62; N, 7.19. LC/MS: 456 (M + H).

Example 212



3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine trifluoroacetate **18a** (0.085g; 0.25 mmole) was dissolved in anhydrous NMP (1 mL), and *N,O*-bis(trimethylsilyl)acetamide (0.134 g; 0.66 mmole) and diisopropylethylamine (0.039 g; 0.30 mole) were added. The reaction mixture was allowed to stir for 6h at room temperature. 3-Hydroxy-1,8-naphthalic anhydride (0.064g; 0.30 mmole) was added. Purification by HPLC afforded the final product. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.60 (dd, *J*=15.30, 7.74 Hz, 1 H) 3.99 (dd, *J*=15.30, 5.85 Hz, 1 H) 6.10 (t, *J*=6.61 Hz, 1 H) 7.20 (td, *J*=9.35, 2.46 Hz, 1 H) 7.50 (dd, *J*=9.07, 2.27 Hz, 1 H) 7.63 (dd, *J*=8.69, 4.53 Hz, 1 H) 7.74 (none, 2 H) 7.99 (d, *J*=2.64 Hz, 1 H) 8.21 - 8.32 (m, 2 H) 10.62 (none, 1 H). Anal. Calcd. For $C_{22}H_{14}FN_3O_4 \cdot 0.75CF_3CO_2H \cdot 0.5H_2O$: C, 54.91; H, 3.07; N, 8.18. Found: C, 54.60; H, 3.64; N, 8.26. LC/MS: 420 (M + H).

Example 213

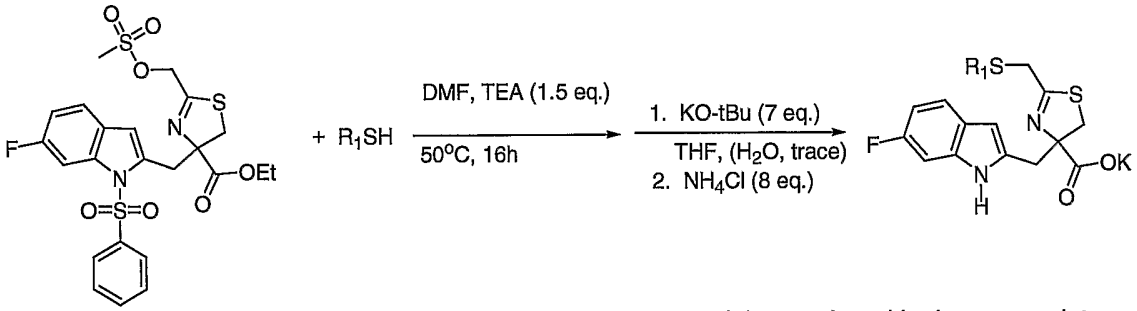


3-Amino-3-(5-chloro-1H-benzoimidazol-2-yl)-propionic acid **46a** was dissolved in water (10 mL), and sodium carbonate and 1,3-dioxo-1,3-dihydro-benzo[f]isoindole-2-carboxylic acid ethyl ester (prepared from the reaction of 2,3-naphthalenedicarboximide with ethyl chloroformate) were added. The reaction was briefly heated with a heat gun and then allowed to stir at room temperature overnight. The precipitate was removed by filtration, and the filtrate was made acidic by the addition of aqueous HCl (4 N; 0.6 mL). The precipitate was collected, washed with water, and lyophilized to afford the product as a gel. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.54 (dd, *J*=15.11, 8.69 Hz, 1 H) 3.75 (dd, *J*=15.11, 5.67 Hz, 1 H) 5.39 - 5.52 (m, 1 H) 7.08 (d, *J*=8.31 Hz, 1 H) 7.40 (d, *J*=8.31 Hz, 1 H) 7.46 (s, 1 H) 7.79 (dd, *J*=5.67, 3.02 Hz, 2 H) 8.26 (dd, *J*=5.29, 3.02 Hz, 2 H) 8.54 (s, 2 H) 13.03 (s, 1 H). Anal. Calcd. For $C_{22}H_{14}ClN_3O_4 \cdot 1.5H_2O$: C, 59.08; H, 3.80; N, 9.40. Found: C, 59.01; H, 3.65; N, 9.04. LC/MS: 421 (M + H).

The following tables describe compound libraries.

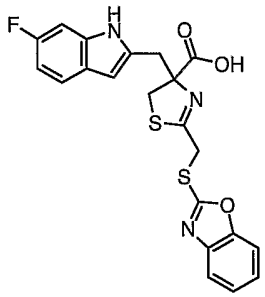
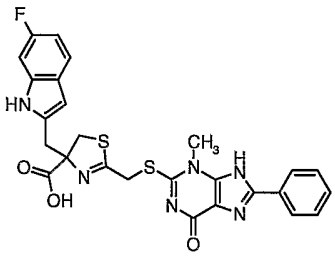
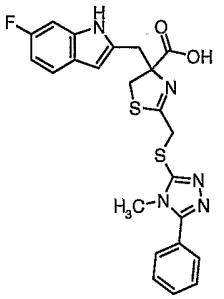
The compounds in the library of Table 1 were made by the following general procedure

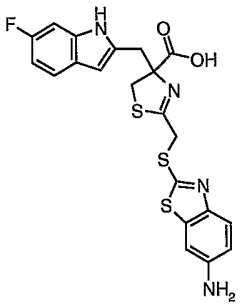
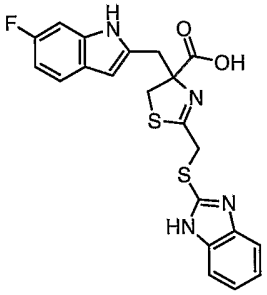
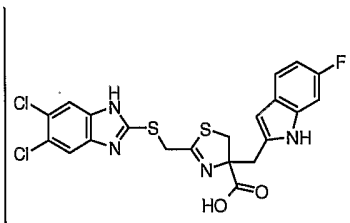
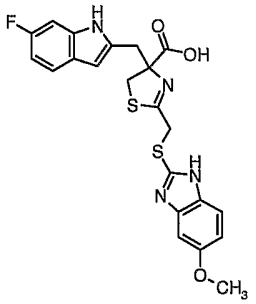
General Procedure for the Alkylation of Thiols with Mesylates Followed by Deprotection and Saponification for Table 1:

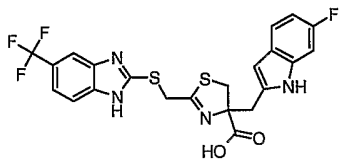
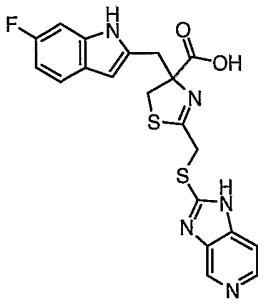
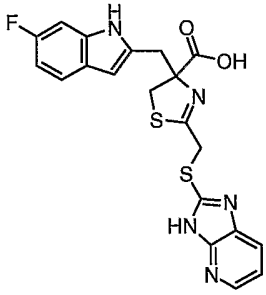
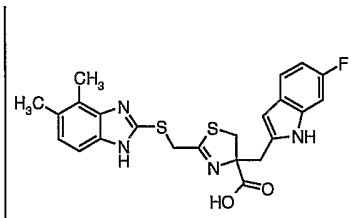


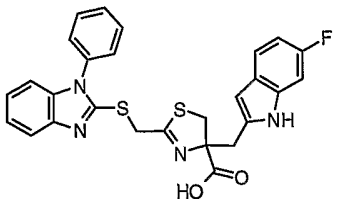
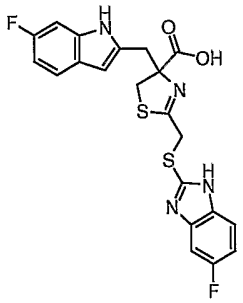
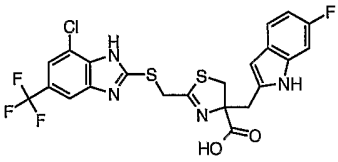
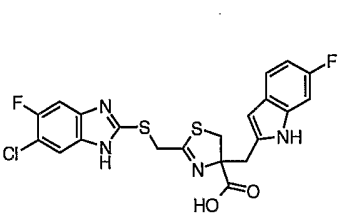
The appropriate thiol solution (0.5 M in DMF, 20 µL, 0.01 mmole) was placed in the appropriate well of a 96-well plate, and the mesylate solution (0.25 M in methylene chloride, 40 µL, 0.01 mmole) and triethylamine (1.0 M in DMF, 15 µL, 0.015 mmole) were added to each well. The plate was sealed and heated at 50 °C for 16 h. The reactions were allowed to cool, and potassium *t*-butoxide (1.0 M in THF, 70 µL, 0.07 mmole) was added to each well. An additional 100 µL of THF was added to each well, and the reactions were allowed to stir for 4 h at RT. DMF (100 µL) was added to each well, and the reactions were allowed to stir for another 4 h. Aqueous ammonium chloride solution (1.0 M, 80 µL, 0.08 mmole) was added, and the reactions were stirred for 5 minutes. The solvents were removed, and the residues were reconstituted in DMSO.

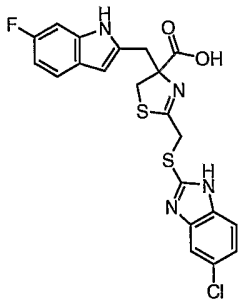
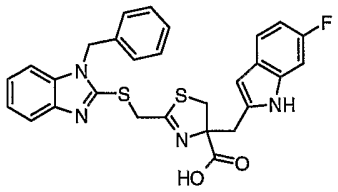
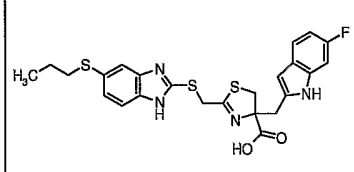
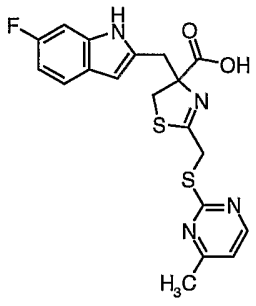
Table 1

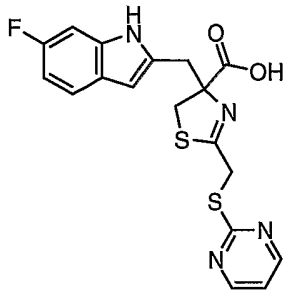
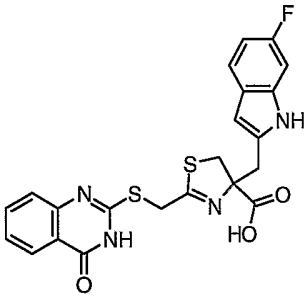
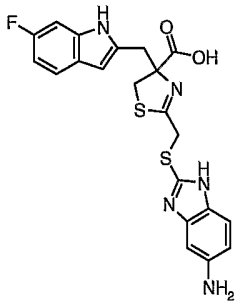
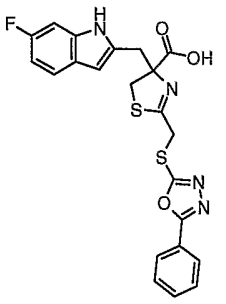
Structure	Name	MW	m/z (MW +1)	% Inhib @ 1 μM	% Inhib @ 10 μM
	2-[(1,3-benzoxazol-2-ylthio)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	441.51	442.51	10	73
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3-methyl-6-oxo-8-phenyl-6,7-dihydro-3H-purin-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	548.62	549.62	28	95
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	481.57	482.57	23	91

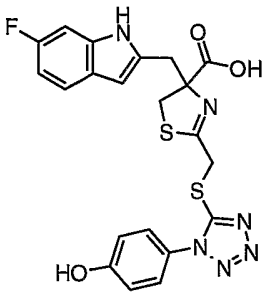
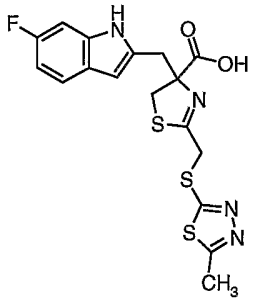
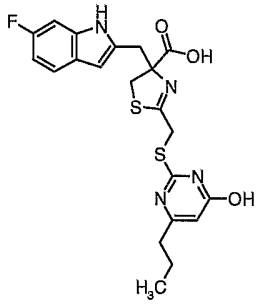
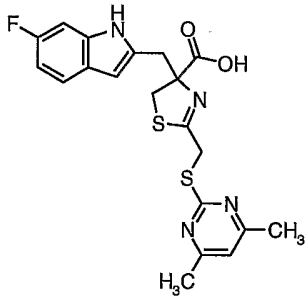
	2-{[(6-amino-1,3-benzothiazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	472.59	473.59	32	93
	2-[(1H-benzimidazol-2-ylthio)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.52	441.52	25	81
	2-{[(5,6-dichloro-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	509.41	510.41	18	58
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-methoxy-1H-benzimidazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	470.55	471.55	21	72

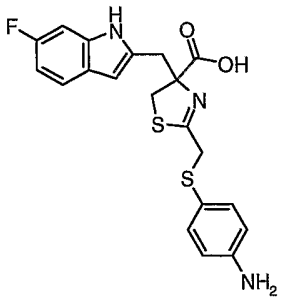
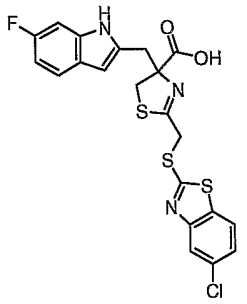
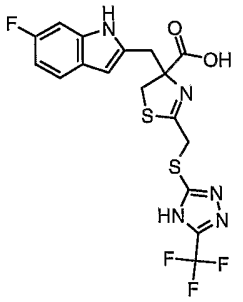
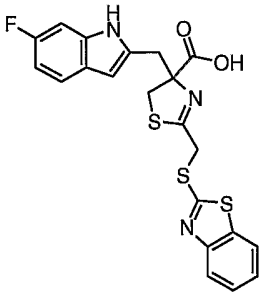
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(trifluoromethyl)-1H-benzimidazol-2-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	508.52	509.52	27	72
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1H-imidazo[4,5-c]pyridin-2-ylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	441.51	442.51	26	69
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1H-imidazo[4,5-b]pyridin-2-ylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	441.51	442.51	36	93
	2-{[(4,5-dimethyl-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.57	469.57	20	51

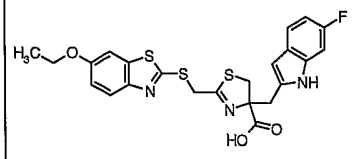
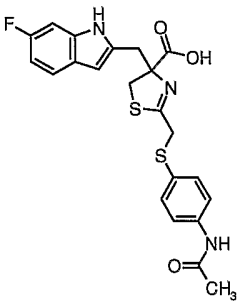
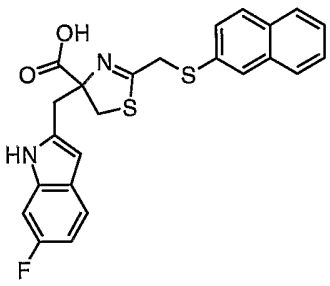
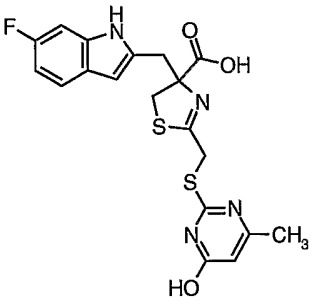
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(1-phenyl-1H-benzimidazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	516.62	517.62	6	71
	2-{[(5-fluoro-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	458.51	459.51	7	72
	2-({[4-chloro-6-(trifluoromethyl)-1H-benzimidazol-2-yl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	542.96	543.96	11	80
	2-{[(5-chloro-6-fluoro-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	492.96	493.96	25	84

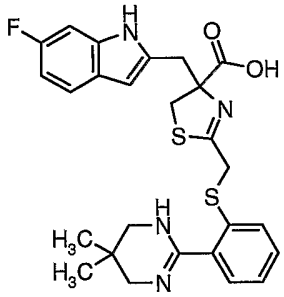
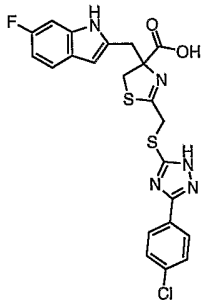
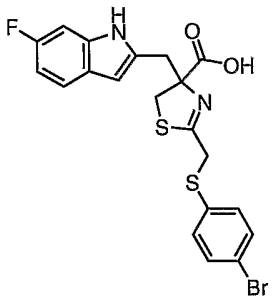
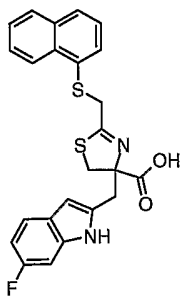
	2-{[(5-chloro-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	474.97	475.97	21	73
	2-{[(1-benzyl-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	530.65	531.65	31	93
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(propylthio)-1H-benzimidazol-2-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	514.67	515.67	27	90
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-2-pyrimidinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	416.50	417.50	28	79

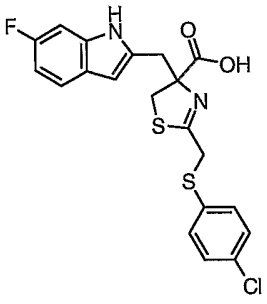
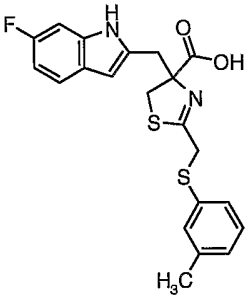
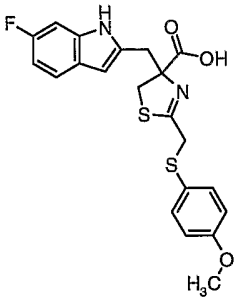
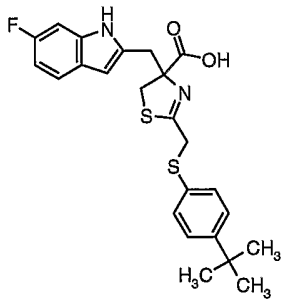
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-pyrimidinylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	402.47	403.47	39	94
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-oxo-1,4-dihydro-2-quinazolinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.53	469.53	23	65
	2-{[(5-amino-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	455.54	456.54	26	74
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.53	469.53	9	72

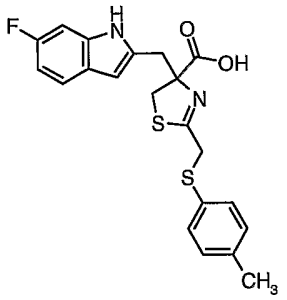
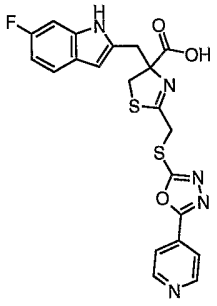
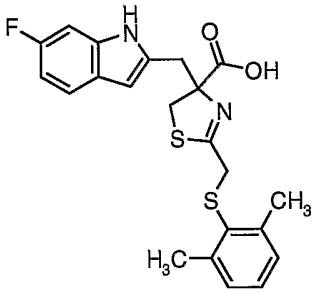
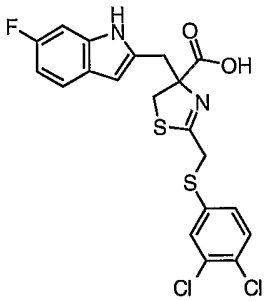
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[1-(4-hydroxyphenyl)-1H-tetrazol-5-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	484.53	485.53	16	86
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	422.53	423.53	37	96
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-oxo-6-propyl-1,4-dihydro-2-pyrimidinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	460.55	461.55	35	90
	2-{[(4,6-dimethyl-2-pyrimidinyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	430.53	431.53	33	92

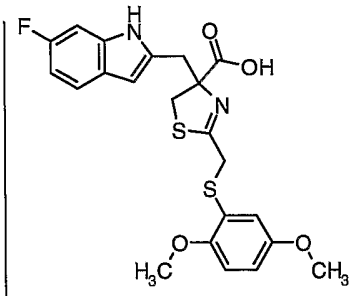
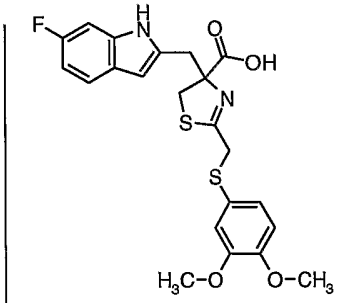
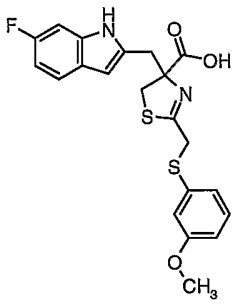
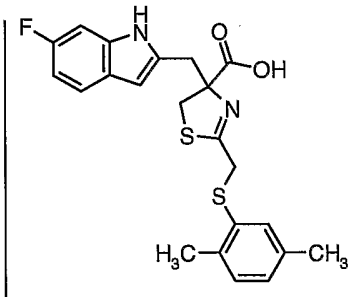
	2-{[(4-aminophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	415.51	416.51	39	94
	2-{[(5-chloro-1,3-benzothiazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	492.02	493.02	39	98
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	459.45	460.45	38	93
	2-[(1,3-benzothiazol-2-ylthio)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	457.57	458.57	45	99

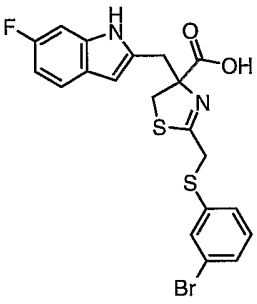
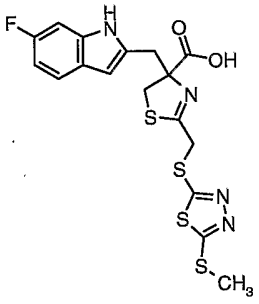
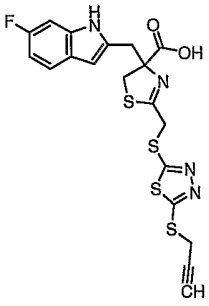
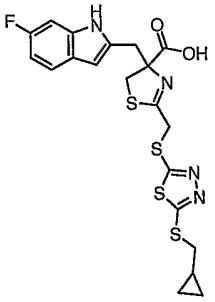
	2-{[(6-ethoxy-1,3-benzothiazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	501.63	502.63	25	80
	2-({[4-(acetylamino)phenyl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	457.55	458.55	36	92
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-naphthylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	450.56	451.56	3	65
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-6-oxo-1,6-dihydro-2-pyrimidinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.50	433.50	12	80

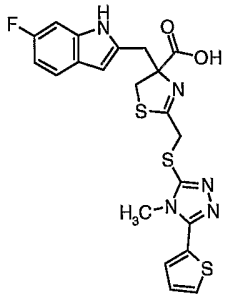
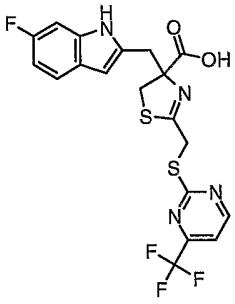
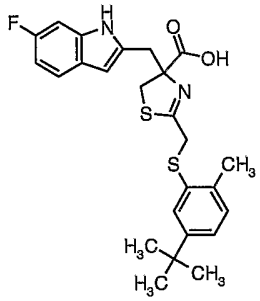
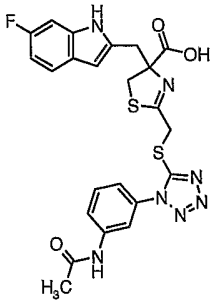
	2-({[2-(5,5-dimethyl-1,4,5,6-tetrahydro-2-pyrimidinyl)phenyl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	510.66	511.66	15	81
	2-({[3-(4-chlorophenyl)-1H-1,2,4-triazol-5-yl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	501.99	502.99	26	82
	2-{[(4-bromophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	479.39	480.39	29	89
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1-naphthylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	450.56	451.56	32	91

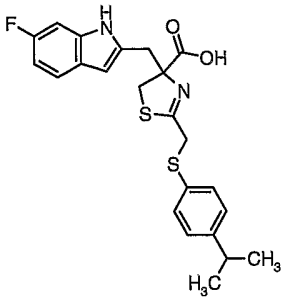
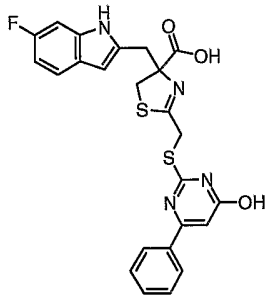
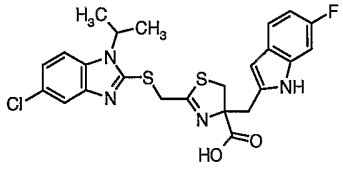
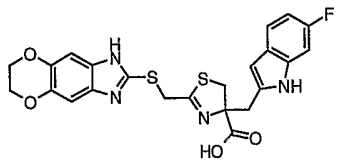
	2-{[(4-chlorophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	434.94	435.94	40	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3-methylphenyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	414.52	415.52	40	95
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methoxyphenyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	430.52	431.52	35	91
	2-{[(4-tert-butylphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	456.60	457.60	32	85

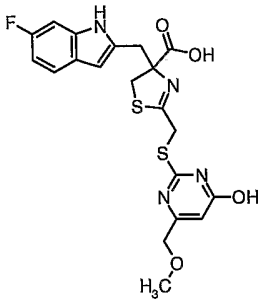
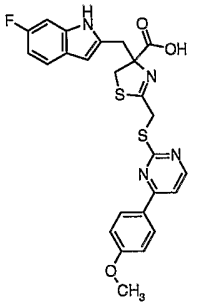
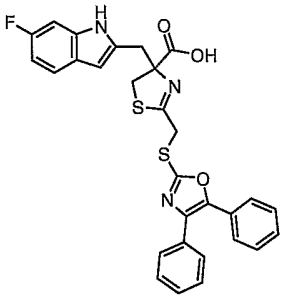
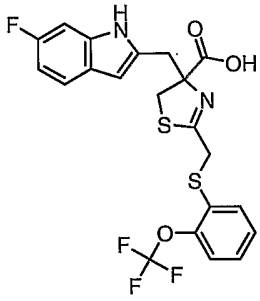
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methylphenyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	414.52	415.52	31	89
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(4-pyridinyl)-1,3,4-oxadiazol-2-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.52	470.52	4	62
	2-{[(2,6-dimethylphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	428.55	429.55	20	86
	2-{[(3,4-dichlorophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.39	470.39	27	95

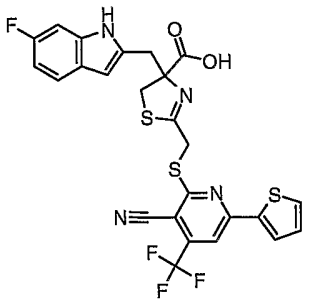
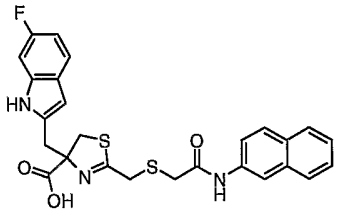
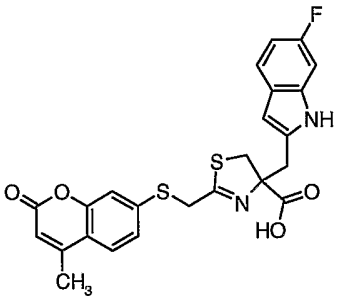
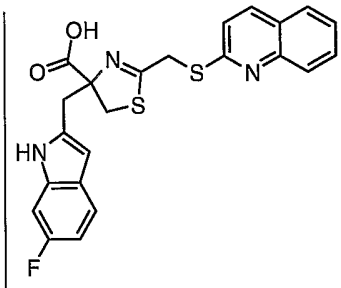
	2-{[(2,5-dimethoxyphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	460.55	461.55	37	93
	2-{[(3,4-dimethoxyphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	460.55	461.55	31	91
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3-methoxyphenyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	430.52	431.52	36	93
	2-{[(2,5-dimethylphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	428.55	429.55	31	90

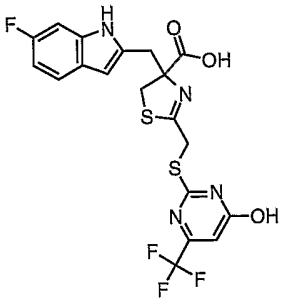
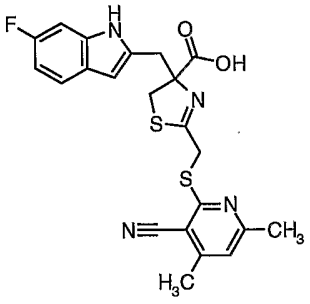
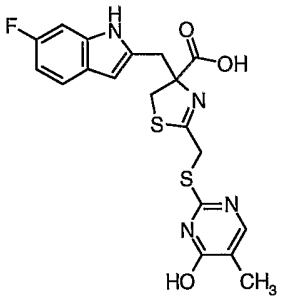
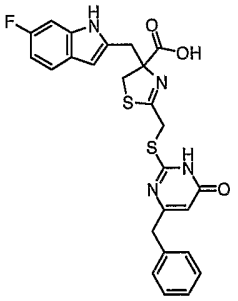
	2-{[(3-bromophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	479.39	480.39	39	93
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(methylthio)-1,3,4-thiadiazol-2-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.59	455.59	48	99
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(2-propyn-1-ylthio)-1,3,4-thiadiazol-2-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	478.62	479.62	43	98
	2-[({5-[(cyclopropylmethyl)thio]-1,3,4-thiadiazol-2-yl}thio)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	494.66	495.66	41	98

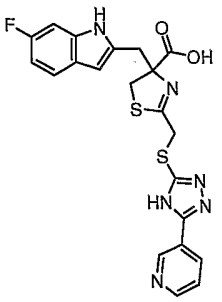
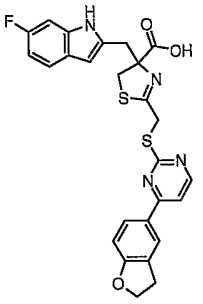
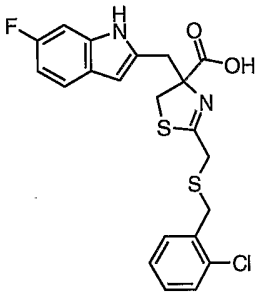
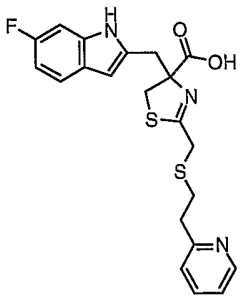
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-methyl-5-(2-thienyl)-4H-1,2,4-triazol-3-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	487.60	488.60	15	85
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-(trifluoromethyl)-2-pyrimidinyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	470.47	471.47	21	90
	2-{[(5-tert-butyl-2-methylphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	470.63	471.63	20	88
	2-[({1-[3-(acetylamino)phenyl]-1H-tetrazol-5-yl}thio)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	525.59	526.59	41	96

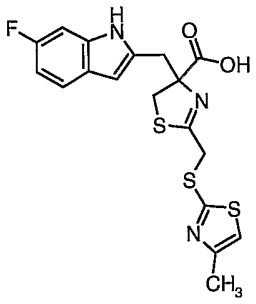
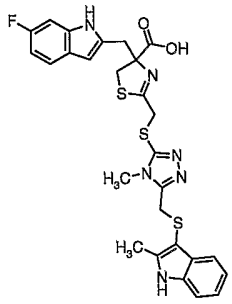
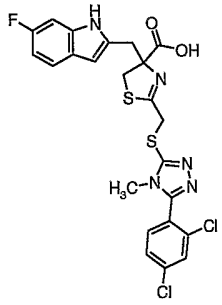
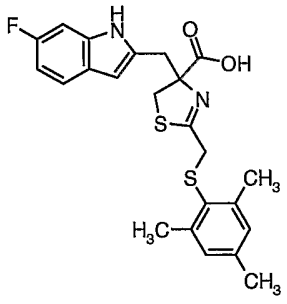
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-isopropylphenyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	442.58	443.58	34	94
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-oxo-6-phenyl-1,4-dihydro-2-pyrimidinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	494.57	495.57	42	92
	2-{[(5-chloro-1-isopropyl-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	517.05	518.05	28	92
	2-[(6,7-dihydro-1H-[1,4]dioxino[2,3-f]benzimidazol-2-ylthio)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	498.56	499.56	32	85

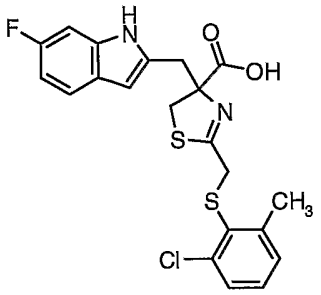
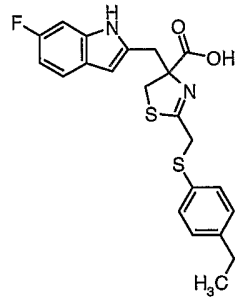
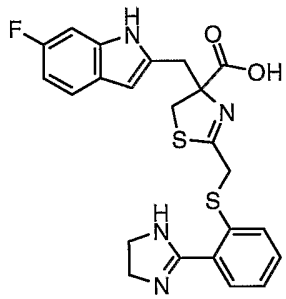
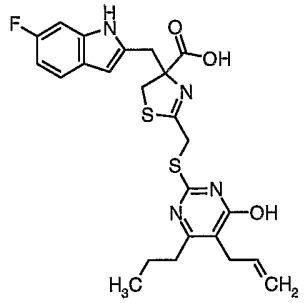
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-(methoxymethyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	462.52	463.52	39	93
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-(4-methoxyphenyl)-2-pyrimidinyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	508.60	509.60	39	94
	2-{[(4,5-diphenyl-1,3-oxazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	543.64	544.64	38	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[2-(trifluoromethoxy)phenyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	484.49	485.49	10	68

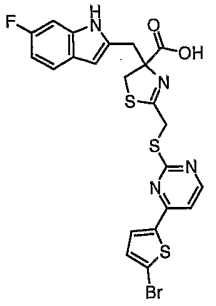
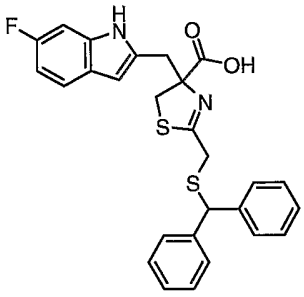
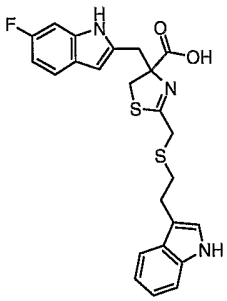
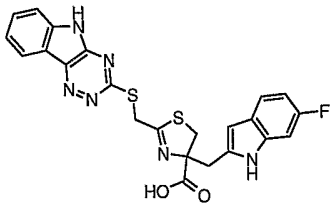
	2-({[3-cyano-6-(2-thienyl)-4-(trifluoromethyl)-2-pyridinyl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	576.62	577.62	10	73
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[2-(2-naphthylamino)-2-oxoethyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	507.61	508.61	21	91
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-2-oxo-2H-chromen-7-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	482.55	483.55	40	92
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-quinolinylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	451.54	452.54	23	89

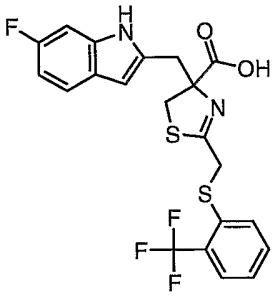
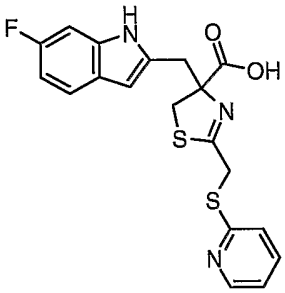
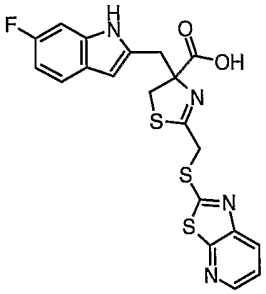
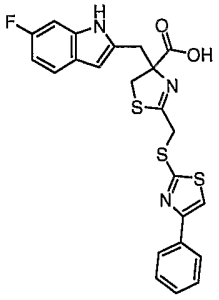
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-oxo-6-(trifluoromethyl)-1,4-dihydro-2-pyrimidinyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	486.47	487.47	34	92
	2-{[(3-cyano-4,6-dimethyl-2-pyridinyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.55	455.55	32	90
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-methyl-4-oxo-1,4-dihydro-2-pyrimidinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.50	433.50	34	89
	2-{[(4-benzyl-6-oxo-1,6-dihydro-2-pyrimidinyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	508.60	509.60	29	85

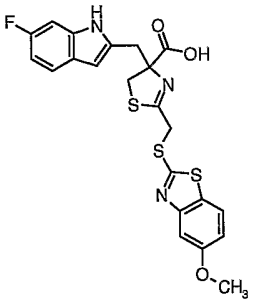
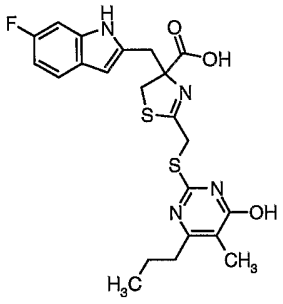
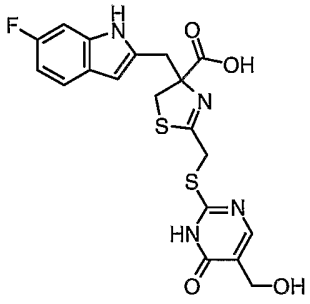
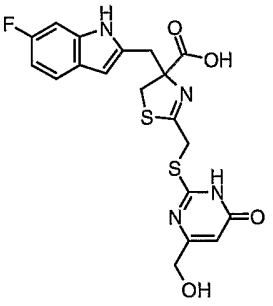
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[3-(3-pyridinyl)-1H-1,2,4-triazol-5-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.54	469.54	29	86
	2-({[4-(2,3-dihydro-1-benzofuran-5-yl)-2-pyrimidinyl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	520.61	521.61	35	95
	2-{[(2-chlorobenzyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	448.97	449.97	10	70
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[2-(2-pyridinyl)ethyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	429.54	430.54	32	92

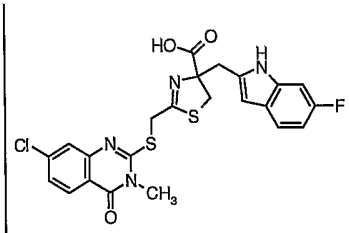
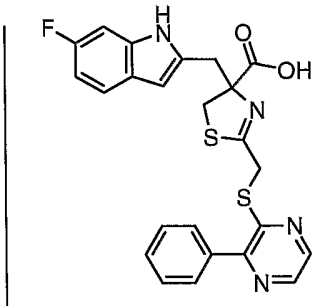
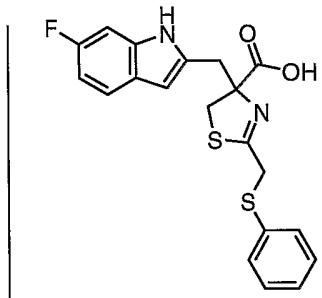
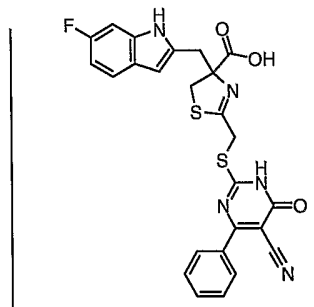
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-1,3-thiazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	421.54	422.54	20	90
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-5-{[(2-methyl-1H-indol-3-yl)thio]methyl}-4H-1,2,4-triazol-3-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	580.73	581.73	32	73
	2-({[5-(2,4-dichlorophenyl)-4-methyl-4H-1,2,4-triazol-3-yl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	550.46	551.46	46	98
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(mesitylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	442.58	443.58	28	84

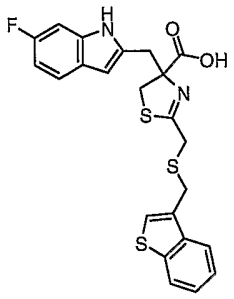
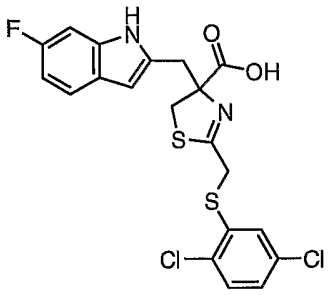
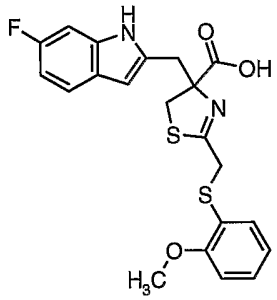
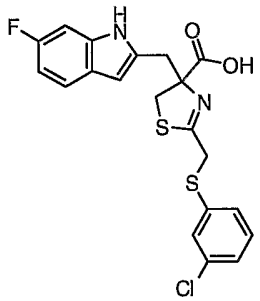
	2-{[(2-chloro-6-methylphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	448.97	449.97	26	86
	2-{[(4-ethylphenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	428.55	429.55	30	86
	2-({[2-(4,5-dihydro-1H-imidazol-2-yl)phenyl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.57	469.57	24	77
	2-{[(5-allyl-4-oxo-6-propyl-1,4-dihydro-2-pyrimidinyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	500.62	501.62	23	72

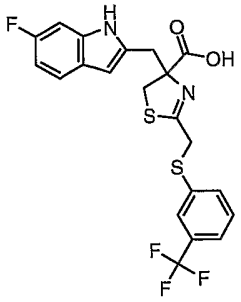
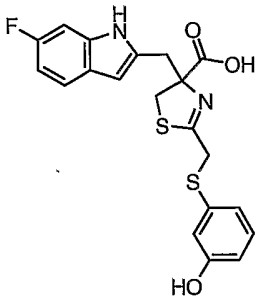
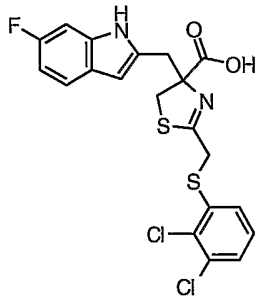
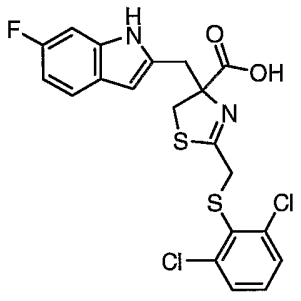
	2-({[4-(5-bromo-2-thienyl)-2-pyrimidinyl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	563.49	564.49	27	90
	2-{[(diphenylmethyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	490.62	491.62	3	29
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[2-(1H-indol-3-yl)ethyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	467.59	468.59	5	40
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2H-[1,2,4]triazino[5,6-b]indol-3-ylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	492.56	493.56	10	60

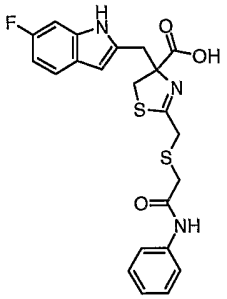
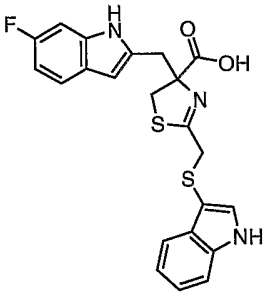
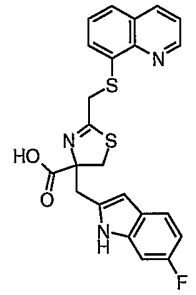
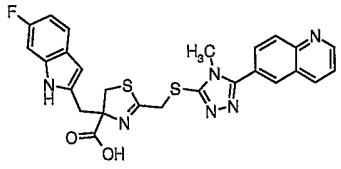
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[2-(trifluoromethyl)phenyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.49	469.49	28	79
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-pyridinylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	401.48	402.48	25	73
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[([1,3]thiazolo[5,4-b]pyridin-2-ylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	458.56	459.56	30	88
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-phenyl-1,3-thiazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	483.61	484.61	27	85

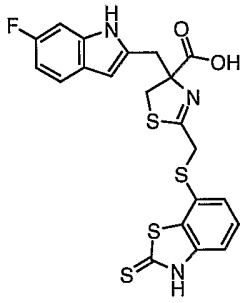
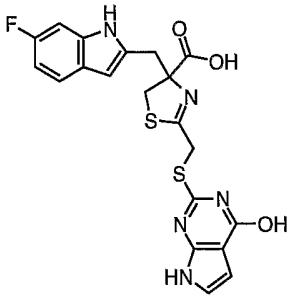
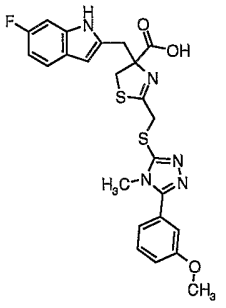
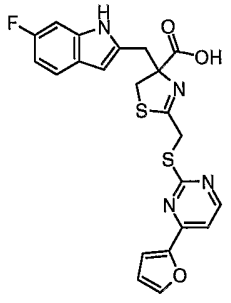
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-methoxy-1,3-benzothiazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	487.60	488.60	17	83
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-methyl-4-oxo-6-propyl-1,4-dihydro-2-pyrimidinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	474.58	475.58	20	47
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(hydroxymethyl)-4-oxo-1,4-dihydro-2-pyrimidinyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	448.50	449.50	42	86
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-(hydroxymethyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	448.50	449.50	44	97

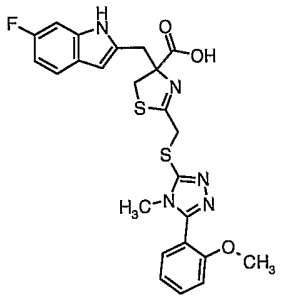
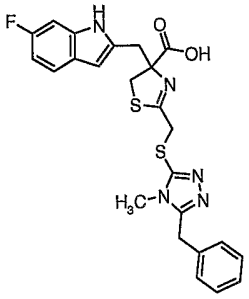
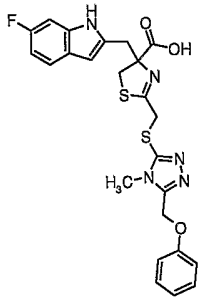
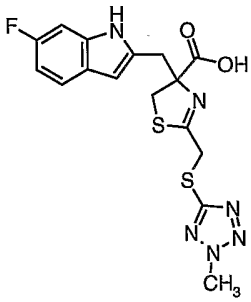
	2-{[(7-chloro-3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	517.00	518.00	3	48
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3-phenyl-2-pyrazinyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	478.57	479.57	11	79
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(phenylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	400.50	401.50	17	81
	2-{[(5-cyano-4-oxo-6-phenyl-1,4-dihydro-2-pyrimidinyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	519.58	520.58	57	98

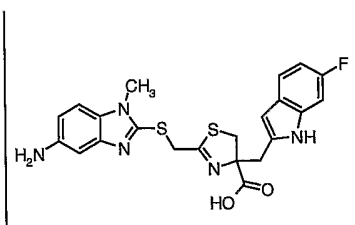
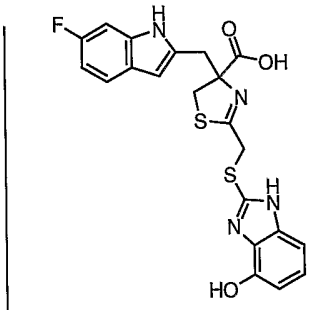
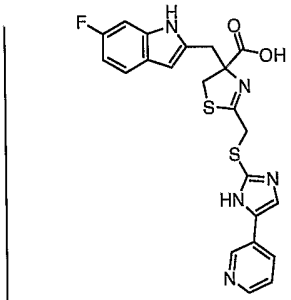
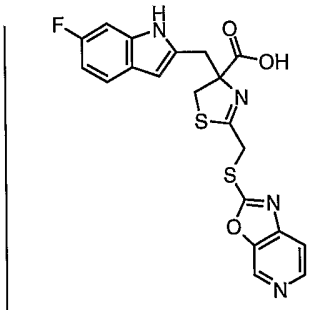
	2-{[(1-benzothien-3-ylmethyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	470.61	471.61	29	86
	2-{[(2,5-dichlorophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.39	470.39	25	84
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-methoxyphenyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	430.52	431.52	19	68
	2-{[(3-chlorophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	434.94	435.94	8	65

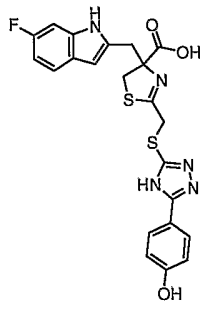
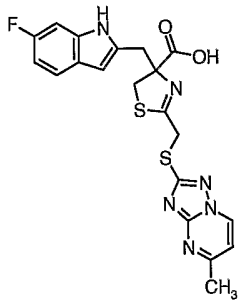
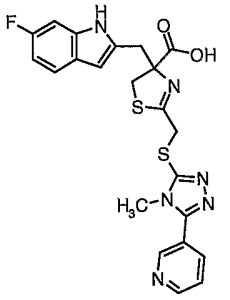
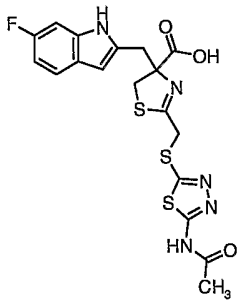
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[3-(trifluoromethyl)phenyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.49	469.49	23	73
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3-hydroxyphenyl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	416.50	417.50	21	64
	2-{[(2,3-dichlorophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.39	470.39	19	76
	2-{[(2,6-dichlorophenyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.39	470.39	10	71

	2-{[(2-anilino-2-oxoethyl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	457.55	458.55	10	70
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1H-indol-3-ylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	439.53	440.53	14	77
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(8-quinolinylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	451.54	452.54	30	86
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-methyl-5-(6-quinolinyl)-4H-1,2,4-triazol-3-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	532.62	533.62	32	90

	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-thioxo-2,3-dihydro-1,3-benzothiazol-7-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	489.64	490.64	21	53
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	457.51	458.51	26	71
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(3-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	511.60	512.60	22	83
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-(2-furyl)-2-pyrimidinyl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.53	469.53	32	85

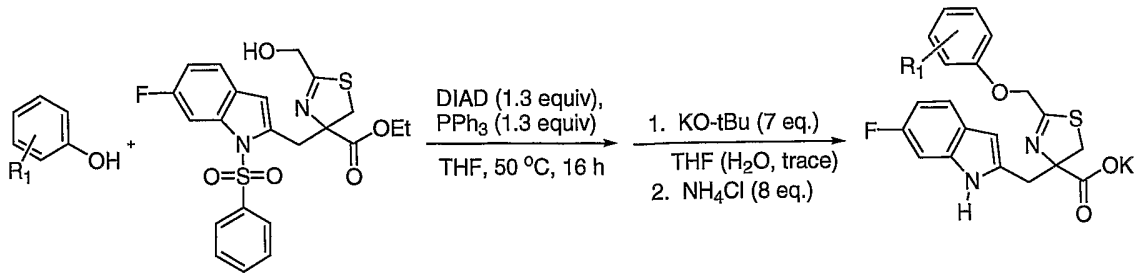
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[5-(2-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	511.60	512.60	33	91
	2-{[(5-benzyl-4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	495.60	496.60	26	89
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-methyl-5-(phenoxymethyl)-4H-1,2,4-triazol-3-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	511.60	512.60	23	84
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-methyl-2H-tetrazol-5-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	406.46	407.46	41	97

	2-{[(5-amino-1-methyl-1H-benzimidazol-2-yl)thio]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.56	470.56	27	82
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-hydroxy-1H-benzimidazol-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	456.52	457.52	39	88
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-(3-pyridinyl)-1H-imidazol-2-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	467.55	468.55	28	86
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[([1,3]oxazolo[5,4-c]pyridin-2-ylthio)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	442.49	443.49	27	82

	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[3-(4-hydroxyphenyl)-1H-1,2,4-triazol-5-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	483.55	484.55	21	60
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)thio]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	456.52	457.52	37	88
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({[4-methyl-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl]thio}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	482.56	483.56	29	89
	2-({[5-(acetylamino)-1,3,4-thiadiazol-2-yl]thio}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	465.55	466.55	29	83

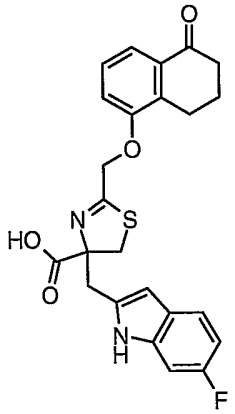
The compounds in Table 2 were made by the following general procedure.

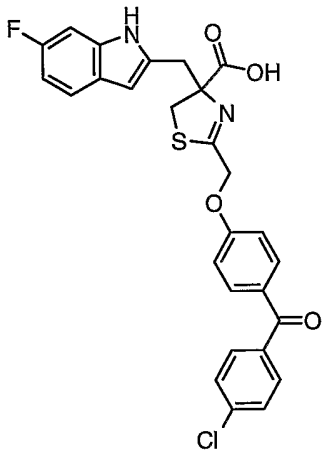
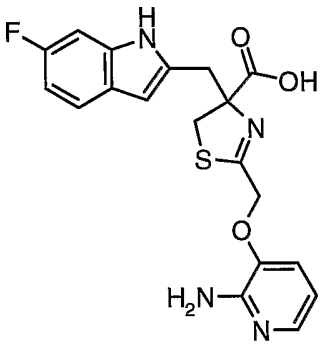
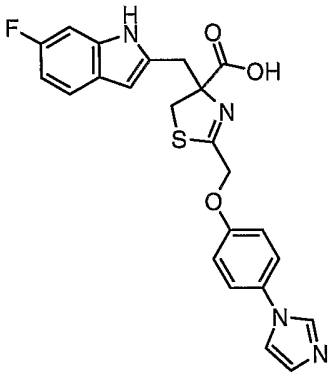
General Procedure for the Alkylation of Phenols with Alcohols followed by Deprotection and Saponification:

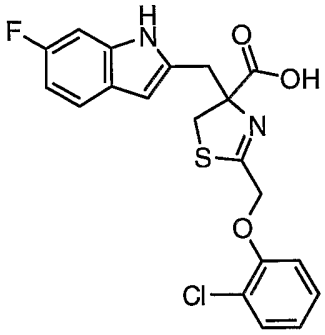
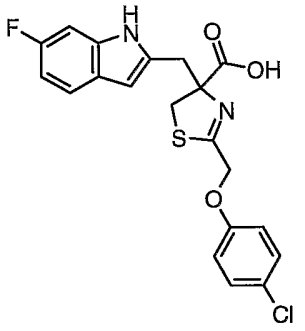
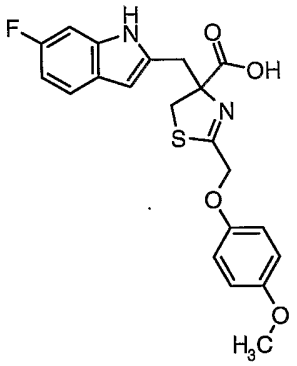
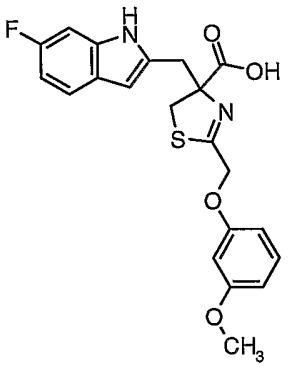


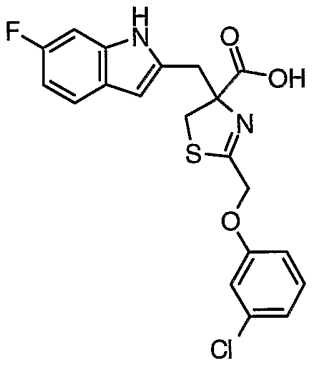
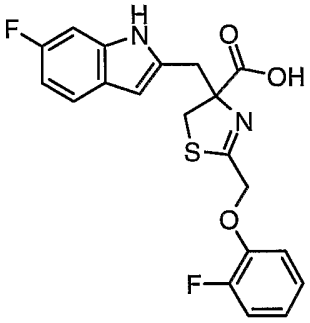
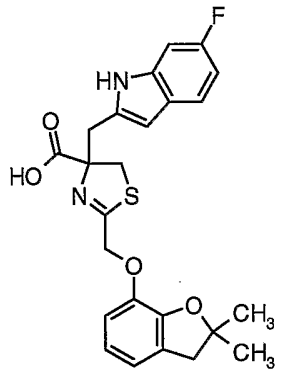
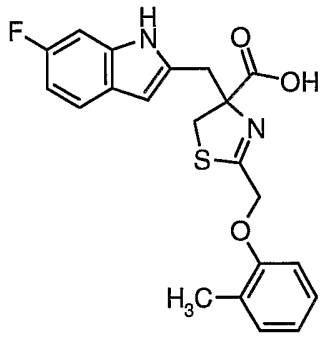
The appropriate alcohol solution (0.4 M in THF, 25 µL, 0.01 mmole) was placed in a 1.5 mL sample vial, and DIAD (1.3 M in THF, 10 µL, 0.013 mmole), the appropriate phenol solution (0.4 M in THF, 25 µL, 0.01 mmole), and PPh_3 (1.3 M in THF, 10 µL, 0.013 mmole) were added to each vial. The vials were capped and heated to 55 °C for 16 h. The reactions were allowed to cool, and potassium *t*-butoxide (1.0 M in THF, 70 µL, 0.07 mmole) was added to each well. The reactions were allowed to stir for 2 h at RT. Aqueous ammonium chloride solution (1.0 M, 80 µL, 0.08 mmole) was added, and the reactions were stirred for 5 minutes. The solvents were removed, and the residues were reconstituted in DMSO.

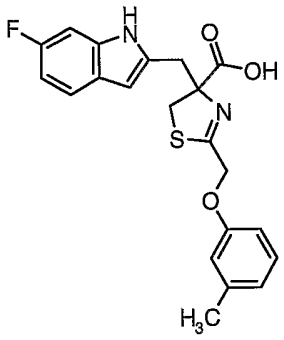
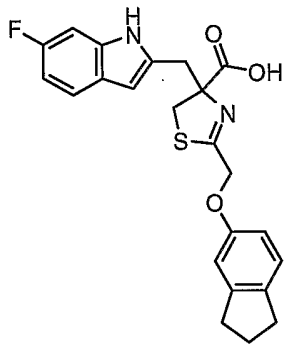
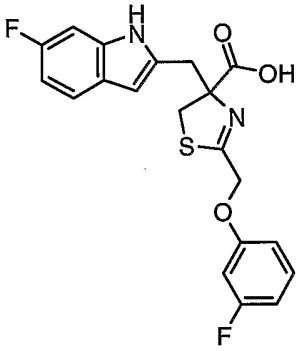
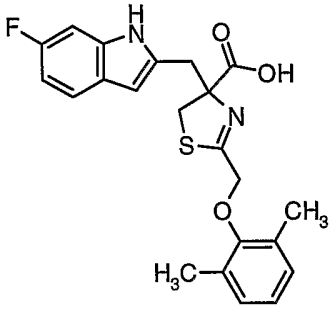
Table 2

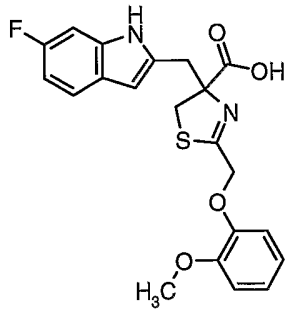
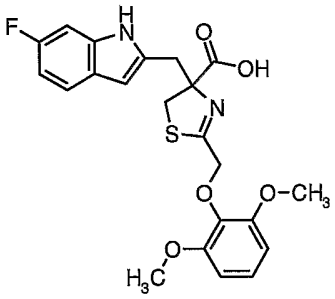
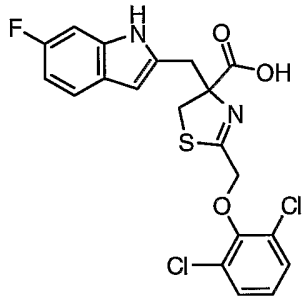
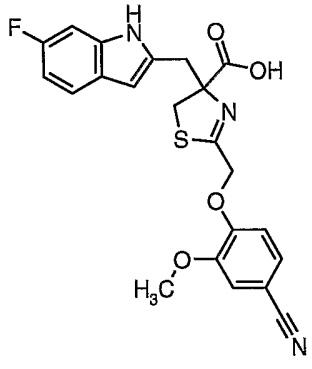
Structure	Name	MW	m/z (MW + 1)	% Inhib @ 1 µM	% Inhib @ 10 µM
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-oxo-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	452.50	453.50	47	94

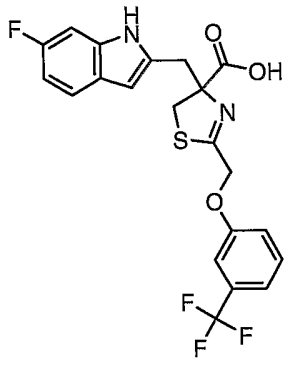
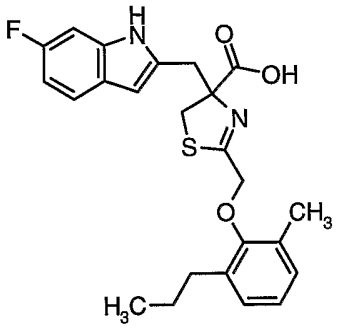
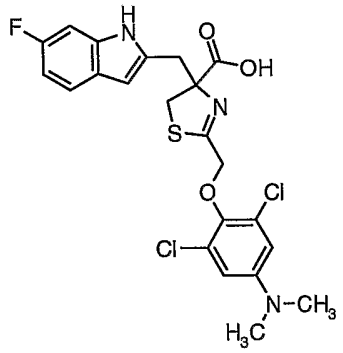
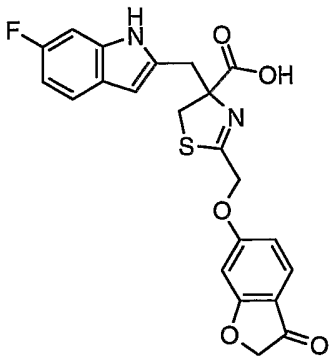
	2-{[4-(4-chlorobenzoyl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	522.98	523.98	43	95
	2-{[(2-amino-3-pyridinyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	400.43	401.43	22	76
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-(1H-imidazol-1-yl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	450.49	451.49	33	0

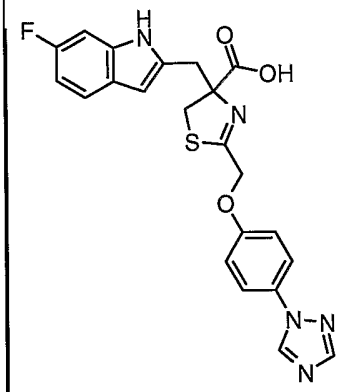
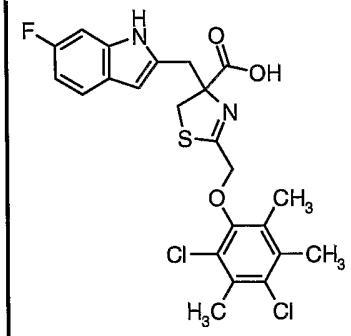
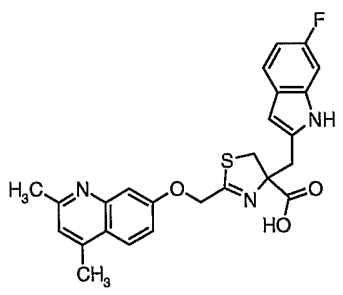
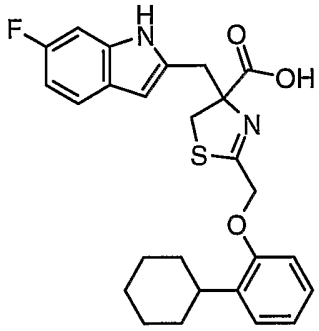
	2-[(2-chlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	418.87	419.87	49	0
	2-[(4-chlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	418.87	419.87	52	0
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(4-methoxyphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	414.46	415.46	50	0
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3-methoxyphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	414.46	415.46	46	93

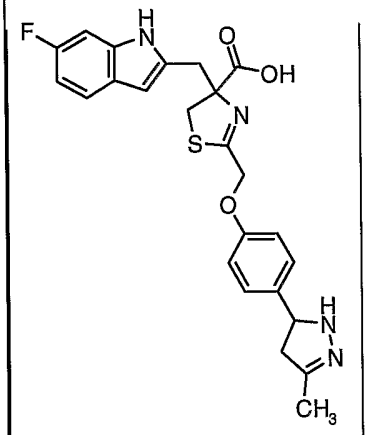
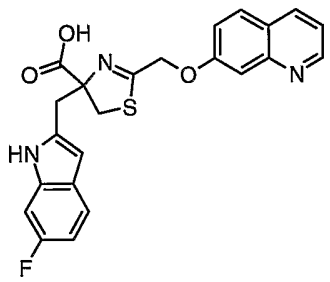
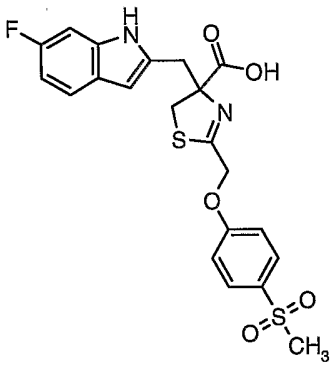
	2-[(3-chlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	418.87	419.87	50	99
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-fluorophenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	402.42	403.42	51	99
	2-{[(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.52	455.52	45	96
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	398.46	399.46	34	87

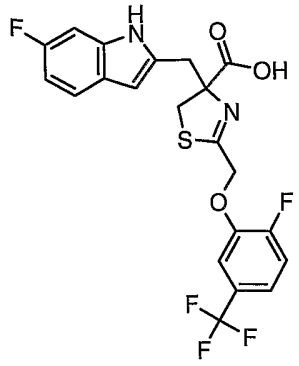
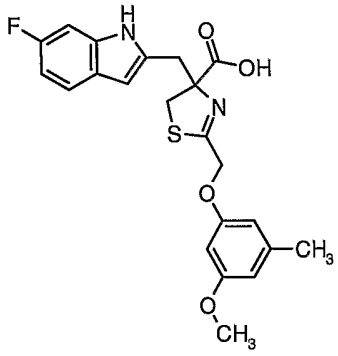
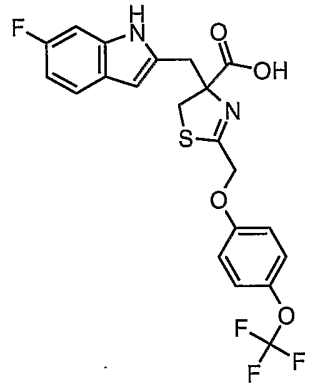
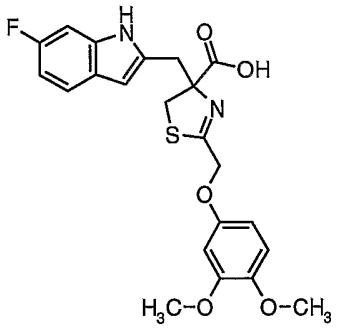
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	398.46	399.46	37	90
	2-[(2,3-dihydro-1H-inden-5-yloxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	424.49	425.49	41	91
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3-fluorophenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	402.42	403.42	39	97
	2-[(2,6-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	412.48	413.48	53	97

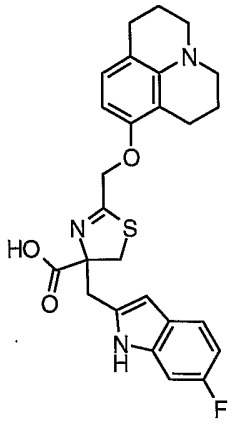
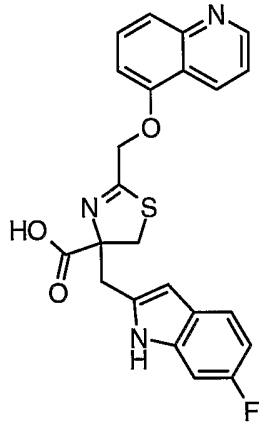
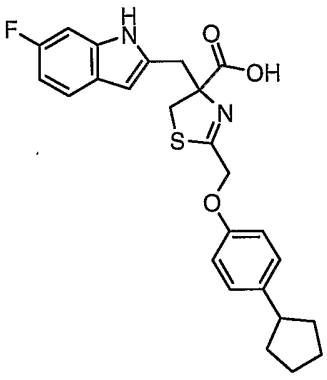
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-methoxyphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	414.46	415.46	52	96
	2-[(2,6-dimethoxyphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	444.48	445.48	57	98
	2-[(2,6-dichlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	453.32	454.32	55	100
	2-[(4-cyano-2-methoxyphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	439.47	440.47	61	100

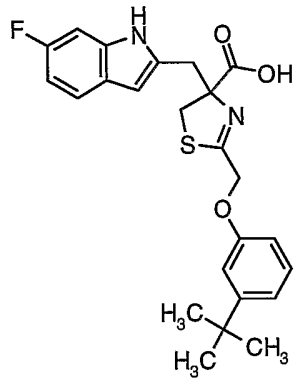
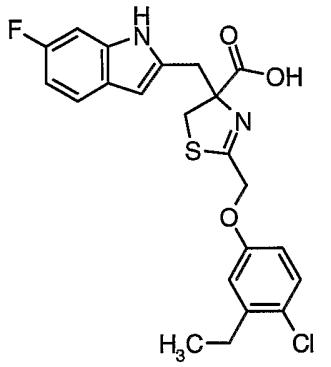
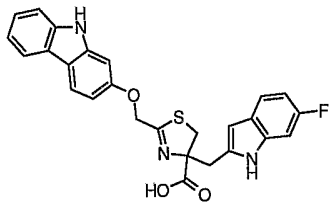
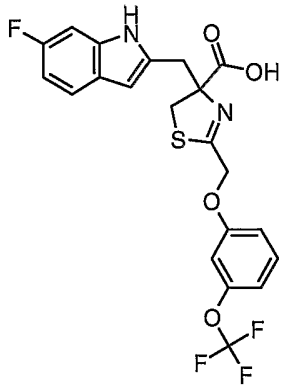
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[3-(trifluoromethyl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	452.43	453.43	50	100
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-methyl-6-propylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.54	441.54	43	93
	2-{[2,6-dichloro-4-(dimethylamino)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	496.39	497.39	38	90
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3-oxo-2,3-dihydro-1-benzofuran-6-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.45	441.45	42	95

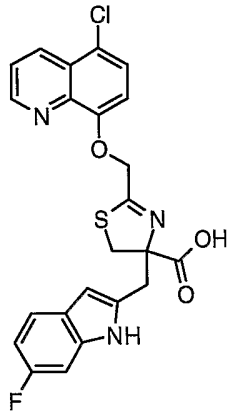
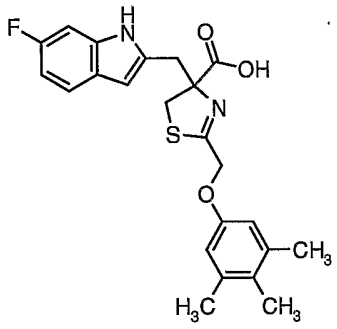
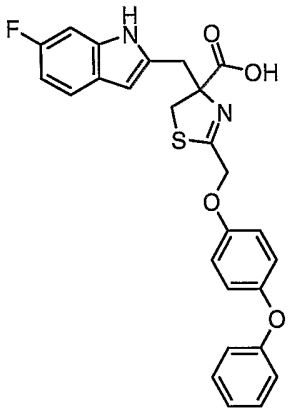
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-(1H-1,2,4-triazol-1-yl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	451.48	452.48	42	93
	2-[(2,4-dichloro-3,5,6-trimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	495.40	496.40	34	90
	2-{[(2,4-dimethyl-7-quinolinyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	463.53	464.53	41	89
	2-[(2-cyclohexylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	466.57	467.57	58	99

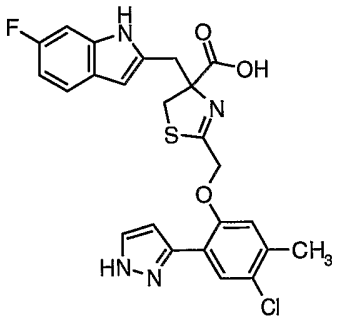
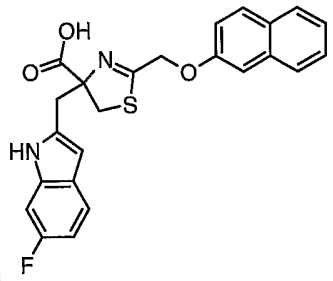
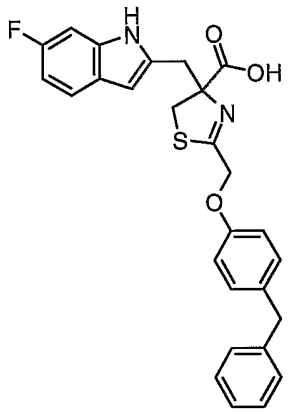
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-(3-methyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	466.53	467.53	54	98
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(7-quinolinyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	435.48	436.48	50	95
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-(methylsulfonyl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	462.52	463.52	55	100

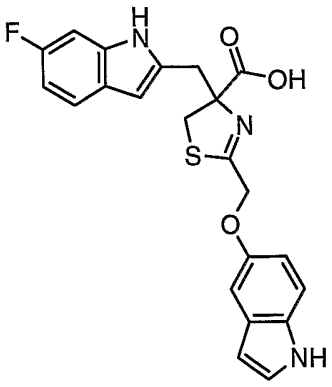
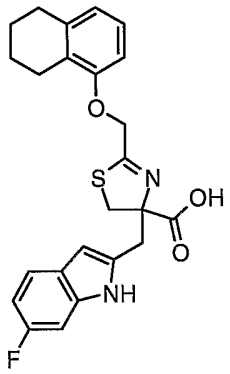
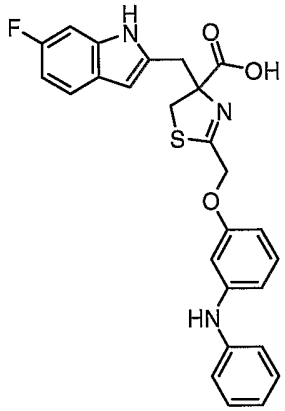
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[2-fluoro-5-(trifluoromethyl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	470.42	471.42	48	100
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3-methoxy-5-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	428.48	429.48	47	95
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-(trifluoromethoxy)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.43	469.43	43	95
	2-[(3,4-dimethoxyphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	444.48	445.48	44	93

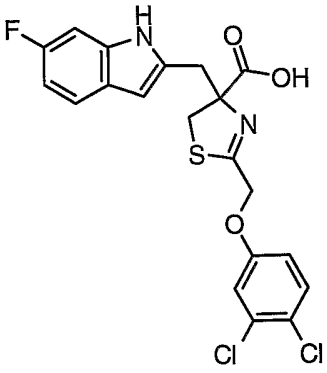
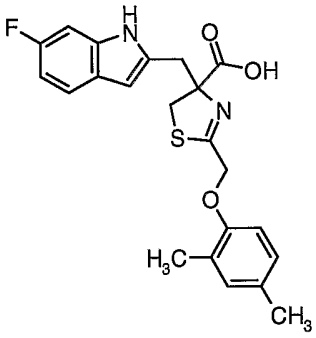
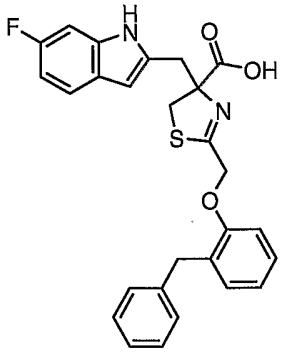
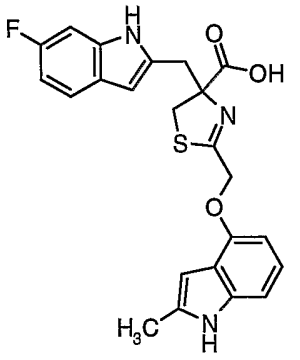
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-8-yloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	479.57	480.57	26	79
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(5-quinolinyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	435.48	436.48	40	96
	2-[(4-cyclopentylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	452.55	453.55	55	98

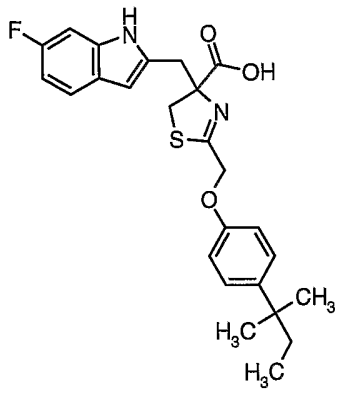
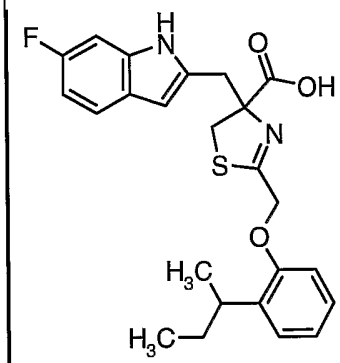
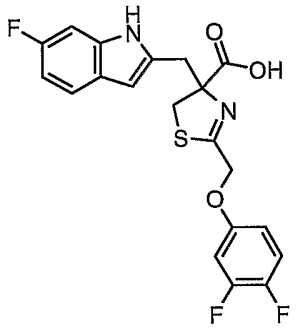
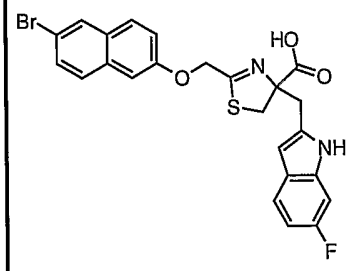
	2-[(3-tert-butylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.54	441.54	52	97
	2-[(4-chloro-3-ethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	446.93	447.93	55	100
	2-[(9H-carbazol-2-yloxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	473.53	474.53	52	96
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[3-(trifluoromethoxy)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.43	469.43	53	99

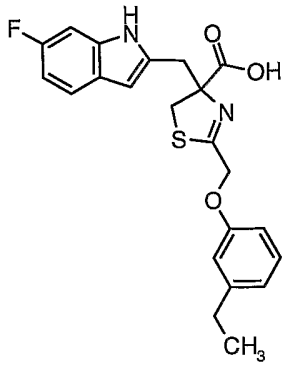
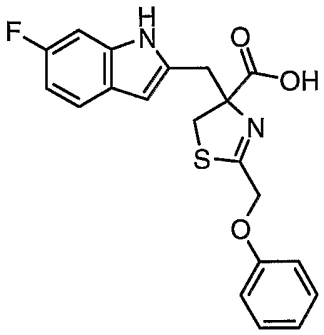
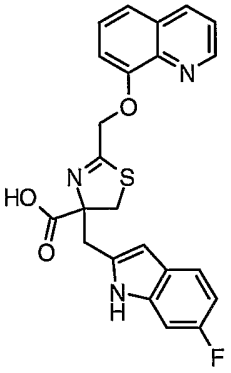
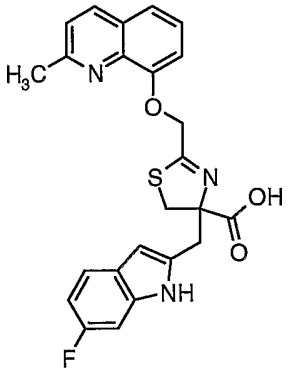
	2-{[(5-chloro-8-quinolinyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.92	470.92	45	94
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3,4,5-trimethylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	426.51	427.51	54	99
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(4-phenoxyphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	476.53	477.53	19	74

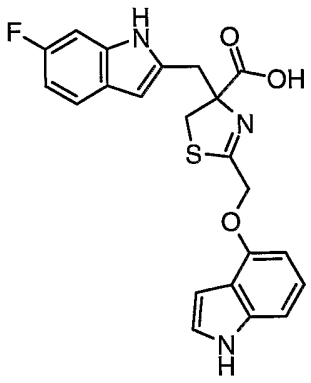
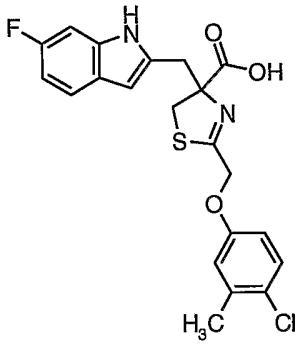
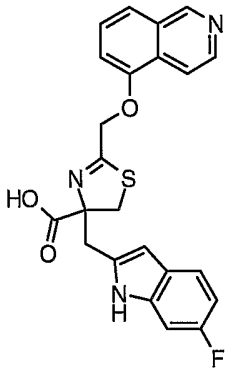
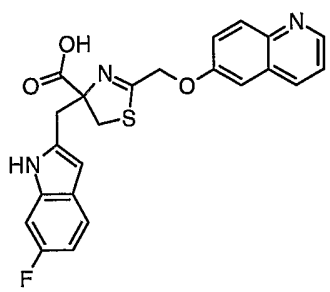
	2-{[4-chloro-5-methyl-2-(1H-pyrazol-3-yl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	498.96	499.96	38	91
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-naphthyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	434.49	435.49	40	91
	2-[(4-benzylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	474.55	475.55	37	95

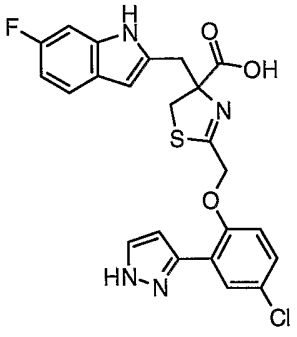
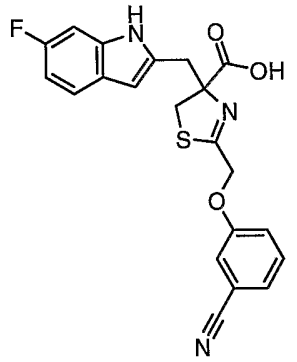
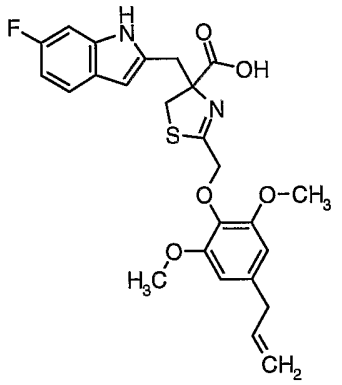
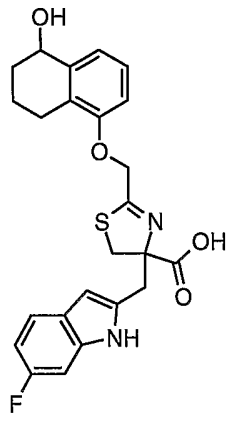
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1H-indol-5-yloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	423.47	424.47	44	94
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	438.52	439.52	51	95
	2-[(3-anilinophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	475.54	476.54	50	96

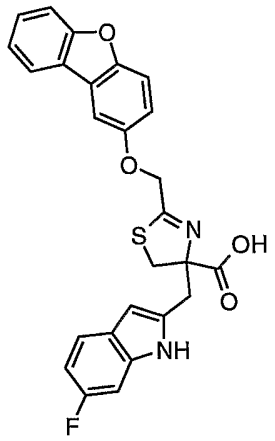
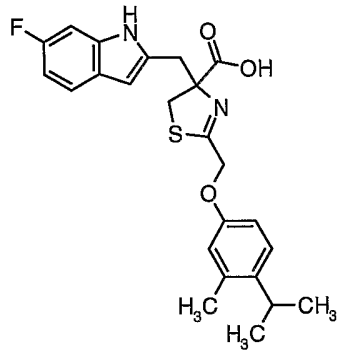
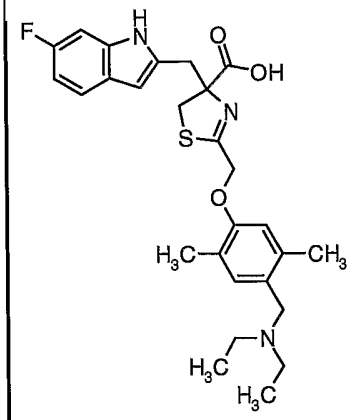
	2-[(3,4-dichlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	453.32	454.32	56	100
	2-[(2,4-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	412.48	413.48	51	95
	2-[(2-benzylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	474.55	475.55	45	93
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-methyl-1H-indol-4-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	437.49	438.49	54	98

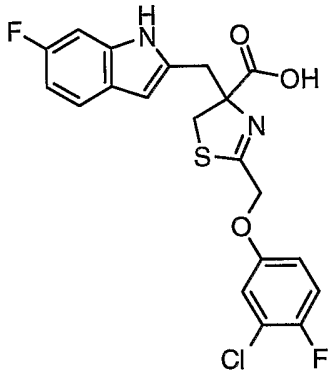
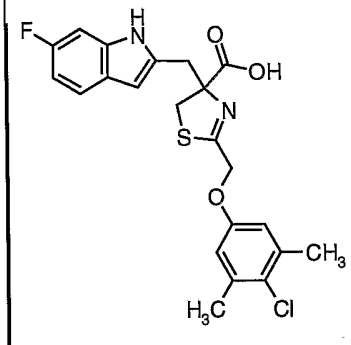
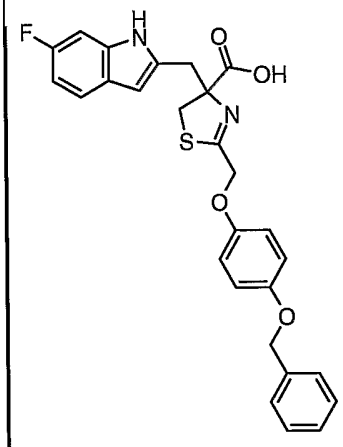
	2-{[4-(1,1-dimethylpropyl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.56	455.56	25	78
	2-[(2-sec-butylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.54	441.54	33	89
	2-[(3,4-difluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	420.41	421.41	49	96
	2-{[(6-bromo-2-naphthyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	513.39	514.39	47	99

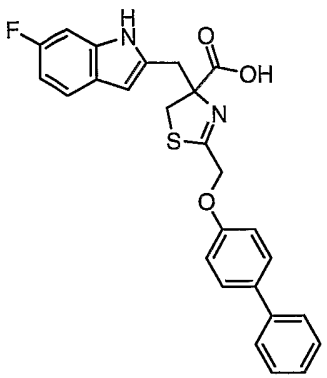
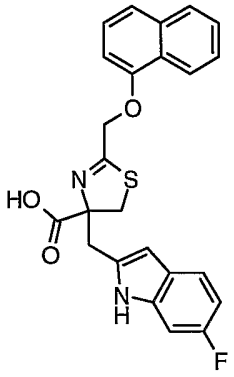
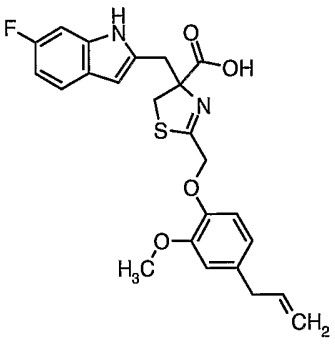
	2-[(3-ethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	412.48	413.48	50	96
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-(phenoxymethyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	384.43	385.43	49	95
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(8-quinolinyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	435.48	436.48	43	90
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-methyl-8-quinolinyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	449.50	450.50	42	90

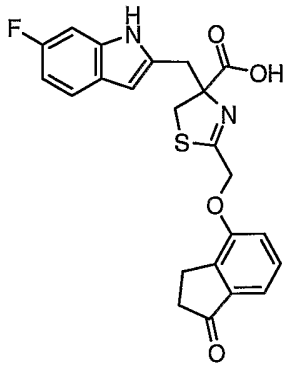
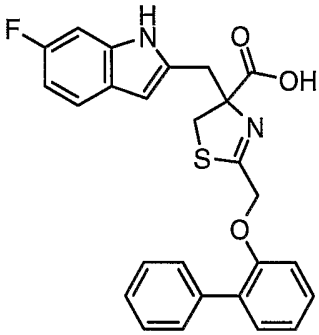
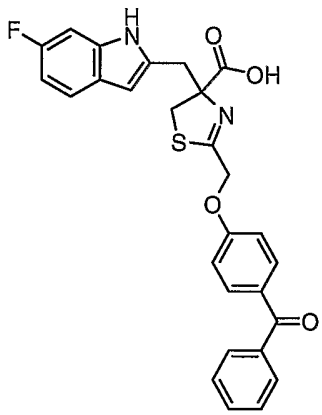
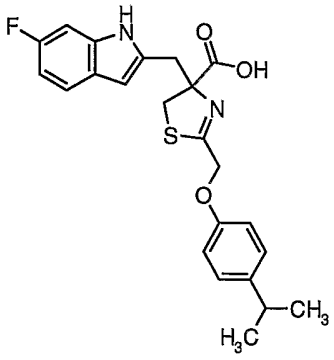
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1H-indol-4-yloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	423.47	424.47	63	95
	2-[(4-chloro-3-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.90	433.90	48	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(5-isoquinolinyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	435.48	436.48	50	93
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(6-quinolinyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	435.48	436.48	29	84

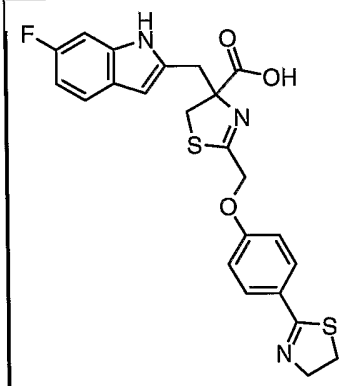
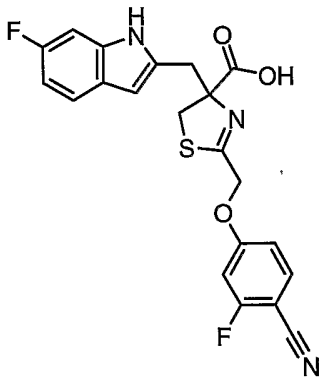
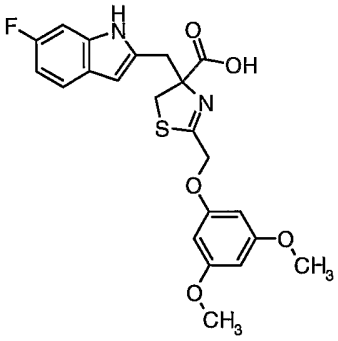
	2-{[4-chloro-2-(1H-pyrazol-3-yl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	484.94	485.94	37	91
	2-[(3-cyanophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	409.44	410.44	27	80
	2-[(4-allyl-2,6-dimethoxyphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	484.55	485.55	42	94
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.52	455.52	58	98

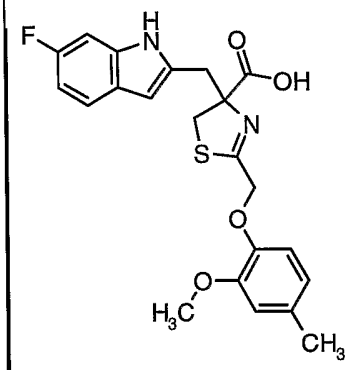
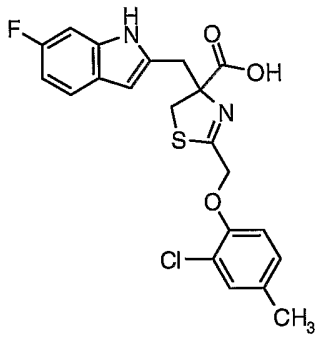
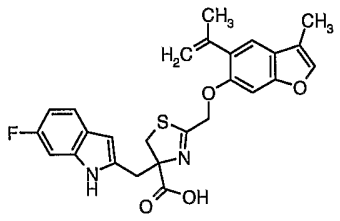
	2-[(dibenzo[b,d]furan-2-yloxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	474.51	475.51	57	98
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(4-isopropyl-3-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.54	441.54	56	98
	2-({4-[(diethylamino)methyl]-2,5-dimethylphenoxy}methyl)-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	497.63	498.63	42	87

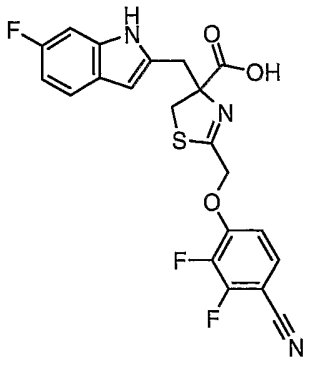
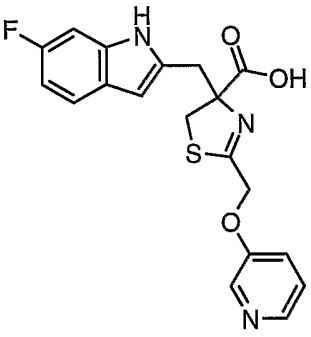
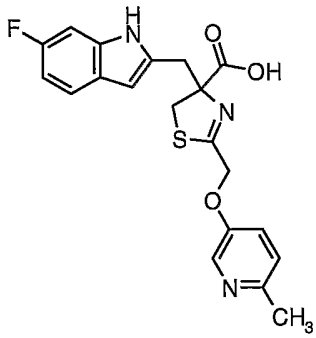
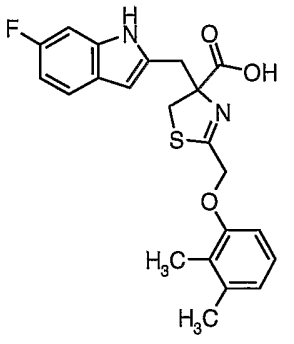
	2-[(3-chloro-4-fluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	436.86	437.86	57	98
	2-[(4-chloro-3,5-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	446.93	447.93	36	86
	2-{[4-(benzyloxy)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	490.55	491.55	53	95

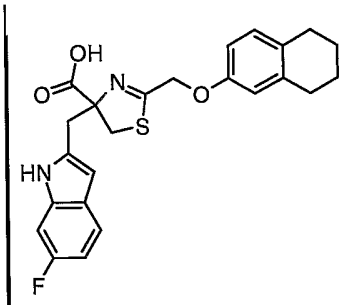
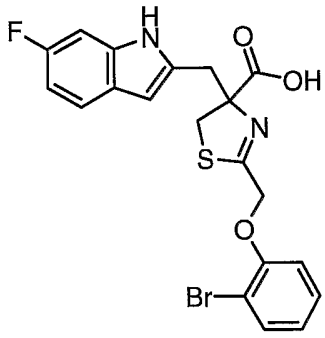
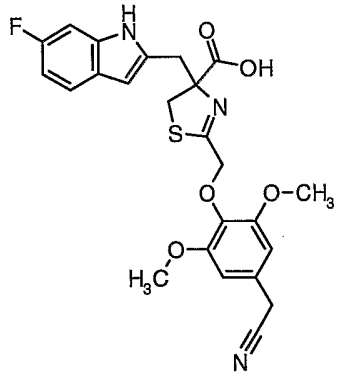
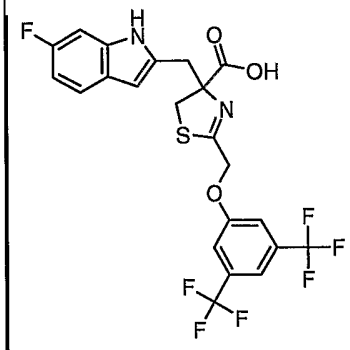
	2-[(4-biphenylyloxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	460.53	461.53	13	54
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1-naphthyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	434.49	435.49	42	91
	2-[(4-allyl-2-methoxyphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.52	455.52	39	90

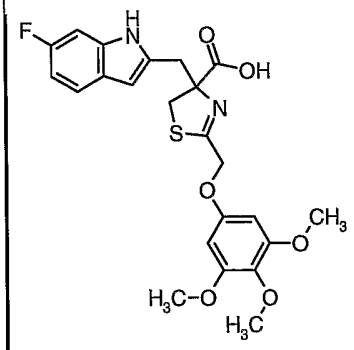
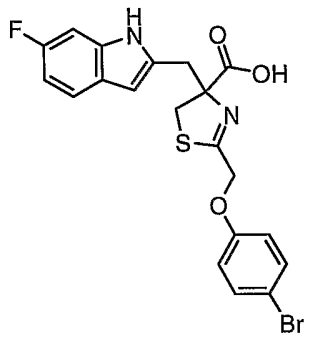
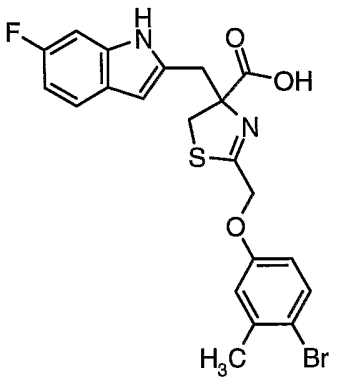
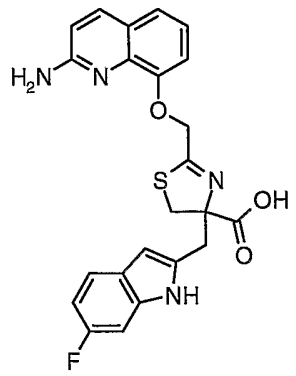
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(1-oxo-2,3-dihydro-1H-inden-4-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	438.48	439.48	49	99
	2-[(2-biphenylyloxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	460.53	461.53	48	96
	2-[(4-benzoylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	488.54	489.54	57	99
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(4-isopropylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	426.51	427.51	46	91

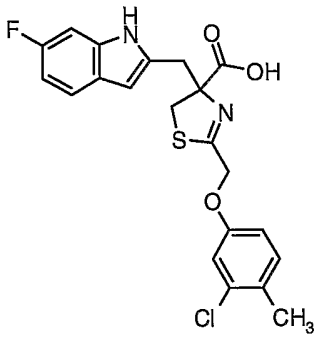
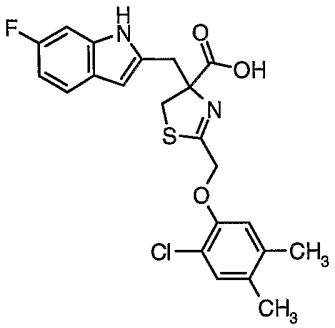
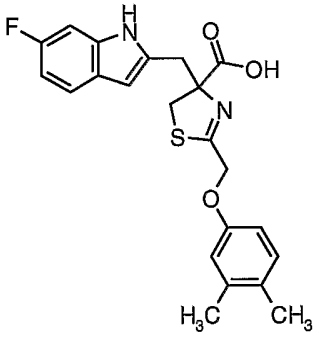
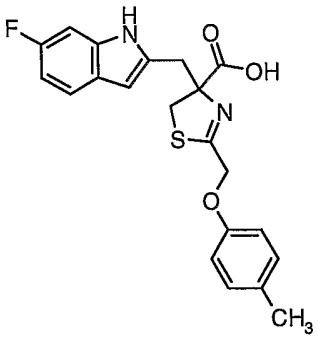
	2-{[4-(4,5-dihydro-1,3-thiazol-2-yl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	469.56	470.56	43	92
	2-[(4-cyano-3-fluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	427.43	428.43	59	98
	2-[(3,5-dimethoxyphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	444.48	445.48	47	94

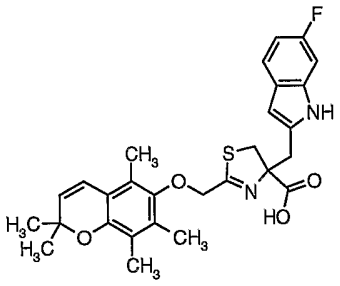
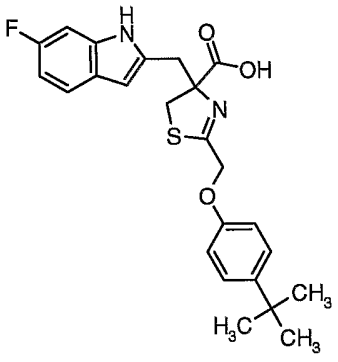
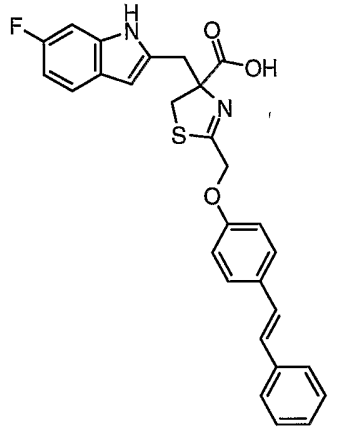
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-methoxy-4-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	428.48	429.48	48	91
	2-[(2-chloro-4-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.90	433.90	44	91
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-isopropenyl-3-methyl-1-benzofuran-6-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	478.54	479.54	46	92

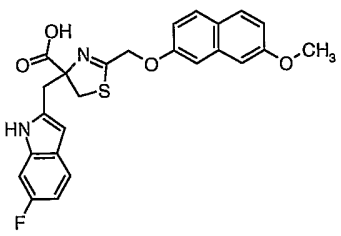
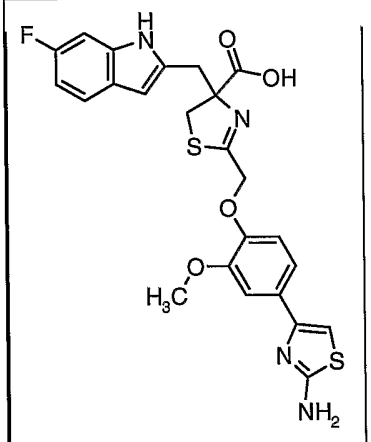
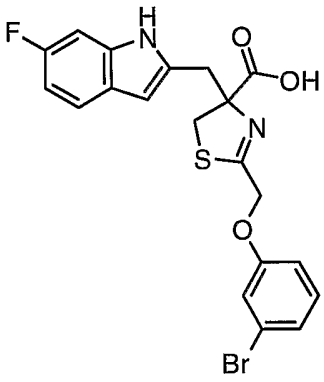
	2-[(4-cyano-2,3-difluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	445.42	446.42	51	92
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3-pyridinyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	385.42	386.42	66	94
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(6-methyl-3-pyridinyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	399.44	400.44	63	93
	2-[(2,3-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	412.48	413.48	70	97

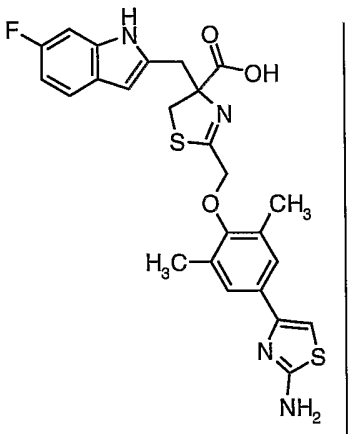
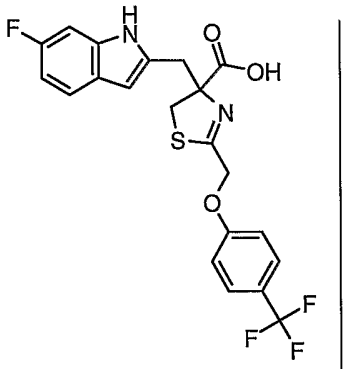
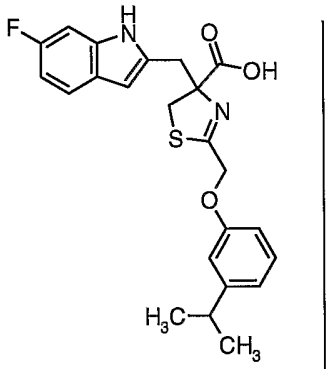
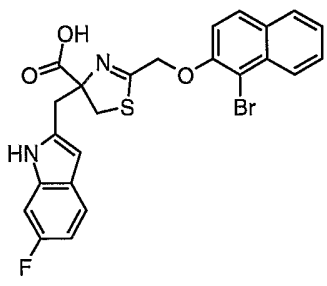
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(5,6,7,8-tetrahydro-2-naphthalenyloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	438.52	439.52	65	96
	2-[(2-bromophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	463.33	464.33	63	98
	2-{[4-(cyanomethyl)-2,6-dimethoxyphenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	483.52	484.52	36	76
	2-{[3,5-bis(trifluoromethyl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	520.42	521.42	60	97

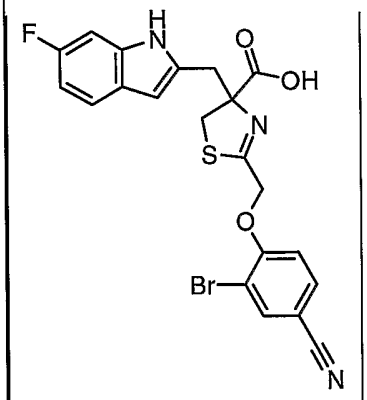
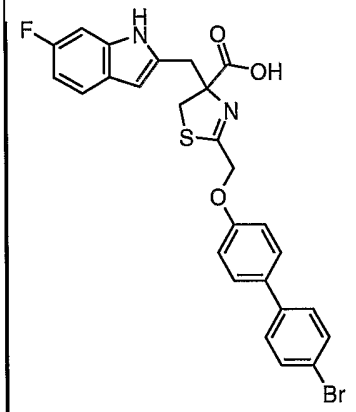
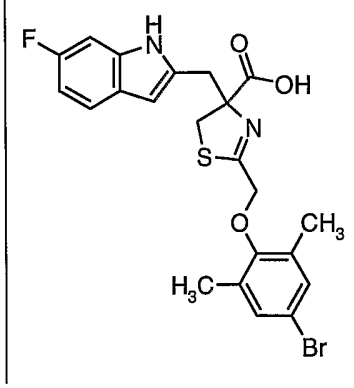
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3,4,5-trimethoxyphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	474.51	475.51	52	93
	2-[(4-bromophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	463.33	464.33	45	91
	2-[(4-bromo-3-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	477.35	478.35	45	91
	2-{[(2-amino-8-quinolinyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	450.49	451.49	33	81

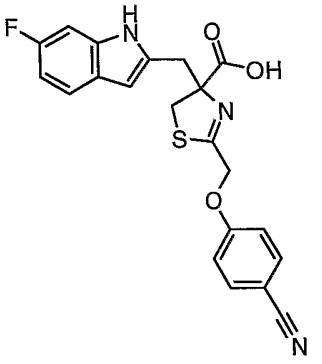
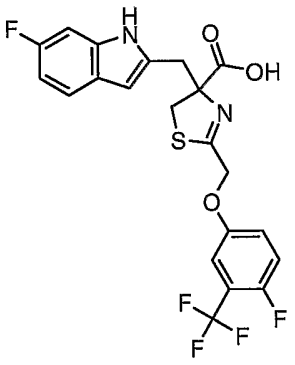
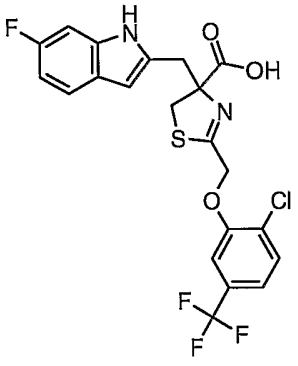
	2-[(3-chloro-4-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.90	433.90	75	97
	2-[(2-chloro-4,5-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	446.93	447.93	64	92
	2-[(3,4-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	412.48	413.48	75	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(4-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	398.46	399.46	70	97

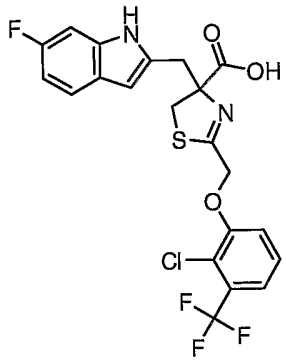
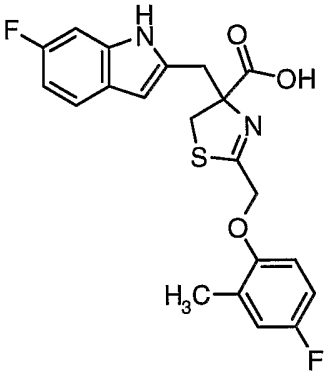
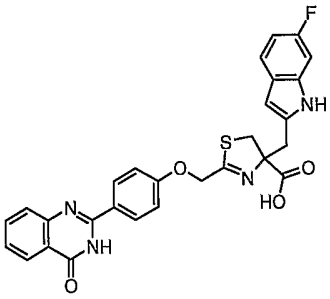
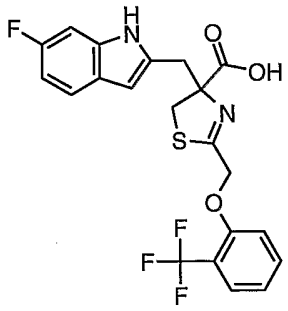
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2,2,5,7,8-pentamethyl-2H-chromen-6-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	508.61	509.61	41	89
	2-[(4-tert-butylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.54	441.54	66	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-({4-[(E)-2-phenylvinyl]phenoxy}methyl)-4,5-dihydro-1,3-thiazole-4-carboxylic acid	486.56	487.56	62	97

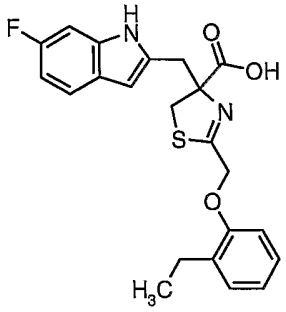
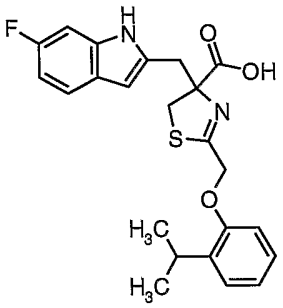
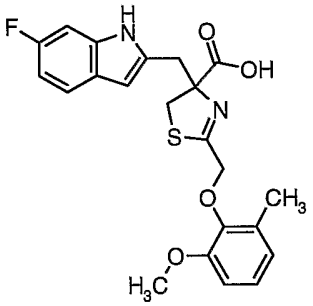
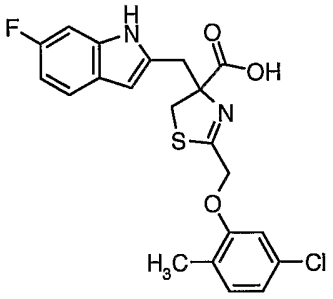
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(7-methoxy-2-naphthyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	464.51	465.51	50	95
	2-{[4-(2-amino-1,3-thiazol-4-yl)-2-methoxyphenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	512.58	513.58	37	88
	2-[(3-bromophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	463.33	464.33	55	94

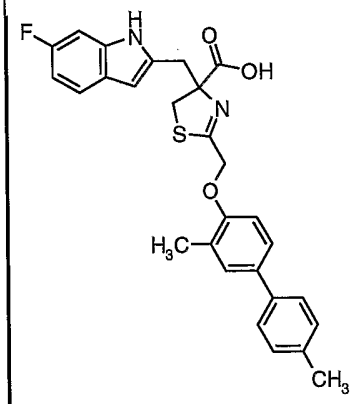
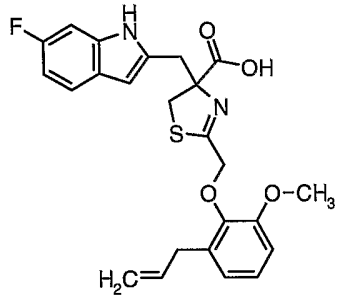
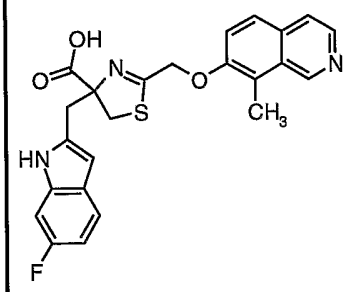
	2-{[4-(2-amino-1,3-thiazol-4-yl)-2,6-dimethylphenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	510.61	511.61	40	87
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-(trifluoromethyl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	452.43	453.43	70	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(3-isopropylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	426.51	427.51	71	96
	2-{[(1-bromo-2-naphthyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	513.39	514.39	73	97

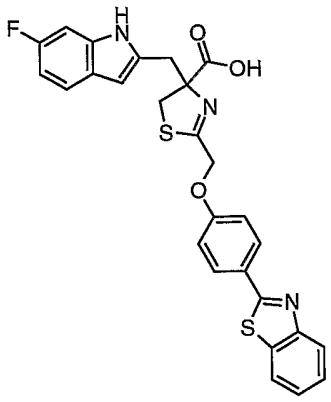
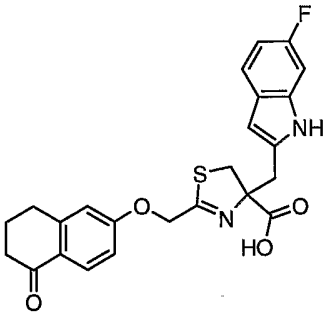
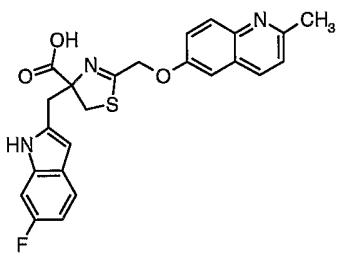
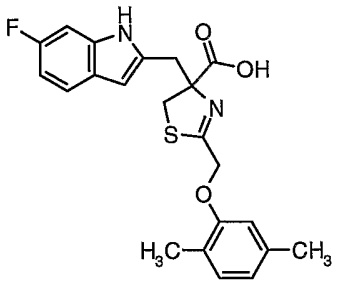
	2-[(2-bromo-4-cyanophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	488.34	489.34	72	98
	2-{[(4'-bromo-4-biphenylyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	539.42	540.42	71	98
	2-[(4-bromo-2,6-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	491.38	492.38	70	98

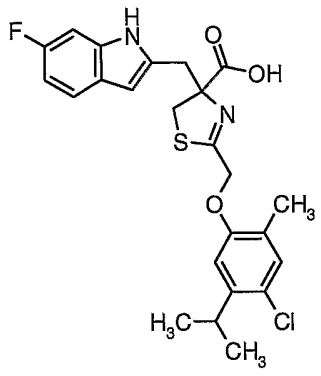
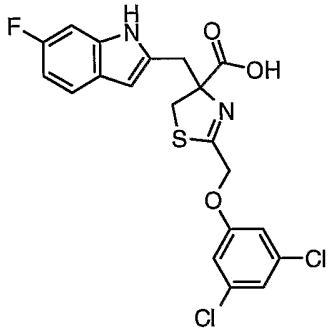
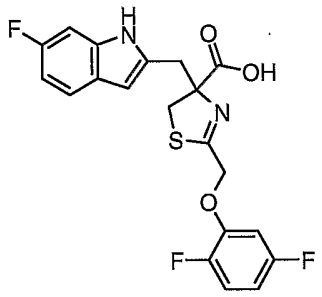
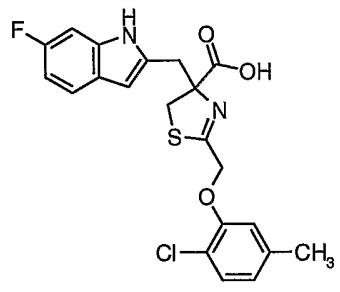
	2-[(4-cyanophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	409.44	410.44	59	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-fluoro-3-(trifluoromethyl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	470.42	471.42	40	95
	2-{[2-chloro-5-(trifluoromethyl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	486.87	487.87	51	94

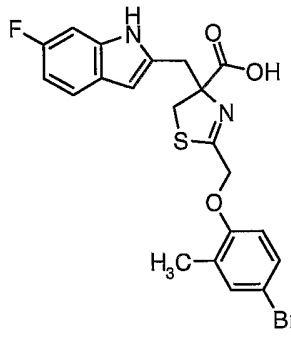
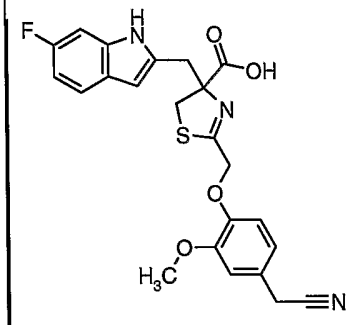
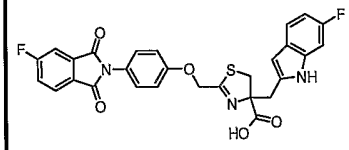
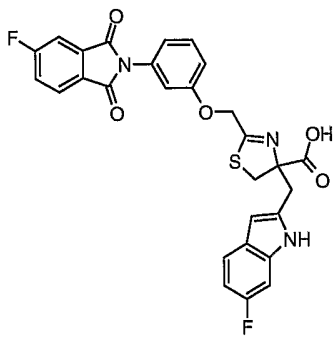
	2-{[2-chloro-3-(trifluoromethyl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	486.87	487.87	51	93
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(4-fluoro-2-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	416.45	417.45	58	94
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[4-(4-oxo-1,4-dihydro-2-quinazolinyl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	528.56	529.56	62	90
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[2-(trifluoromethyl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	452.43	453.43	72	97

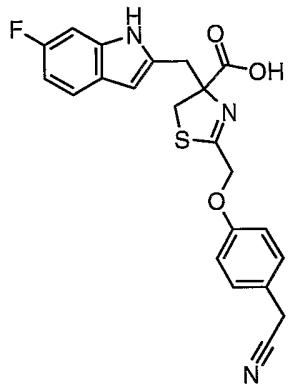
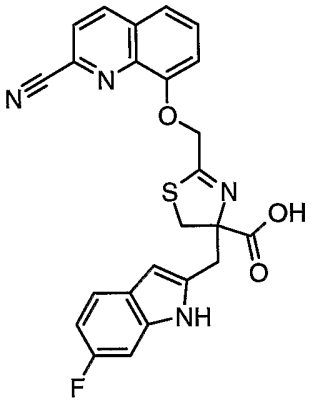
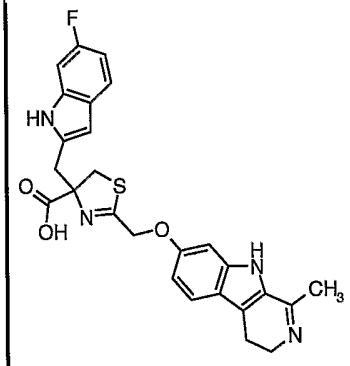
	2-[(2-ethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	412.48	413.48	76	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-isopropylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	426.51	427.51	70	96
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2-methoxy-6-methylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	428.48	429.48	72	98
	2-[(5-chloro-2-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.90	433.90	68	98

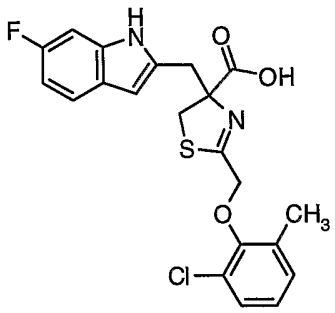
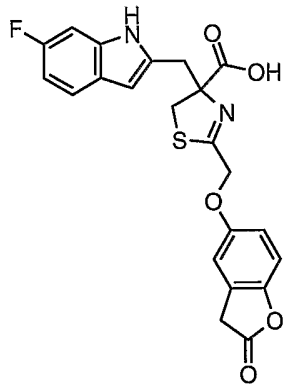
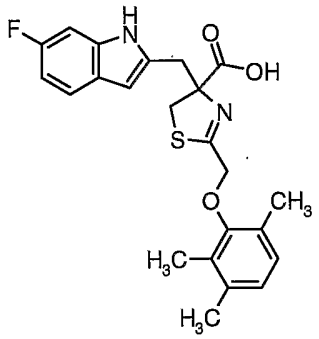
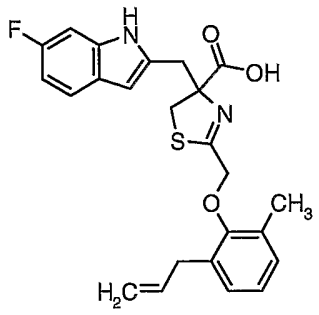
	2-{[(3,4'-dimethyl-4-biphenylyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	488.58	489.58	36	89
	2-[(2-allyl-6-methoxyphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.52	455.52	0	67
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(8-methyl-7-isoquinolinyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	449.50	450.50	28	75

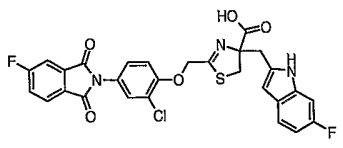
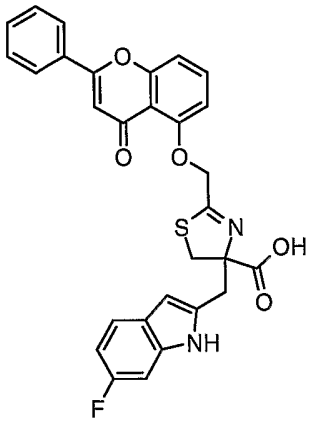
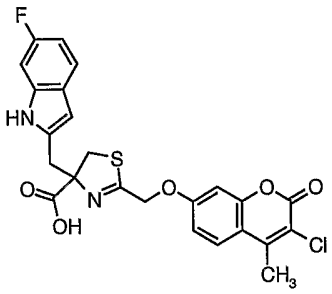
	2-{[4-(1,3-benzothiazol-2-yl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	517.60	518.60	24	68
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	452.50	453.50	50	91
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-methyl-6-quinolinyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	449.50	450.50	62	92
	2-[(2,5-dimethylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	412.48	413.48	58	88

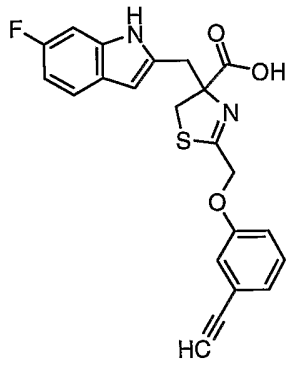
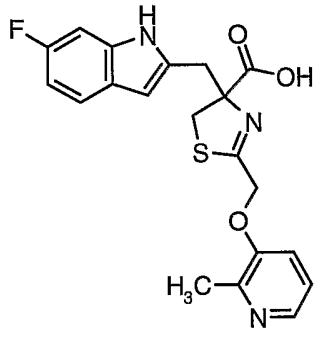
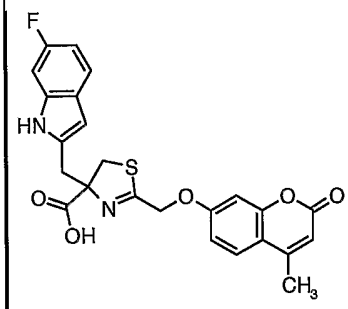
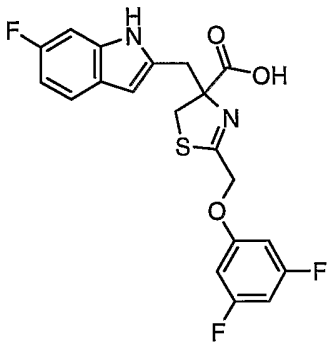
	2-[(4-chloro-5-isopropyl-2-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	474.98	475.98	59	90
	2-[(3,5-dichlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	453.32	454.32	53	84
	2-[(2,5-difluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	420.41	421.41	62	97
	2-[(2-chloro-5-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.90	433.90	64	97

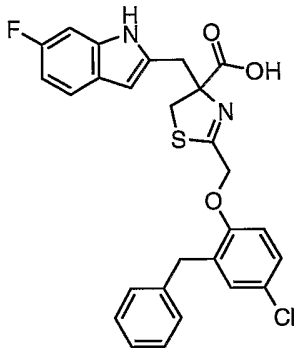
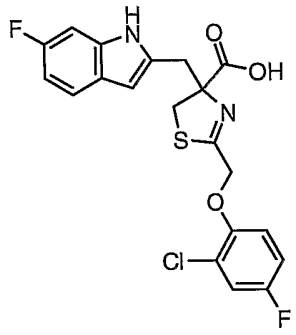
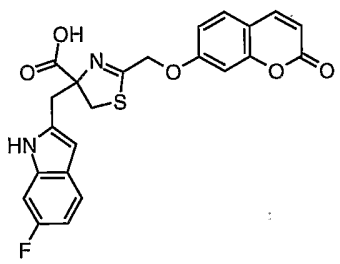
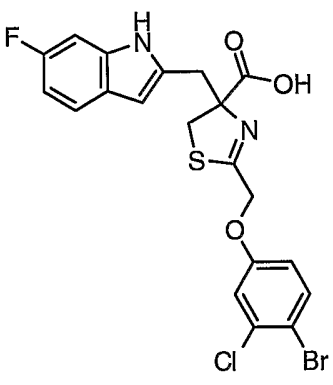
	2-[(4-bromo-2-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	477.35	478.35	36	86
	2-{[4-(cyanomethyl)-2-methoxyphenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	453.49	454.49	31	88
	2-{[4-(5-fluoro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	547.54	548.54	37	85
	2-{[3-(5-fluoro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	547.54	548.54	36	77

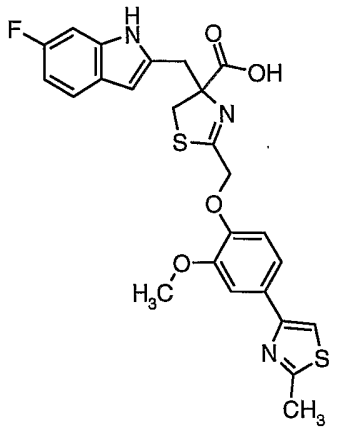
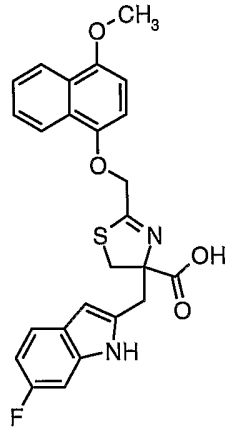
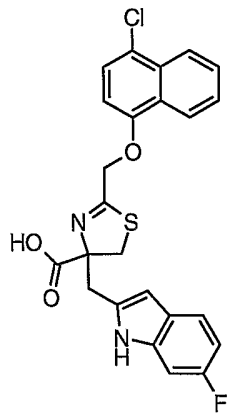
	2-{[4-(cyanomethyl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	423.47	424.47	36	74
	2-{[(2-cyano-8-quinolinyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	460.49	461.49	65	90
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(1-methyl-4,9-dihydro-3H-beta-carbolin-7-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	490.56	491.56	60	88

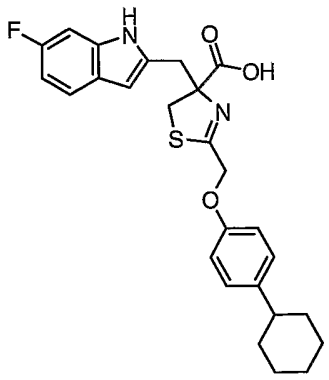
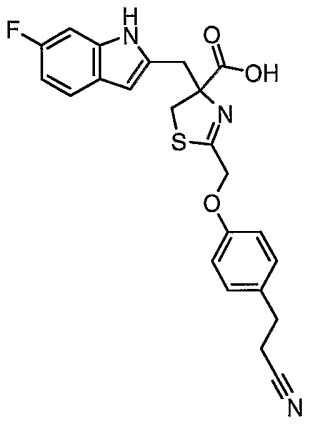
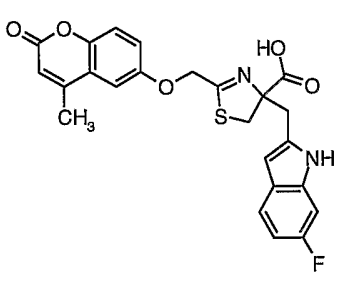
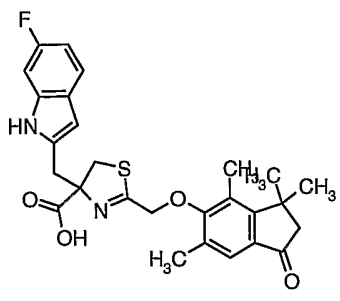
	2-[(2-chloro-6-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	432.90	433.90	60	88
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-oxo-2,3-dihydro-1-benzofuran-5-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	440.45	441.45	73	96
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(2,3,6-trimethylphenoxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	426.51	427.51	49	90
	2-[(2-allyl-6-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	438.52	439.52	40	86

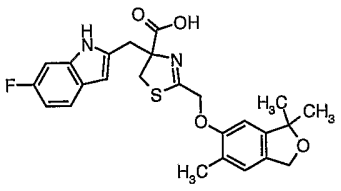
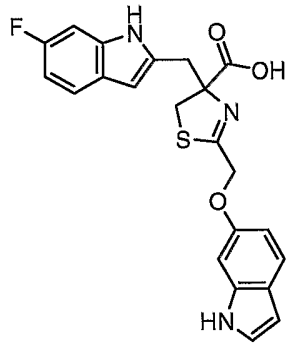
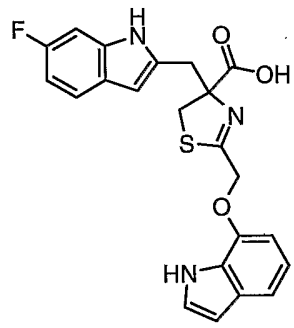
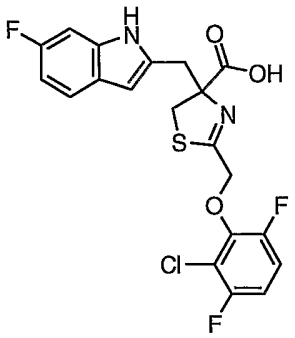
	2-{[2-chloro-4-(5-fluoro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	581.98	582.98	38	84
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-oxo-2-phenyl-4H-chromen-5-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	528.56	529.56	26	85
	2-{[(3-chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	500.93	501.93	57	67

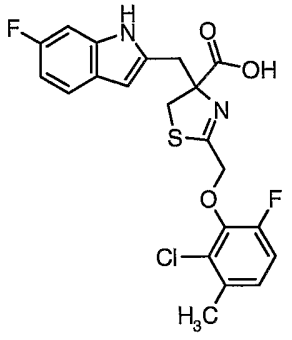
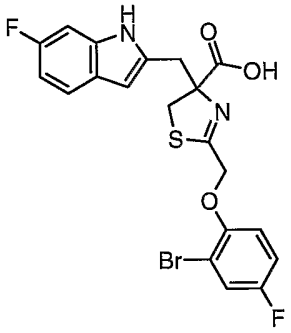
	2-[(3-ethynylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	408.45	409.45	63	93
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-methyl-3-pyridinyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	399.44	400.44	41	77
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	466.49	467.49	67	95
	2-[(3,5-difluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	420.41	421.41	68	96

	2-[(2-benzyl-4-chlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	509.00	510.00	53	82
	2-[(2-chloro-4-fluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	436.86	437.86	65	97
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(2-oxo-2H-chromen-7-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	452.46	453.46	49	90
	2-[(4-bromo-3-chlorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	497.77	498.77	53	95

	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[2-methoxy-4-(2-methyl-1,3-thiazol-4-yl)phenoxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	511.60	512.60	37	85
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methoxy-1-naphthyl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	464.51	465.51	26	82
	2-{[(4-chloro-1-naphthyl)oxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.93	469.93	61	76

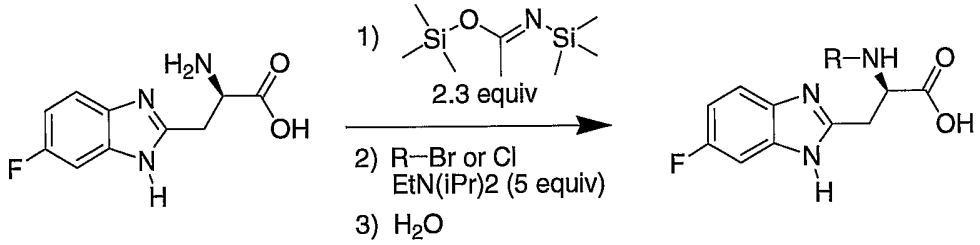
	2-[(4-cyclohexylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	466.57	467.57	45	79
	2-{[4-(2-cyanoethyl)phenoxy]methyl}-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	437.49	438.49	38	71
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(4-methyl-2-oxo-2H-chromen-6-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	466.49	467.49	70	95
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3,3,4,6-tetramethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	494.58	495.58	64	91

	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-{[(3,3,6-trimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]methyl}-4,5-dihydro-1,3-thiazole-4-carboxylic acid	468.55	469.55	54	87
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1H-indol-6-yloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	423.47	424.47	54	82
	4-[(6-fluoro-1H-indol-2-yl)methyl]-2-[(1H-indol-7-yloxy)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	423.47	424.47	43	84
	2-[(2-chloro-3,6-difluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	454.85	455.85	61	93

	2-[(2-chloro-6-fluoro-3-methylphenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	450.89	451.89	57	89
	2-[(2-bromo-4-fluorophenoxy)methyl]-4-[(6-fluoro-1H-indol-2-yl)methyl]-4,5-dihydro-1,3-thiazole-4-carboxylic acid	481.32	482.32	36	76

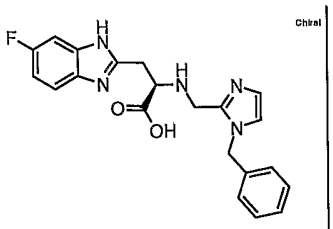
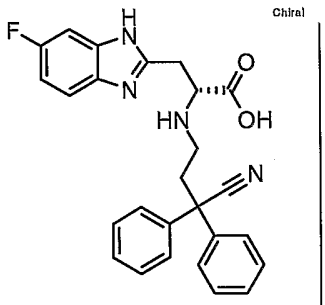
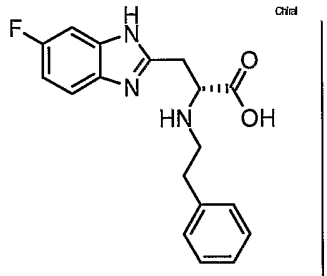
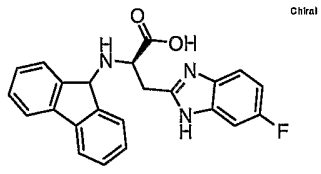
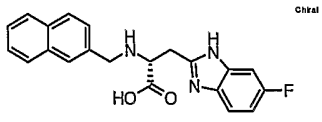
The compounds of Table 3 were made by the following general procedure.

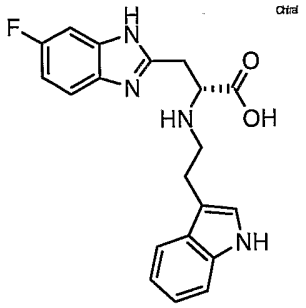
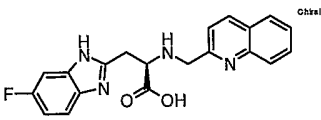
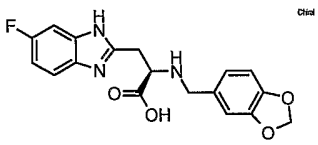
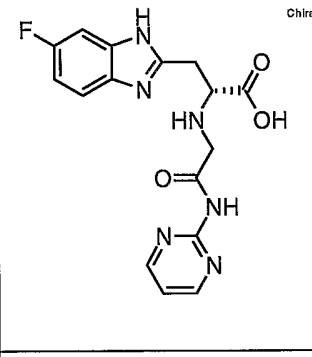
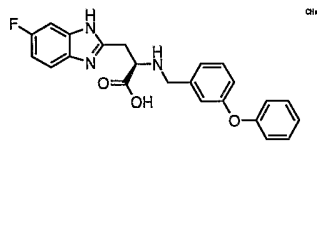
General Procedure for Alkylation of Amino Acids with Alkyl Halides:

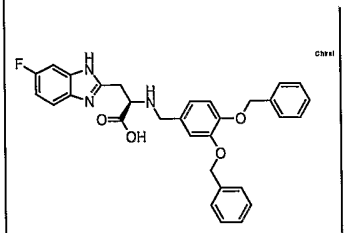
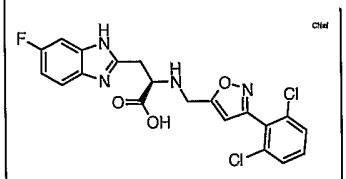
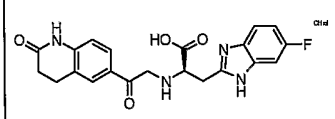
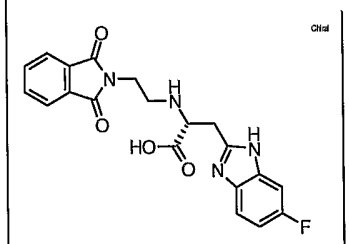
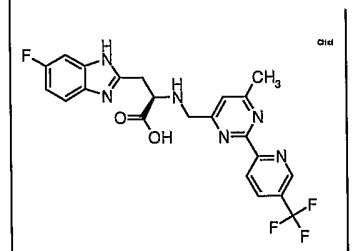


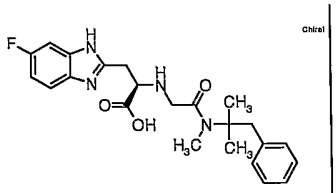
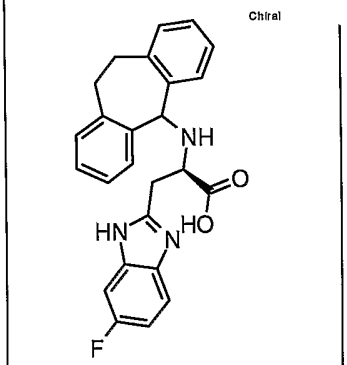
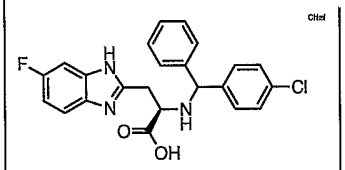
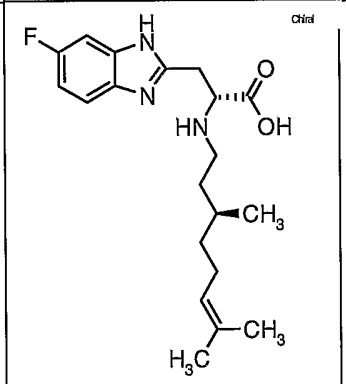
In a glovebox, each aminoacid (10 mmole) was placed into a labeled 50 mL reaction tube of a J-KEM™ Shaker, and 10 mL of anhydrous acetonitrile was added. Hexamethyldisilazane (5.0 mL, 23 mmole) was added to each tube, and the reaction mixtures were allowed to reflux under nitrogen until the amino acids dissolved. The appropriate silylated amino acid solution (0.5 M, 160 µL, 0.08 mmole) was added to the corresponding wells of a 96-well plate, and the appropriate solution of the alkyl halide in DMA (0.4 M, 200 µL, 0.08 mmole) was added. Neat *N,N*-diisopropylethylamine (70 µL, 0.4 mmole) was added to each well. The reaction was removed from the glovebox and heated at 50 ^{o}C overnight. Water (16 µL) was added to each well, and the reaction mixtures were agitated for 15 minutes. The solvents were removed, and the residues were reconstituted in DMSO.

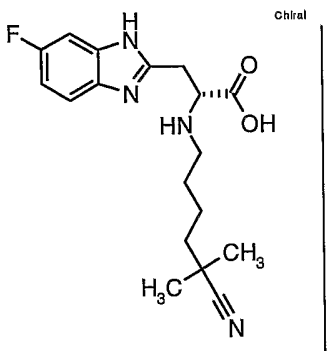
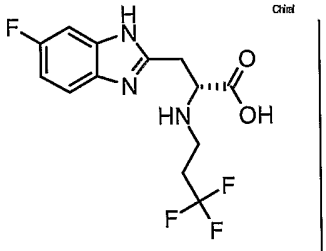
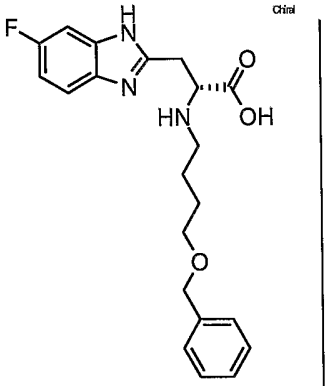
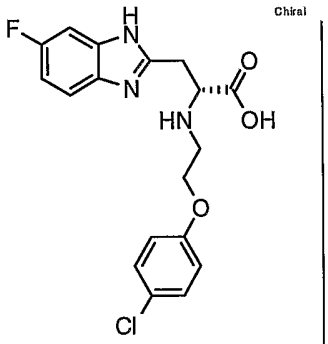
Table 3

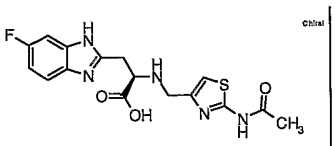
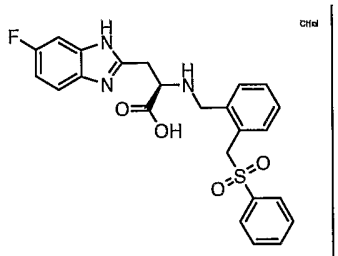
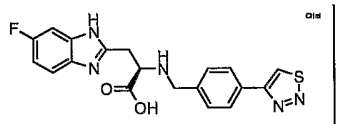
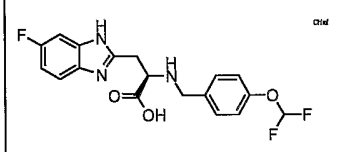
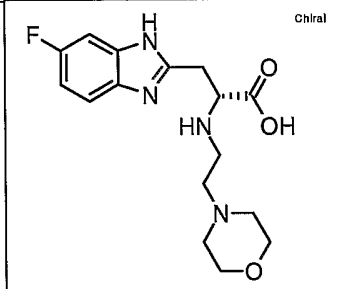
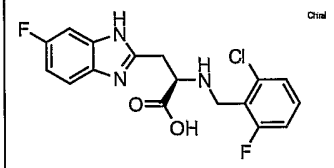
Name	Structure	MW	m/z MW + 1	% Inhibition at 10 μM
N-[(1-benzyl-1H-imidazol-2-yl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		393.42	394.42	43
N-(3-cyano-3,3-diphenylpropyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		442.4917	443.4917	22
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-phenylethyl)-D-alanine		327.3572	328.3572	26
N-9H-fluoren-9-yl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		387.4122	388.4122	30
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-naphthylmethyl)-D-alanine		363.3902	364.3902	28

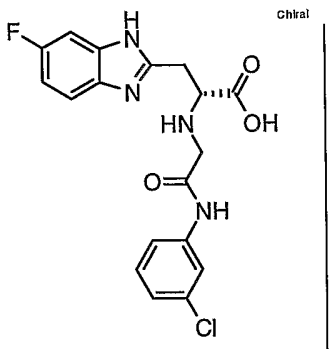
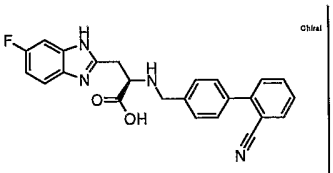
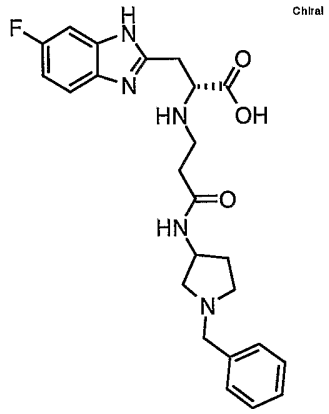
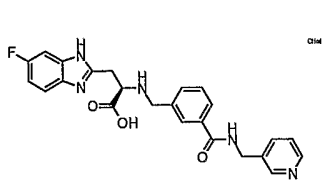
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(1H-indol-3-yl)ethyl]-D-alanine		366.3941	367.3941	34
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(quinolin-2-ylmethyl)-D-alanine		364.3783	365.3783	38
N-(1,3-benzodioxol-5-ylmethyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		357.3394	358.3394	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-oxo-2-(pyrimidin-2-ylamino)ethyl]-D-alanine		358.3315	359.3315	33
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-phenoxybenzyl)-D-alanine		405.427	406.427	30

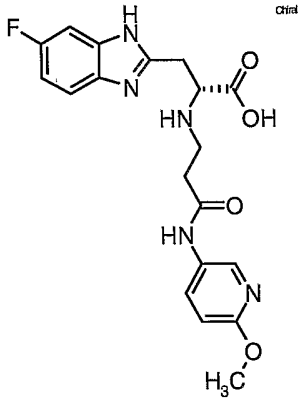
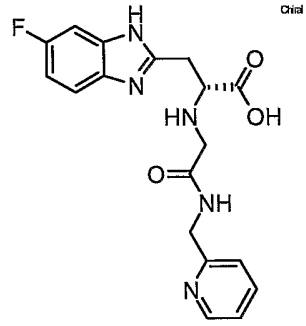
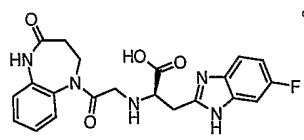
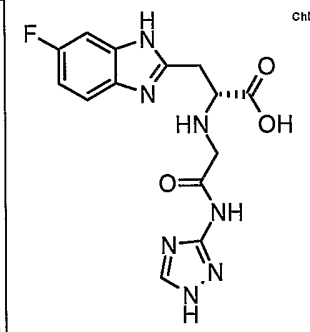
N-[3,4-bis(benzyloxy)benzyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		525.5772	526.5772	27
N-{[3-(2,6-dichlorophenyl)isoxazol-5-yl]methyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		449.2675	450.2675	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-oxo-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)ethyl]-D-alanine		410.4031	411.4031	32
N-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		396.3763	397.3763	28
3-(6-fluoro-1H-benzimidazol-2-yl)-N-({6-methyl-2-[5-(trifluoromethyl)pyridin-2-yl]pyrimidin-4-yl}methyl)-D-alanine		474.4162	475.4162	41

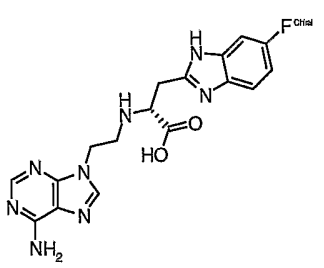
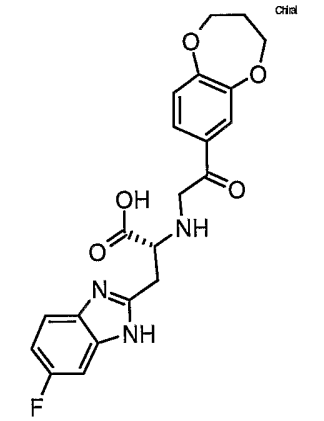
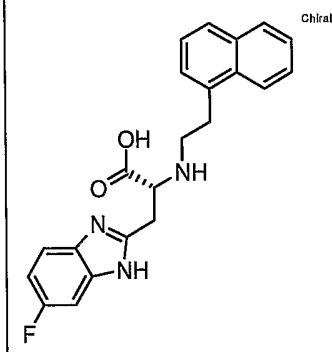
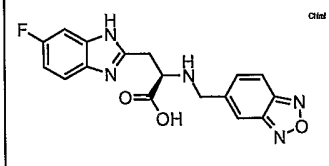
N-{2-[(1,1-dimethyl-2-phenylethyl)(methyl)amino]-2-oxoethyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		426.4893	427.4893	38
N-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		415.4658	416.4658	14
N-[(4-chlorophenyl)(phenyl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		423.8731	424.8731	31
N-[(3S)-3,7-dimethyloct-6-en-1-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		361.4582	362.4582	26

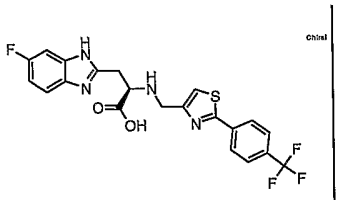
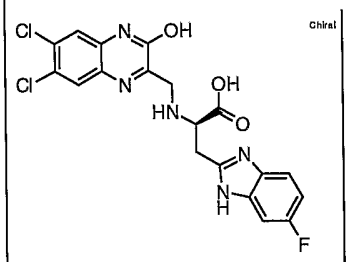
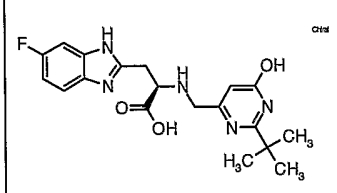
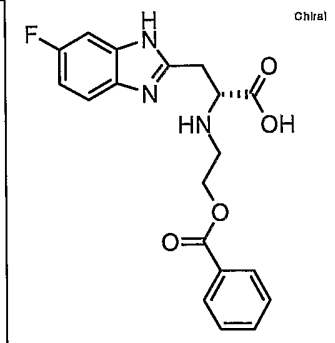
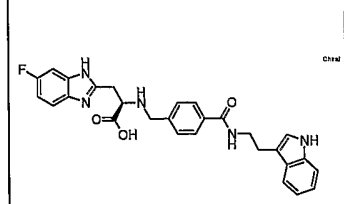
N-(5-cyano-5-methylhexyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		346.4037	347.4037	23
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3,3,3-trifluoropropyl)-D-alanine		319.2567	320.2567	26
N-[4-(benzyloxy)butyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		385.4366	386.4366	21
N-[2-(4-chlorophenoxy)ethyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		377.8013	378.8013	21

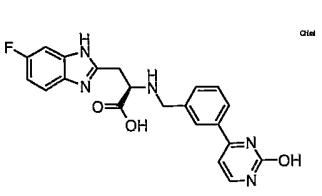
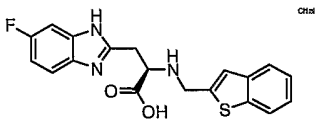
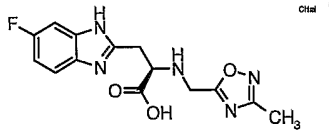
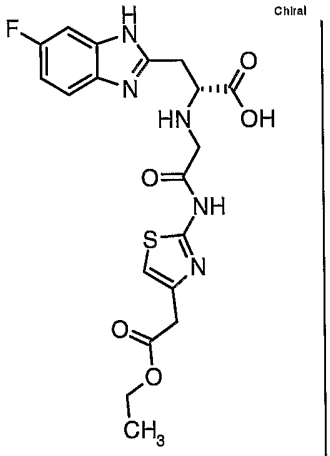
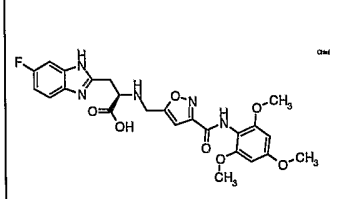
N-{[2-(acetylamino)-1,3-thiazol-4-yl]methyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		377.3984	378.3984	31
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{2-[(phenylsulfonyl)methyl]benzyl}-D-alanine		467.5188	468.5188	36
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-D-alanine		397.4324	398.4324	32
N-[4-(difluoromethoxy)benzyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		379.3364	380.3364	30
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-morpholin-4-ylethyl)-D-alanine		336.3649	337.3649	33
N-(2-chloro-6-fluorobenzyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		365.7656	366.7656	26

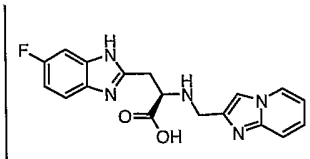
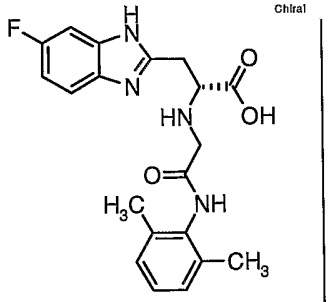
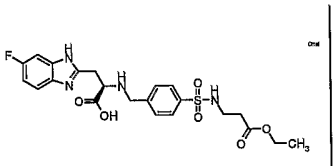
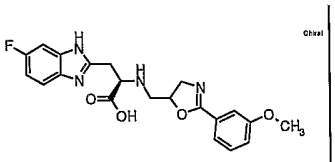
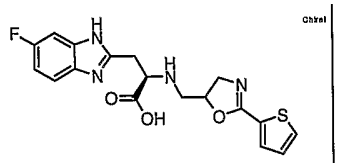
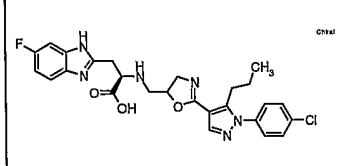
N-{2-[(3-chlorophenyl)amino]-2-oxoethyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		390.8004	391.8004	32
N-[(2'-cyanobiphenyl-4-yl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		414.4381	415.4381	38
N-{3-[(1-benzylpyrrolidin-3-yl)amino]-3-oxopropyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		453.5152	454.5152	32
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-{[(pyridin-3-ylmethyl)amino]carbonyl}benzyl)-D-alanine		447.4678	448.4678	20

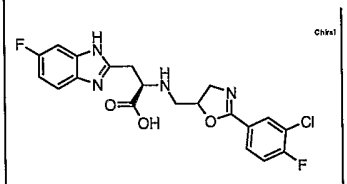
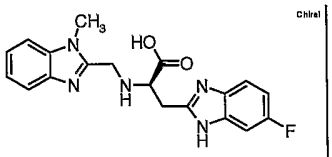
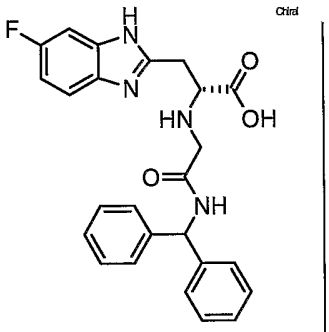
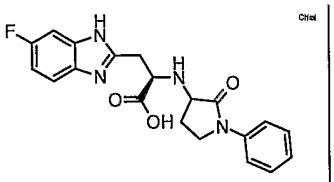
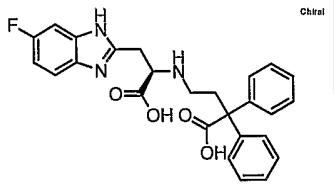
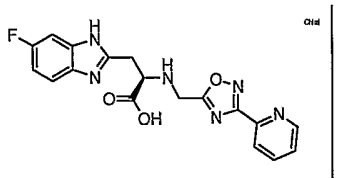
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{3-[(6-methoxypyridin-3-yl)amino]-3-oxopropyl}-D-alanine		401.396	402.396	43
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{2-oxo-2-[(pyridin-2-ylmethyl)amino]ethyl}-D-alanine		371.3702	372.3702	40
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-oxo-2-(4-oxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-yl)ethyl]-D-alanine		425.418	426.418	26
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-oxo-2-(1H-1,2,4-triazol-3-ylamino)ethyl]-D-alanine		347.3086	348.3086	39

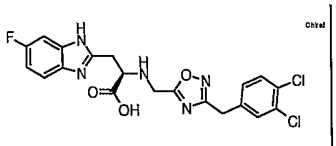
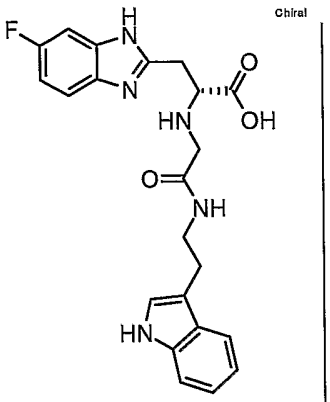
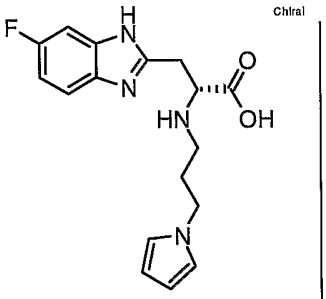
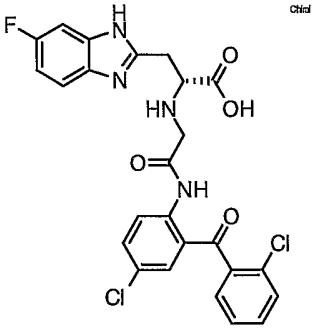
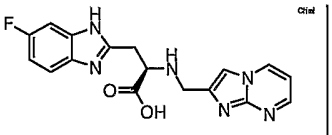
N-[2-(6-amino-9H-purin-9-yl)ethyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		384.3733	385.3733	35
N-[2-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-2-oxoethyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		413.403	414.403	33
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(1-naphthyl)ethyl]-D-alanine		377.417	378.417	36
N-(2,1,3-benzoxadiazol-5-ylmethyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		355.3276	356.3276	39

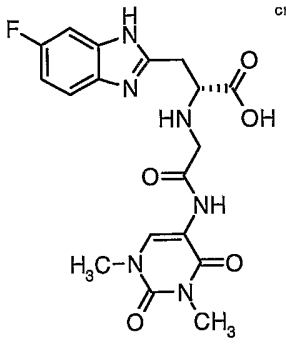
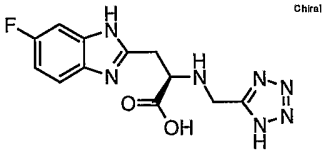
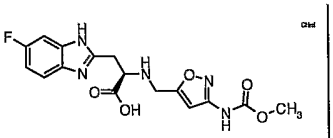
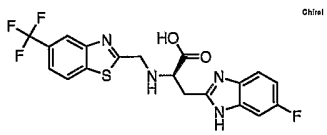
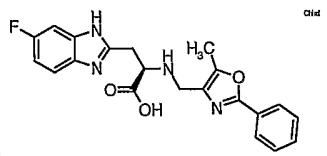
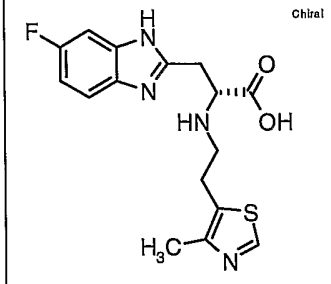
3-(6-fluoro-1H-benzimidazol-2-yl)-N-({2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}methyl)-D-alanine		464.4414	465.4414	34
N-[(6,7-dichloro-3-hydroxyquinoxalin-2-yl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		450.2556	451.2556	25
N-[(2-tert-butyl-6-hydroxypyrimidin-4-yl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		387.4128	388.4128	25
N-[2-(benzoyloxy)ethyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		371.3662	372.3662	16
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[4-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)benzyl]-D-alanine		499.5434	500.5434	22

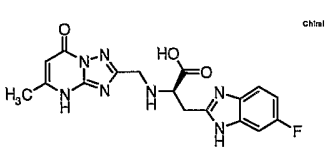
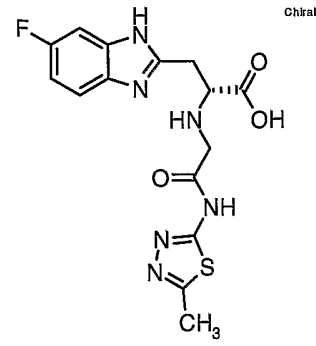
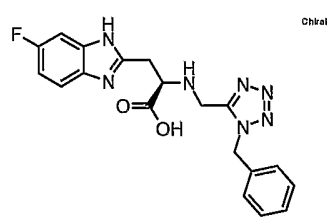
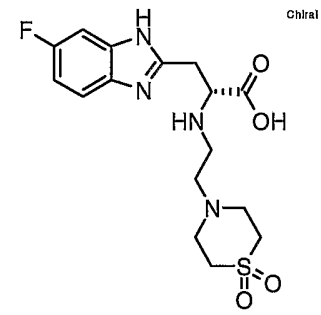
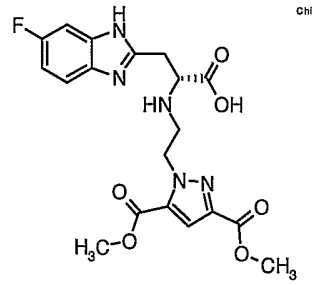
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(2-hydroxypyrimidin-4-yl)benzyl]-D-alanine		407.4032	408.4032	26
N-(1-benzothien-2-ylmethyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		369.4184	370.4184	32
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-D-alanine		319.2946	320.2946	29
N-(2-{[4-(2-ethoxy-2-oxoethyl)-1,3-thiazol-2-yl]amino}-2-oxoethyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		449.461	450.461	36
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-{[(2,4,6-trimethoxyphenyl)amino]carbonyl}isoxazol-5-yl)methyl]-D-alanine		513.4796	514.4796	32

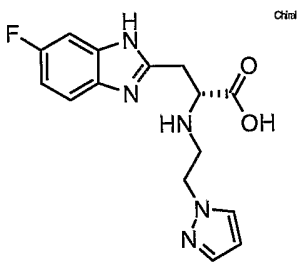
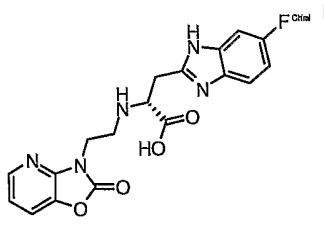
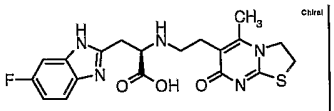
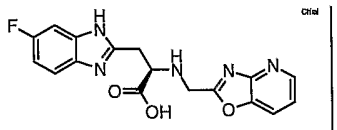
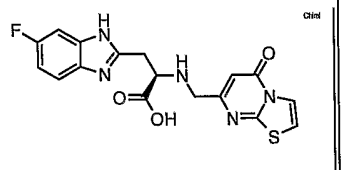
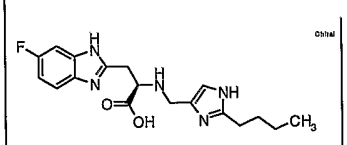
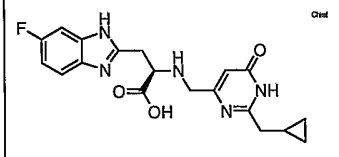
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(imidazo[1,2-a]pyridin-2-ylmethyl)-D-alanine		353.3554	354.3554	41
N-{2-[(2,6-dimethylphenyl)amino]-2-oxoethyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		384.4089	385.4089	32
N-(4-{[(3-ethoxy-3-oxopropyl)amino]sulfonyl}benzyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		492.5255	493.5255	36
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[2-(3-methoxyphenyl)-4,5-dihydro-1,3-oxazol-5-yl]methyl}-D-alanine		412.4189	413.4189	22
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[2-(2-thienyl)-4,5-dihydro-1,3-oxazol-5-yl]methyl}-D-alanine		388.4213	389.4213	18
N-({2-[1-(4-chlorophenyl)-5-propyl-1H-pyrazol-4-yl]-4,5-dihydro-1,3-oxazol-5-yl}methyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		524.9814	525.9814	24

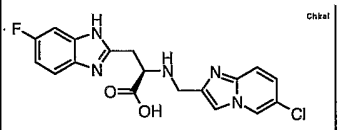
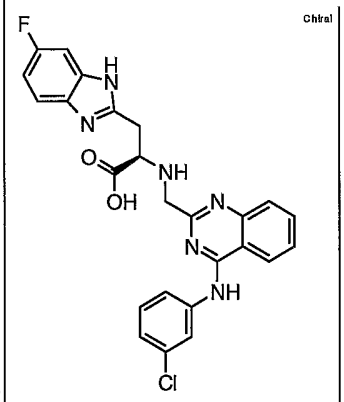
N-{[2-(3-chloro-4-fluorophenyl)-4,5-dihydro-1,3-oxazol-5-yl]methyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		434.8283	435.8283	23
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]-D-alanine		367.3822	368.3822	43
N-{2-[(diphenylmethyl)amino]-2-oxoethyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		446.4797	447.4797	41
(2R)-3-(6-fluoro-1H-benzimidazol-2-yl)-2-[(2-oxo-1-phenylpyrrolidin-3-yl)amino]propanoic acid		382.3931	383.3931	28
4-{[(1R)-1-carboxy-2-(6-fluoro-1H-benzimidazol-2-yl)ethyl]amino}-2,2-diphenylbutanoic acid		461.4906	462.4906	37
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)methyl]-D-alanine		382.3535	383.3535	30

N-{[3-(3,4-dichlorobenzyl)-1,2,4-oxadiazol-5-yl]methyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		464.2824	465.2824	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-{[2-(1H-indol-3-yl)ethyl]amino}-2-oxoethyl)-D-alanine		423.4458	424.4458	18
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(1H-pyrrol-1-yl)propyl]-D-alanine		330.3611	331.3611	28
N-(2-{[4-chloro-2-(2-chlorobenzoyl)phenyl]amino}-2-oxoethyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		529.3531	530.3531	26
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(imidazo[1,2-a]pyrimidin-2-ylmethyl)-D-alanine		354.3435	355.3435	40

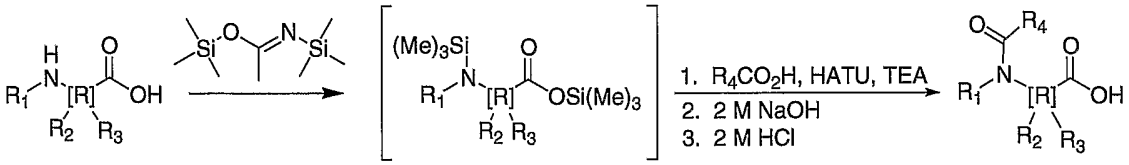
N-{2-[(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)amino]-2-oxoethyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		418.3831	419.3831	30
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(1H-tetrazol-5-ylmethyl)-D-alanine		305.2718	306.2718	40
3-(6-fluoro-1H-benzimidazol-2-yl)-N-({3-[(methoxycarbonyl)amino]isoxazol-5-yl}methyl)-D-alanine		377.3304	378.3304	26
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]methyl}-D-alanine		438.4036	439.4036	25
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-D-alanine		394.4041	395.4041	26
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]-D-alanine		348.4003	349.4003	23

3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-methyl-7-oxo-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-D-alanine		385.3574	386.3574	45
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl}-D-alanine		378.3865	379.3865	39
N-[(1-benzyl-1H-tetrazol-5-yl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		395.3962	396.3962	18
N-[2-(1,1-dioxidothiomorpholin-4-yl)ethyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		384.4299	385.4299	21
N-{2-[3,5-bis(methoxycarbonyl)-1H-pyrazol-1-yl]ethyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		433.394	434.394	20

3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(1H-pyrazol-1-yl)ethyl]-D-alanine		317.3224	318.3224	35
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(2-oxo[1,3]oxazolo[4,5-b]pyridin-3(2H)-yl)ethyl]-D-alanine		385.3534	386.3534	30
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(5-methyl-7-oxo-2,3-dihydro-7H-[1,3]thiazolo[3,2-a]pyrimidin-6-yl)ethyl]-D-alanine		417.463	418.463	30
3-(6-fluoro-1H-benzimidazol-2-yl)-N-([1,3]oxazolo[4,5-b]pyridin-2-ylmethyl)-D-alanine		355.3276	356.3276	39
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidin-7-yl)methyl]-D-alanine		387.3936	388.3936	36
N-[(2-butyl-1H-imidazol-4-yl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		359.4028	360.4028	42
N-{[2-(cyclopropylmethyl)-6-oxo-1,6-dihydropyrimidin-4-yl]methyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		385.397	386.397	29

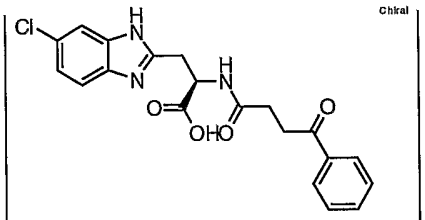
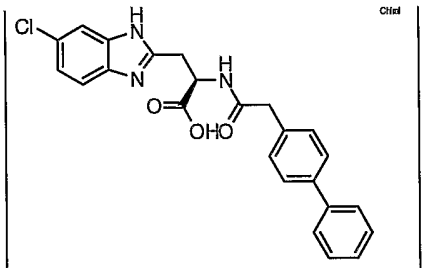
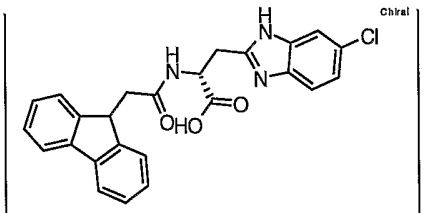
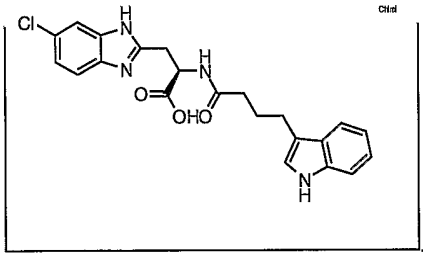
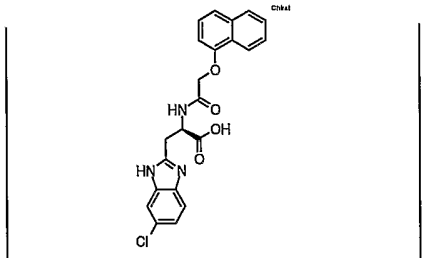
N-[(6-chloroimidazo[1,2-a]pyridin-2-yl)methyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		387.8005	388.8005	8
N-({4-[(3-chlorophenyl)amino]quinazolin-2-yl}methyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		490.924	491.924	35

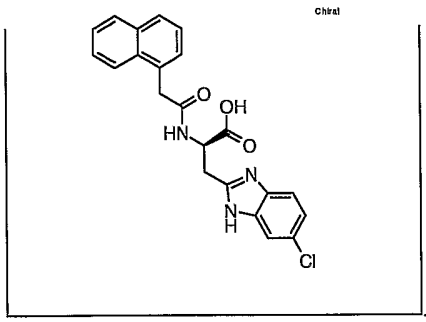
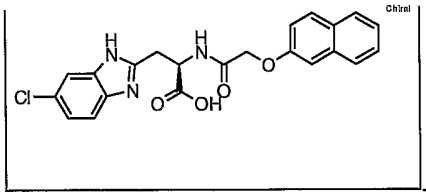
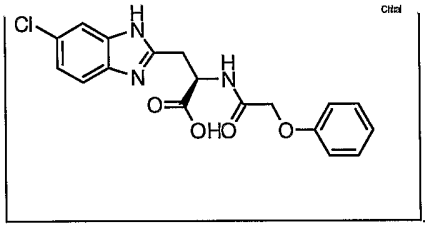
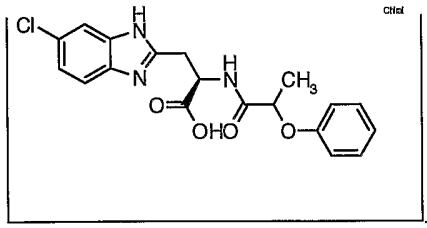
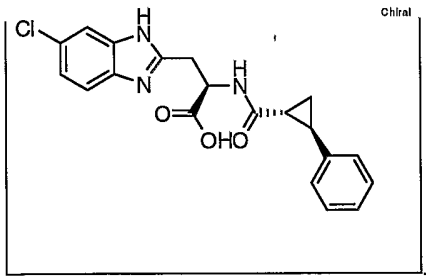
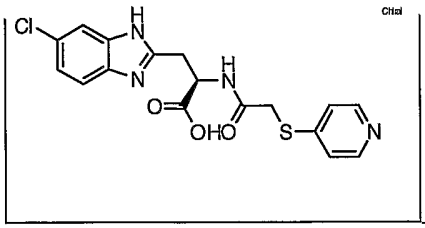
General Procedure for Acylation of Amino Acids with Carboxylic Acids:

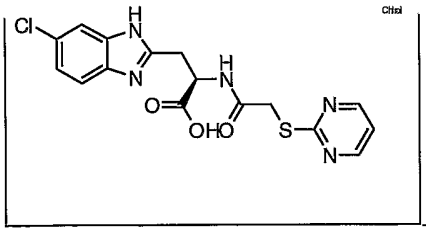
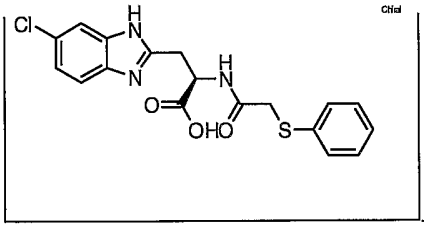
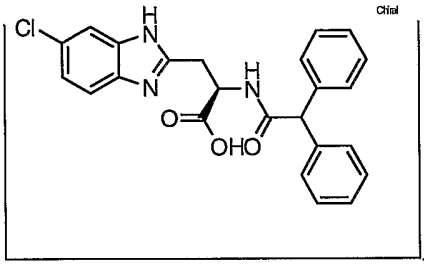
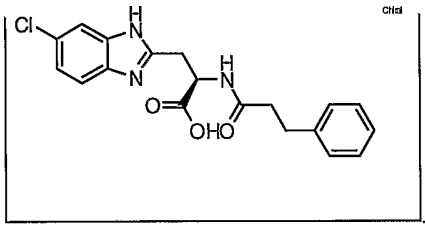
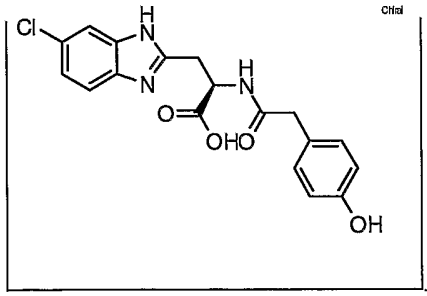
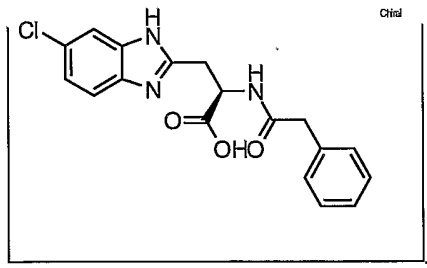


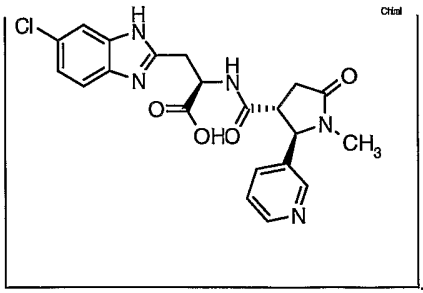
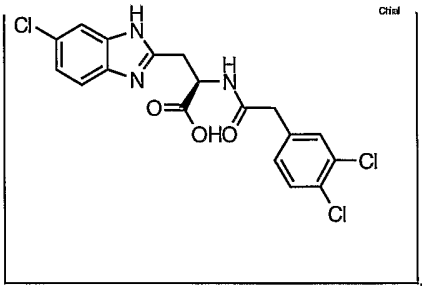
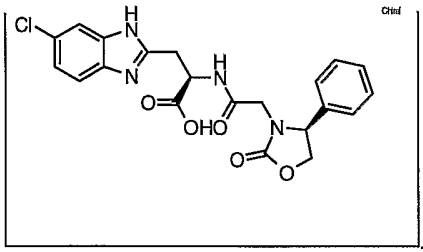
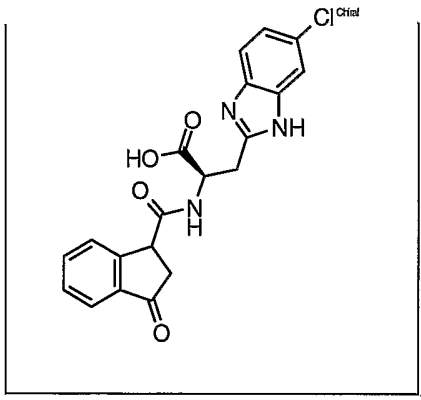
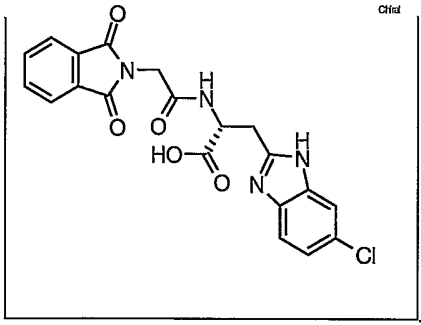
In a glovebox, each aminoacid (10 mmole) was placed into a labeled 50 mL reaction vial, and 30 mL of anhydrous DMF was added. *N,O*-bis(trimethylsilyl)acetamide (5.4 mL, 22 mmole) was added to each vial, and the reaction mixtures were allowed to stir for 16-24 h at room temperature in the glove box. A solution of the appropriate carboxylic acid in DMF (0.2 M, 400 µL, 0.08 mmole), a solution of HATU in DMF (0.5 M, 160 µL, 0.08 mmole), and a solution of TEA (0.5 M, 160 µL, 0.08 mmole) were combined in the appropriate test tubes, and the prepared silylated amino acid solutions (0.2 M, 400 µL 0.08 mmole) were added. The reactions were allowed to stir at room temperature overnight. The reactions were removed from the glovebox, and an aqueous NaOH solution (2M, 160 µL, 0.32 mmole) was added to each tube. The reaction mixtures were agitated for 1h, and the solvents were removed. An aqueous HCl solution (2.0 M, 200 µL, 0.4 mmole) was added to the residues, and the mixtures were allowed to stir for 60 min. The solvents were removed, and the residues were reconstituted in DMSO.

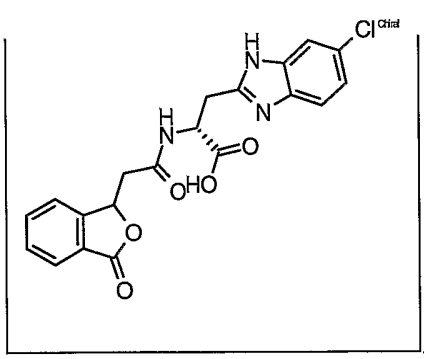
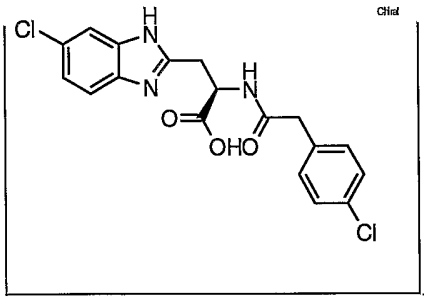
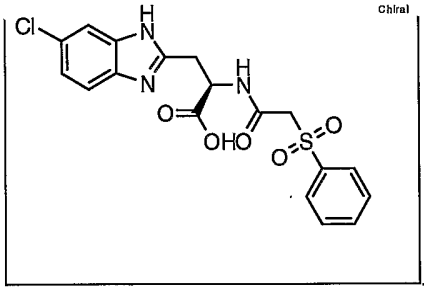
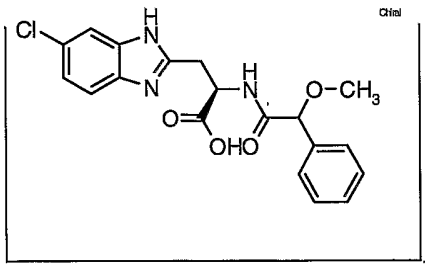
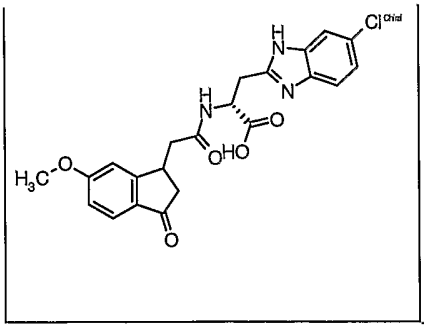
Table 4

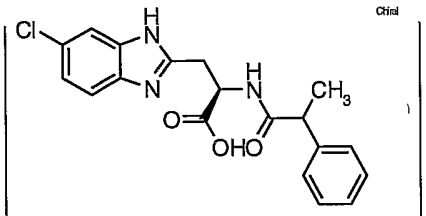
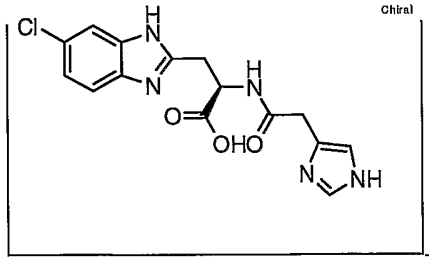
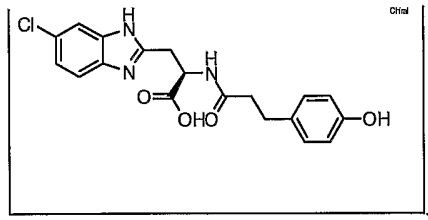
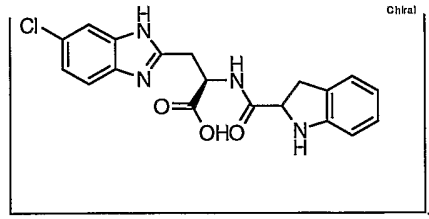
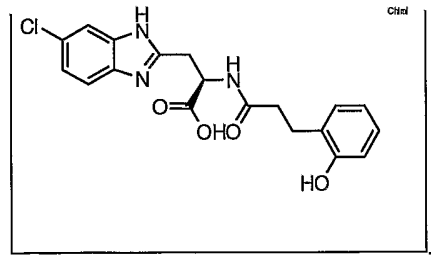
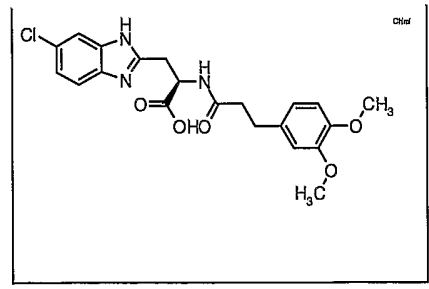
Structure	Name	MW	m/z MW + 1	% Inhibition at 10 μM
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(4-oxo-4-phenylbutanoyl)-D-alanine	399.8322	400.8322	7
	N-(biphenyl-4-ylacetyl)-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	433.893	434.893	4
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(9H-fluoren-9-ylacetyl)-D-alanine	445.904	446.904	55
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[4-(1H-indol-3-yl)butanoyl]-D-alanine	424.8859	425.8859	19
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(1-naphthyloxy)acetyl]-D-alanine	423.8542	424.8542	36

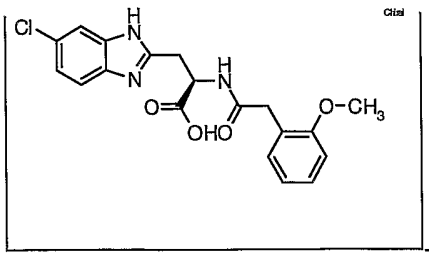
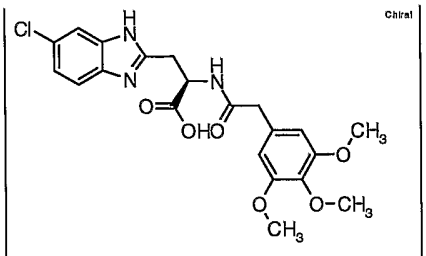
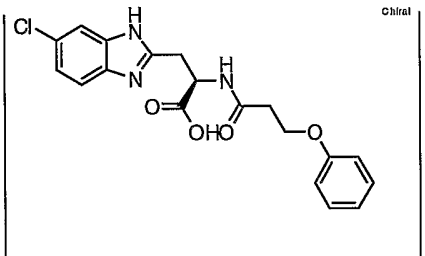
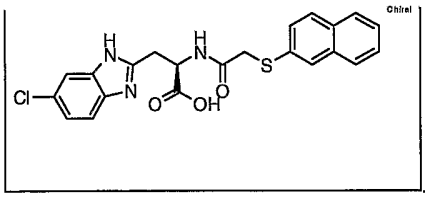
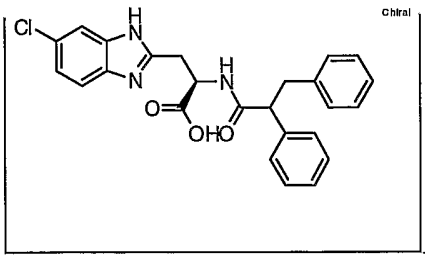
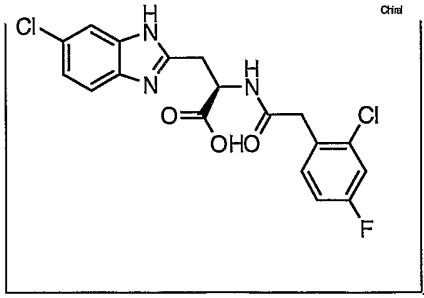
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(1-naphthylacetyl)-D-alanine	407.8552	408.8552	18
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-naphthyloxy)acetyl]-D-alanine	423.8542	424.8542	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(phenoxyacetyl)-D-alanine	373.7944	374.7944	10
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(2-phenoxypropanoyl)-D-alanine	387.8212	388.8212	11
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(1R,2R)-2-phenylcyclopropyl]carbonyl}-D-alanine	383.8332	384.8332	19
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(pyridin-4-ylthio)acetyl]-D-alanine	390.8495	391.8495	4

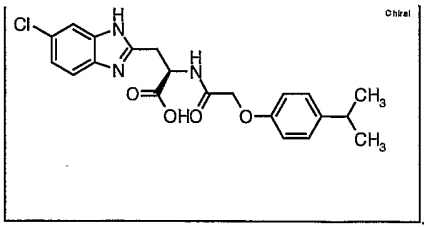
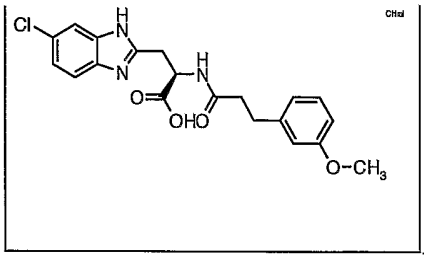
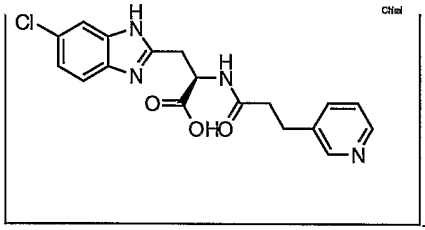
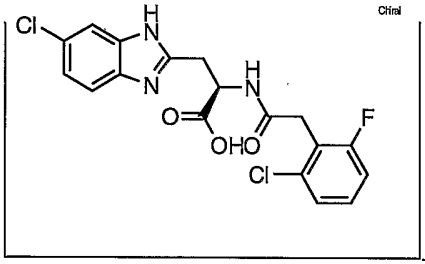
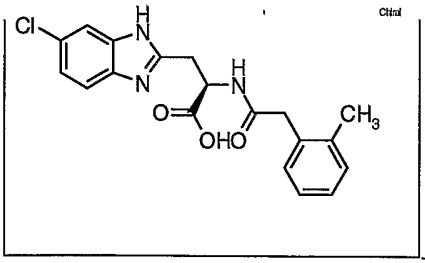
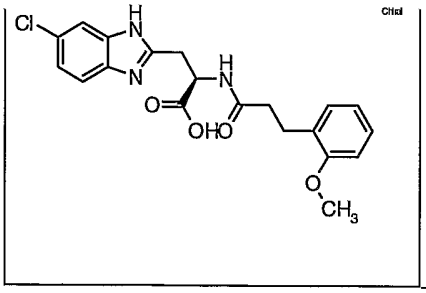
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(pyrimidin-2-ylthio)acetyl]-D-alanine	391.8376	392.8376	4
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(phenylthio)acetyl]-D-alanine	389.8614	390.8614	14
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(diphenylacetyl)-D-alanine	433.893	434.893	17
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-phenylpropanoyl)-D-alanine	371.8222	372.8222	18
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-hydroxyphenyl)acetyl]-D-alanine	373.7944	374.7944	16
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(phenylacetyl)-D-alanine	357.7954	358.7954	16

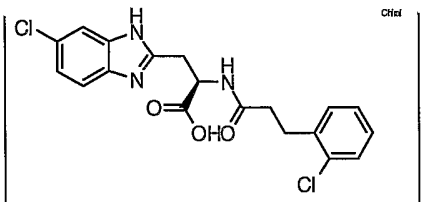
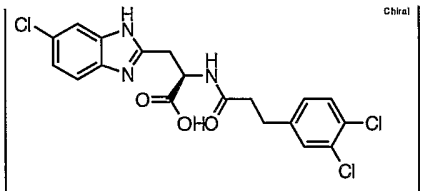
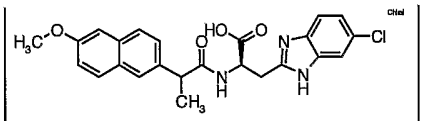
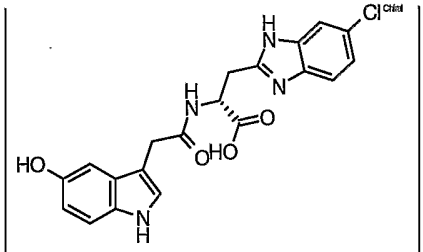
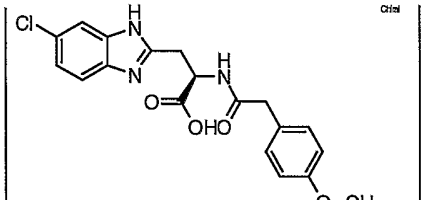
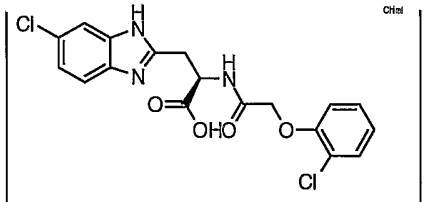
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(2R,3R)-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidin-3-yl]carbonyl}-D-alanine	441.873	442.873	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3,4-dichlorophenyl)acetyl]-D-alanine	426.6856	427.6856	5
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(4S)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]acetyl}-D-alanine	442.8571	443.8571	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-oxo-2,3-dihydro-1H-inden-1-yl)carbonyl]-D-alanine	397.8164	398.8164	5
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyl]-D-alanine	426.8145	427.8145	2

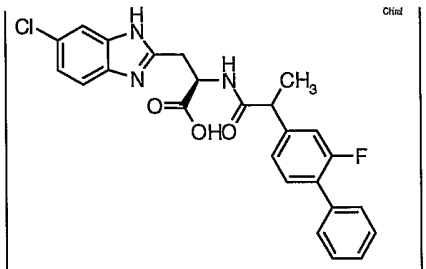
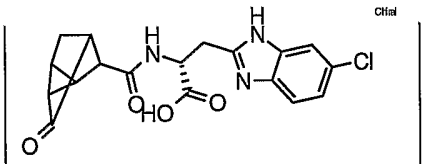
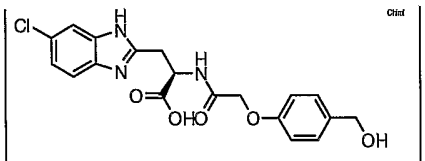
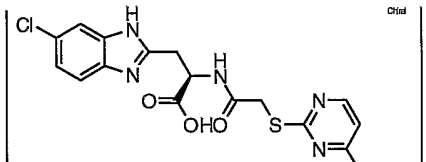
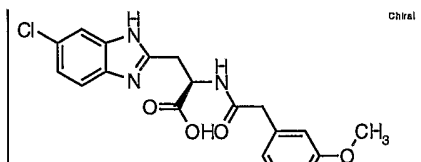
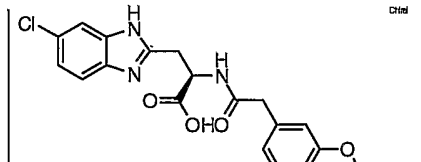
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-oxo-1,3-dihydro-2-benzofuran-1-yl)acetyl]-D-alanine	413.8154	414.8154	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-chlorophenyl)acetyl]-D-alanine	392.2405	393.2405	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(phenylsulfonyl)acetyl]-D-alanine	421.8594	422.8594	3
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[methoxy(phenyl)acetyl]-D-alanine	387.8212	388.8212	9
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetyl]-D-alanine	441.869	442.869	33

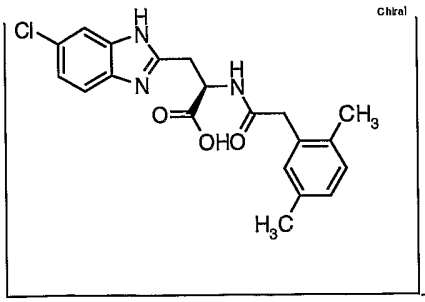
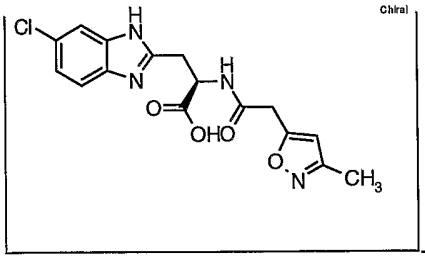
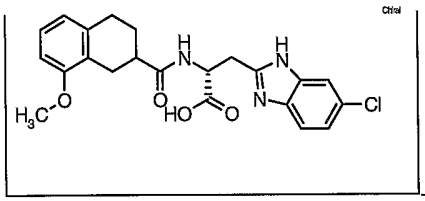
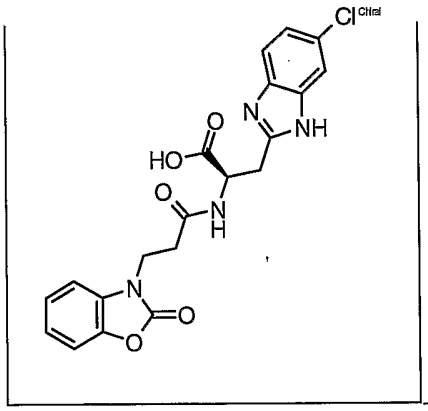
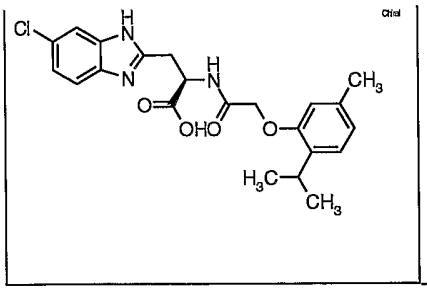
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(2-phenylpropanoyl)-D-alanine	371.8222	372.8222	18
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(1H-imidazol-4-ylacetyl)-D-alanine	347.7606	348.7606	18
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(4-hydroxyphenyl)propanoyl]-D-alanine	387.8212	388.8212	17
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(2,3-dihydro-1H-indol-2-ylcarbonyl)-D-alanine	384.8213	385.8213	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(2-hydroxyphenyl)propanoyl]-D-alanine	387.8212	388.8212	17
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(3,4-dimethoxyphenyl)propanoyl]-D-alanine	431.8738	432.8738	5

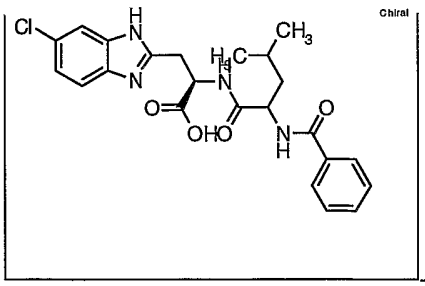
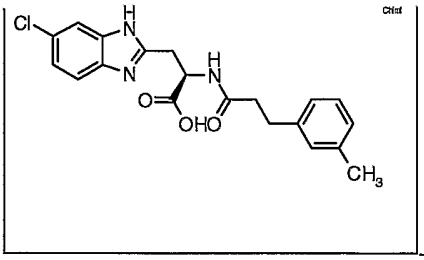
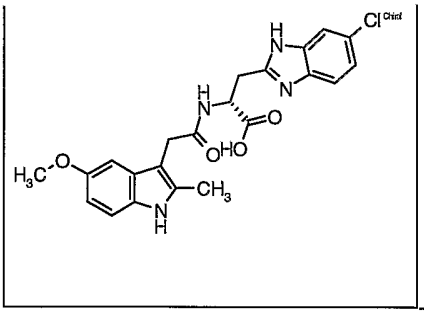
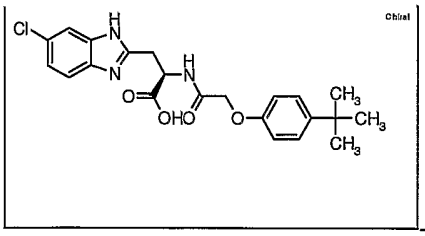
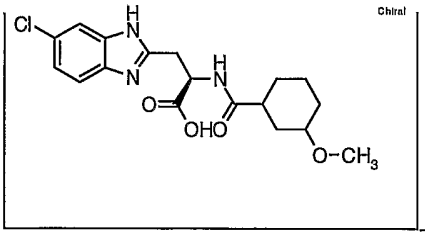
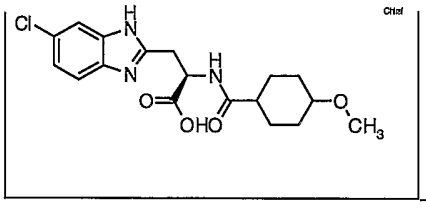
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-methoxyphenyl)acetyl]-D-alanine	387.8212	388.8212	16
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3,4,5-trimethoxyphenyl)acetyl]-D-alanine	447.8728	448.8728	15
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-phenoxypropanoyl)-D-alanine	387.8212	388.8212	9
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-naphthylthio)acetyl]-D-alanine	439.9212	440.9212	27
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(2,3-diphenylpropanoyl)-D-alanine	447.9198	448.9198	23
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-chloro-4-fluorophenyl)acetyl]-D-alanine	410.2306	411.2306	19

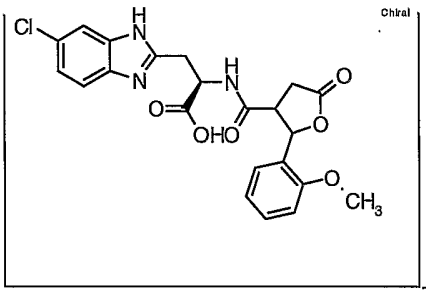
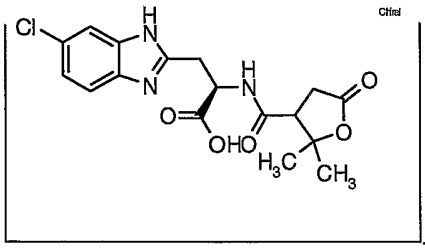
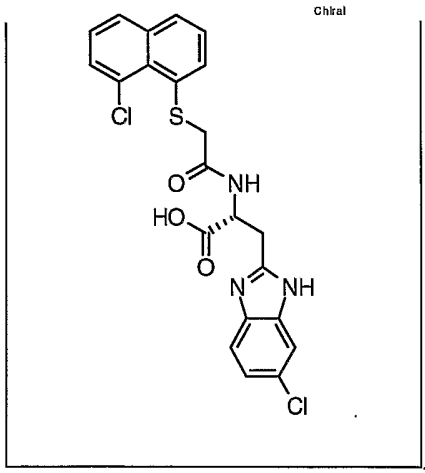
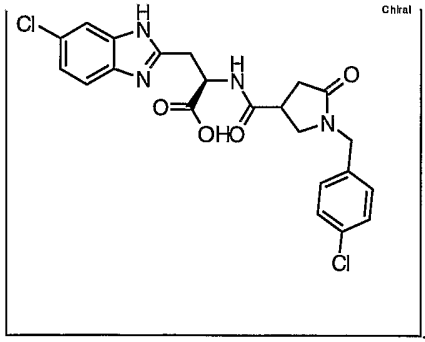
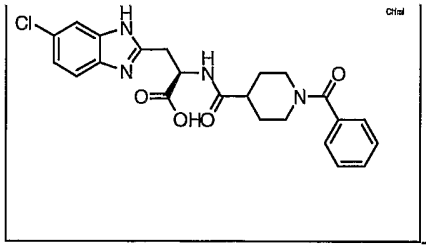
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-isopropylphenoxy)acetyl]-D-alanine	415.8748	416.8748	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(3-methoxyphenyl)propanoyl]-D-alanine	401.848	402.848	29
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-pyridin-3-ylpropanoyl)-D-alanine	372.8103	373.8103	22
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-chloro-6-fluorophenyl)acetyl]-D-alanine	410.2306	411.2306	19
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-methylphenyl)acetyl]-D-alanine	371.8222	372.8222	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(2-methoxyphenyl)propanoyl]-D-alanine	401.848	402.848	20

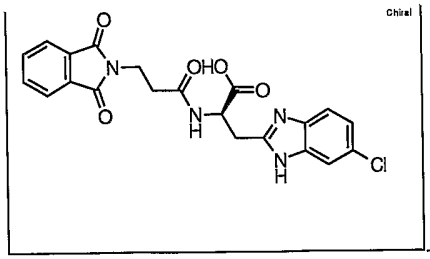
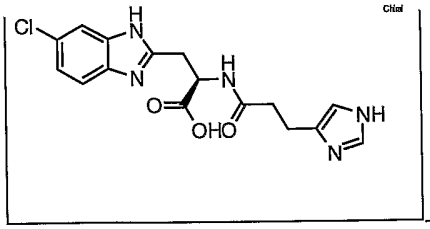
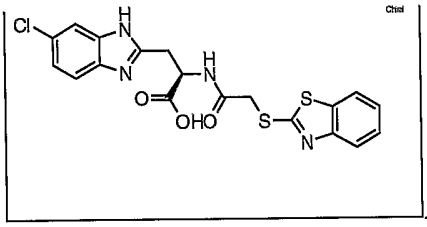
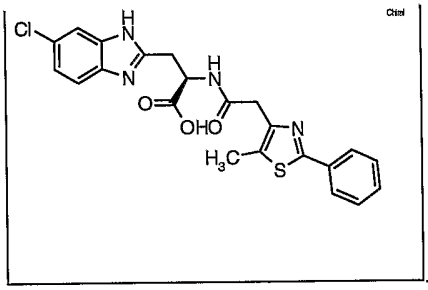
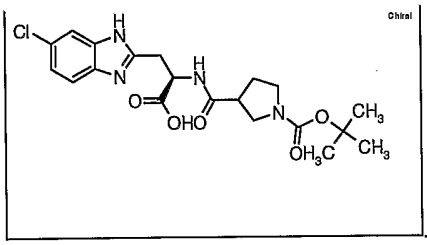
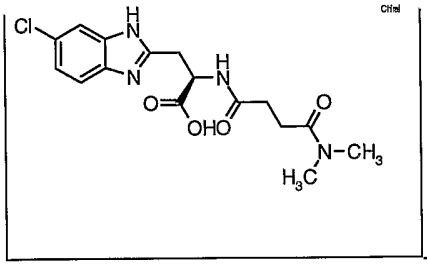
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(2-chlorophenyl)propanoyl]-D-alanine	406.2673	407.2673	22
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(3,4-dichlorophenyl)propanoyl]-D-alanine	440.7124	441.7124	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[2-(6-methoxy-2-naphthyl)propanoyl]-D-alanine	451.9078	452.9078	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(5-hydroxy-1H-indol-3-yl)acetyl]-D-alanine	412.8313	413.8313	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-methoxyphenyl)acetyl]-D-alanine	387.8212	388.8212	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-chlorophenoxy)acetyl]-D-alanine	408.2395	409.2395	3

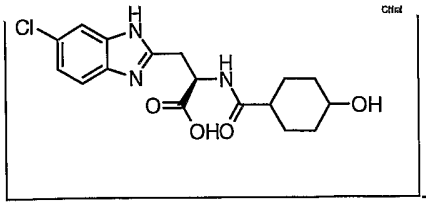
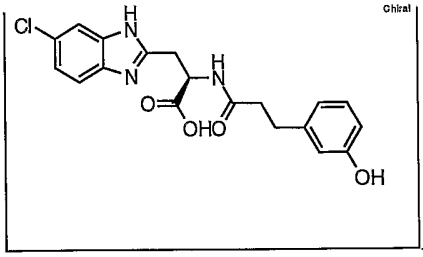
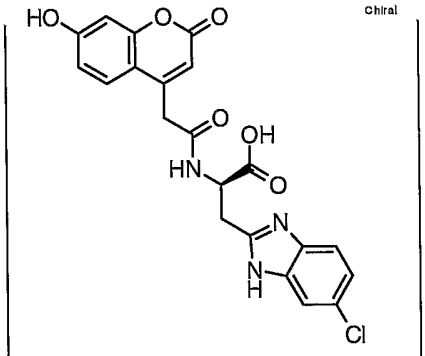
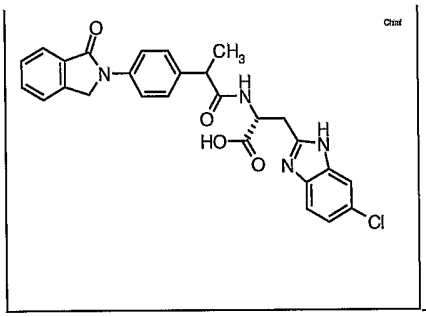
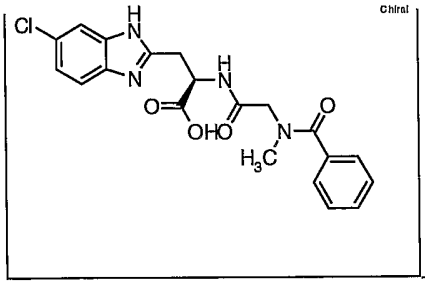
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[2-(2-fluorobiphenyl-4-yl)propanoyl]-D-alanine	465.9099	466.9099	4
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(5-oxotricyclo[2.2.1.0~2,6~]hept-3-yl)carbonyl]-D-alanine	373.7944	374.7944	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[4-(hydroxymethyl)phenoxy]acetyl}-D-alanine	403.8202	404.8202	14
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(4-methylpyrimidin-2-yl)thio]acetyl}-D-alanine	405.8644	406.8644	11
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3,4-dimethoxyphenyl)acetyl]-D-alanine	417.847	418.847	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-methoxyphenyl)acetyl]-D-alanine	387.8212	388.8212	3

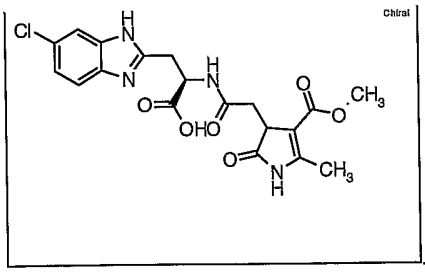
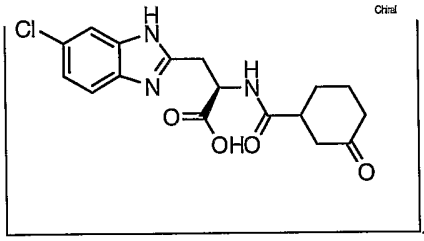
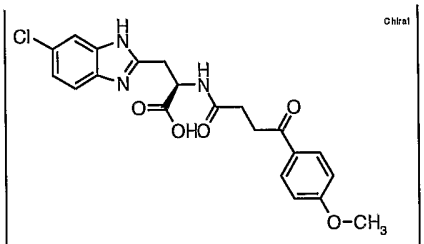
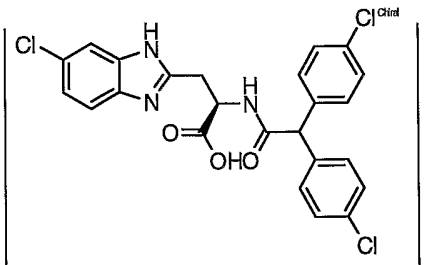
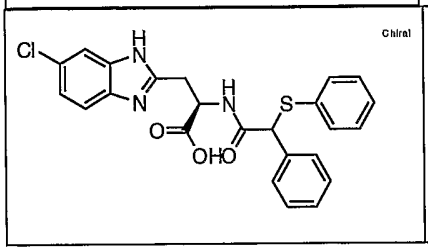
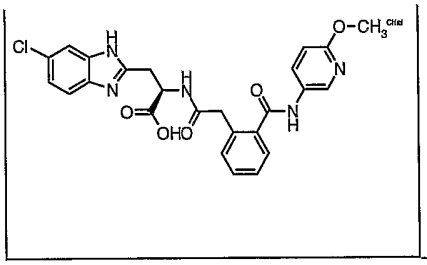
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2,5-dimethylphenyl)acetyl]-D-alanine	385.849	386.849	17
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-methylisoxazol-5-yl)acetyl]-D-alanine	362.7715	363.7715	1
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)carbonyl]-D-alanine	427.8858	428.8858	19
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanoyl]-D-alanine	428.8303	429.8303	22
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-isopropyl-5-methylphenoxy)acetyl]-D-alanine	429.9016	430.9016	29

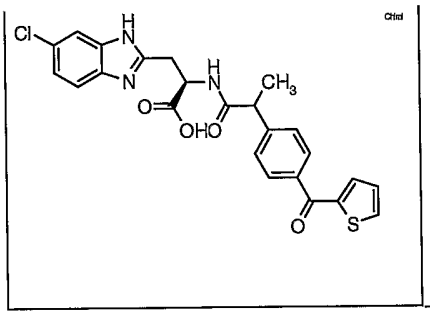
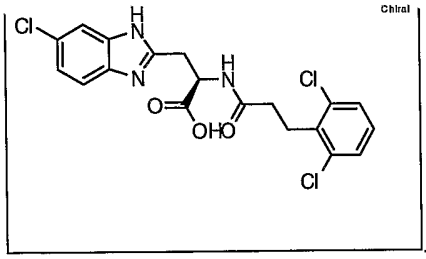
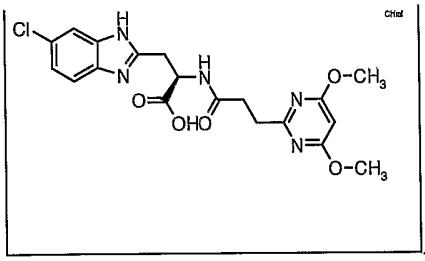
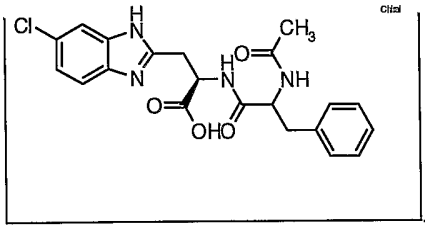
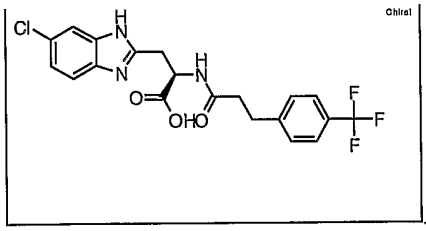
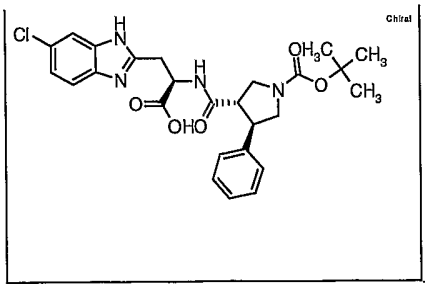
	N-benzoylleucyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	456.9275	457.9275	9
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(3-methylphenyl)propanoyl]-D-alanine	385.849	386.849	24
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]-D-alanine	440.8849	441.8849	17
	N-[(4-tert-butylphenoxy)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	429.9016	430.9016	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-methoxycyclohexyl)carbonyl]-D-alanine	379.8418	380.8418	9
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-methoxycyclohexyl)carbonyl]-D-alanine	379.8418	380.8418	9

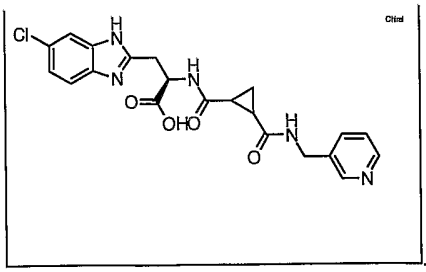
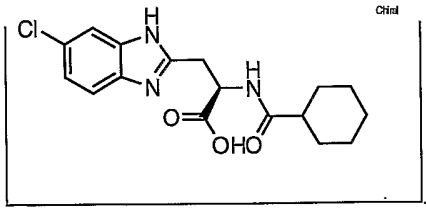
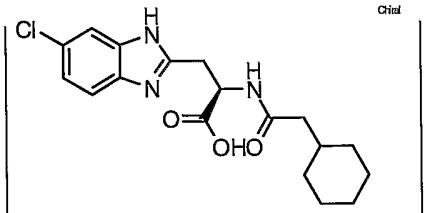
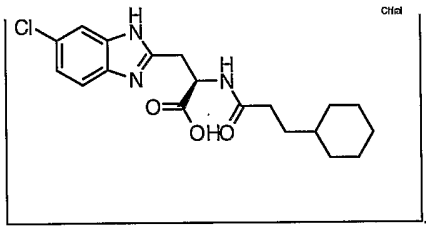
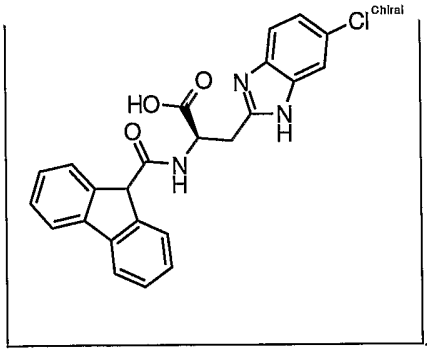
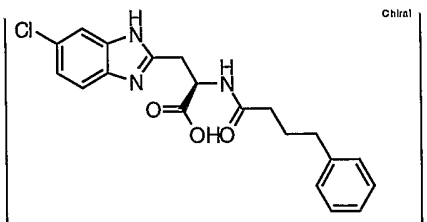
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[2-(2-methoxyphenyl)-5-oxotetrahydrofuran-3-yl]carbonyl}-D-alanine	457.868	458.868	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)carbonyl]-D-alanine	379.7982	380.7982	3
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(8-chloro-1-naphthyl)thio]acetyl}-D-alanine	474.3663	475.3663	9
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[1-(4-chlorobenzyl)-5-oxopyrrolidin-3-yl]carbonyl}-D-alanine	475.33	476.33	8
	N-[(1-benzoylpiperidin-4-yl)carbonyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	454.9117	455.9117	12

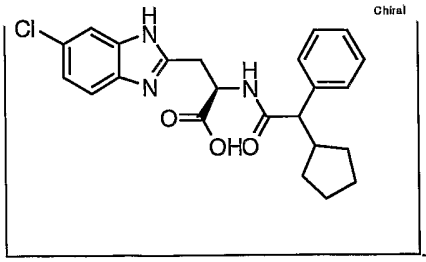
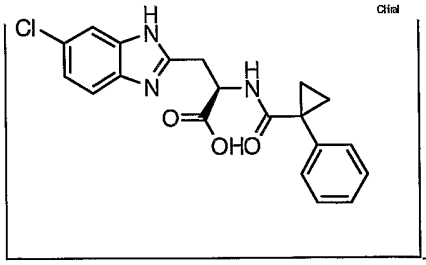
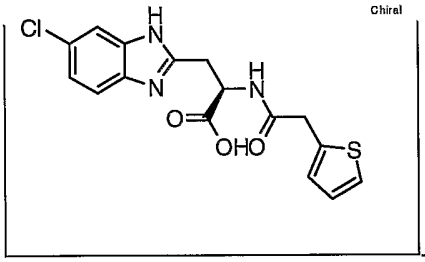
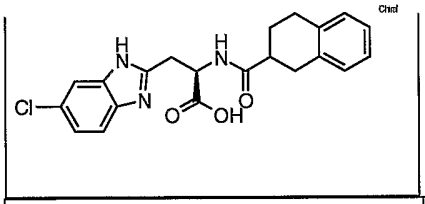
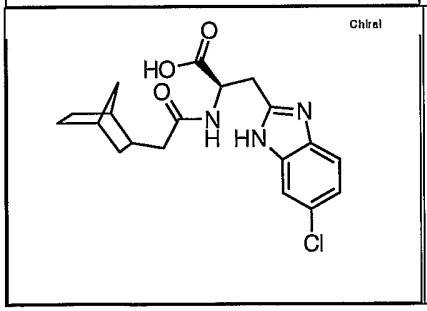
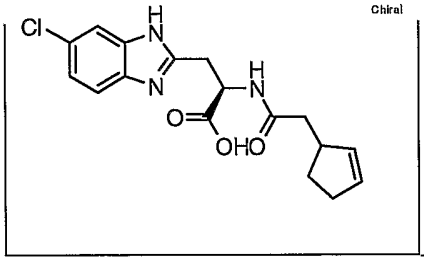
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoyl]-D-alanine	440.8413	441.8413	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(1H-imidazol-4-yl)propanoyl]-D-alanine	361.7874	362.7874	6
	N-[(1,3-benzothiazol-2-ylthio)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	446.9375	447.9375	4
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(5-methyl-2-phenyl-1,3-thiazol-4-yl)acetyl]-D-alanine	454.9361	455.9361	8
	N-{[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]carbonyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	436.8935	437.8935	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[4-(dimethylamino)-4-oxobutanoyl]-D-alanine	366.8031	367.8031	1

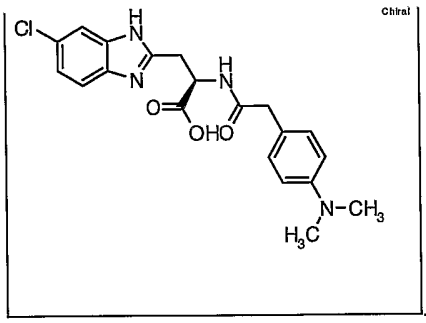
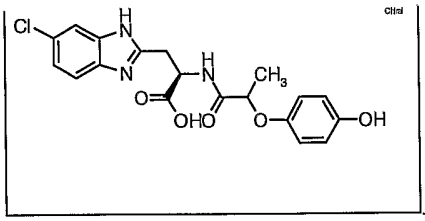
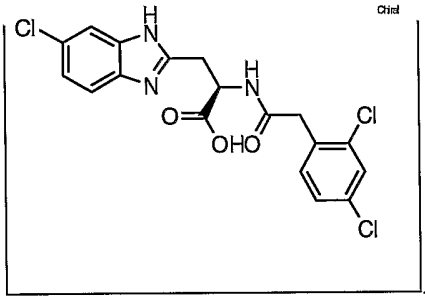
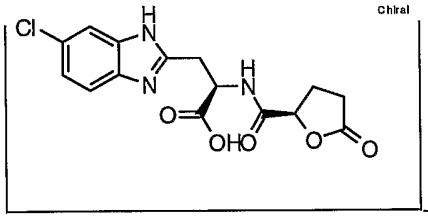
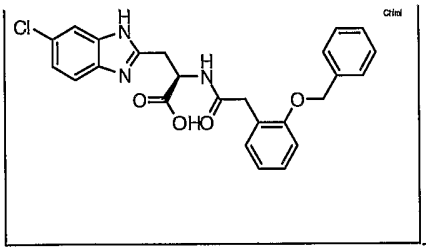
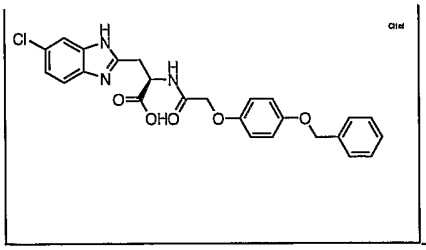
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-hydroxycyclohexyl)carbonyl]-D-alanine	365.815	366.815	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(3-hydroxyphenyl)propanoyl]-D-alanine	387.8212	388.8212	29
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(7-hydroxy-2-oxo-2H-chromen-4-yl)acetyl]-D-alanine	441.8254	442.8254	8
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{2-[4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanoyl}-D-alanine	502.9557	503.9557	1
	N-benzoyl-N-methylglycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	414.8471	415.8471	9

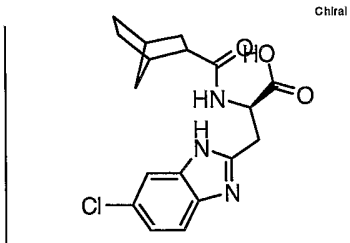
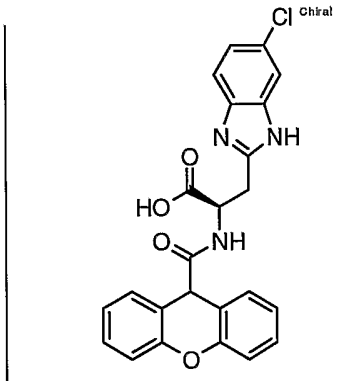
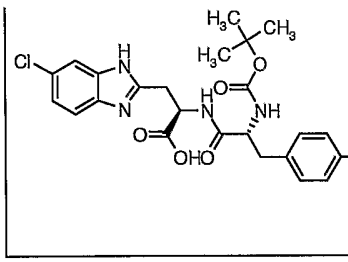
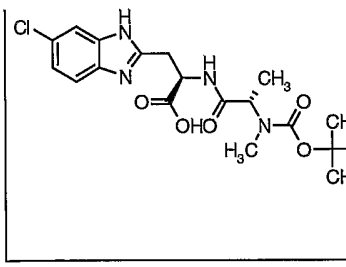
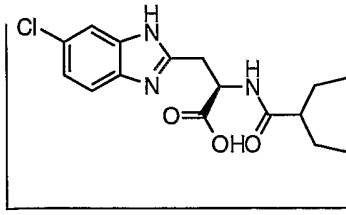
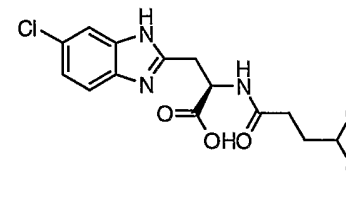
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[4-(methoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetyl}-D-alanine	434.8341	435.8341	30
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-oxocyclohexyl)carbonyl]-D-alanine	363.7992	364.7992	11
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[4-(4-methoxyphenyl)-4-oxobutanoyl]-D-alanine	429.858	430.858	22
	N-[bis(4-chlorophenyl)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	502.7832	503.7832	10
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[phenyl(phenylthio)acetyl]-D-alanine	465.959	466.959	20
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-{[(6-methoxypyridin-3-yl)amino]carbonyl}phenyl)acetyl]-D-alanine	507.9318	508.9318	17

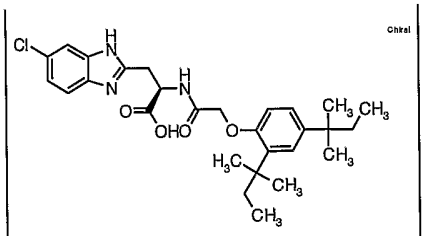
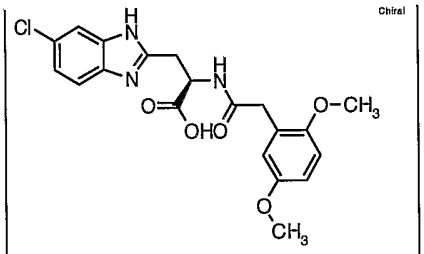
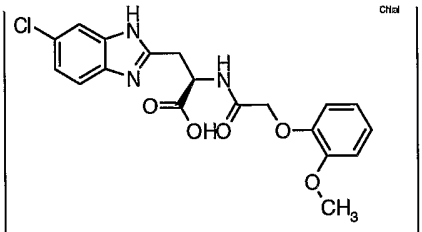
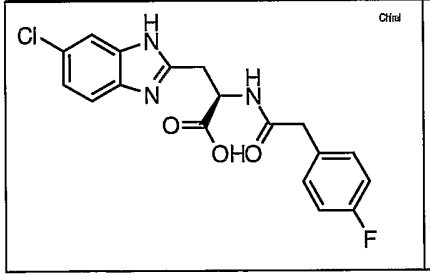
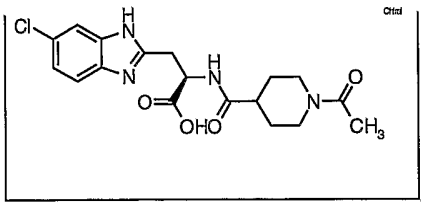
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{2-[4-(2-thienylcarbonyl)phenyl]propanoyl}-D-alanine	481.958	482.958	3
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(2,6-dichlorophenyl)propanoyl]-D-alanine	440.7124	441.7124	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(4,6-dimethoxypyrimidin-2-yl)propanoyl]-D-alanine	433.85	434.85	4
	N-acetylphenylalanyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	428.8739	429.8739	20
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{3-[4-(trifluoromethyl)phenyl]propanoyl}-D-alanine	439.8193	440.8193	1
	N-{[(3S,4R)-1-(tert-butoxycarbonyl)-4-phenylpyrrolidin-3-yl]carbonyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	512.9911	513.9911	8

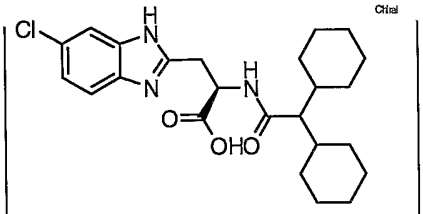
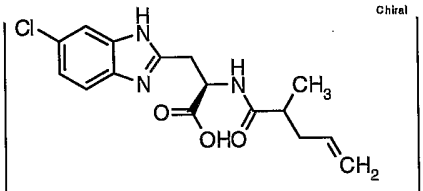
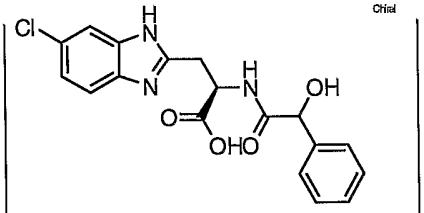
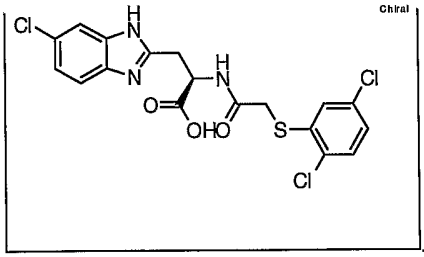
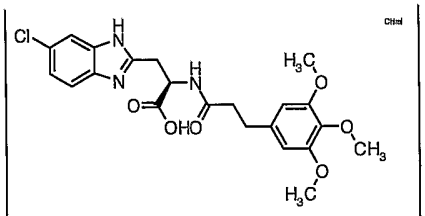
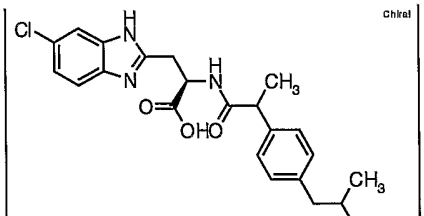
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-{[(pyridin-3-ylmethyl)amino]carbonyl}cyclopropyl)carbonyl]-D-alanine	441.873	442.873	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cyclohexylcarbonyl)-D-alanine	349.816	350.816	15
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cyclohexylacetyl)-D-alanine	363.8428	364.8428	16
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-cyclohexylpropanoyl)-D-alanine	377.8696	378.8696	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(9H-fluoren-9-ylcarbonyl)-D-alanine	431.8772	432.8772	8
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(4-phenylbutanoyl)-D-alanine	385.849	386.849	12

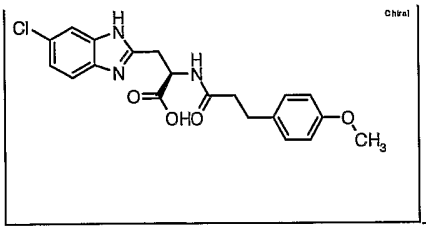
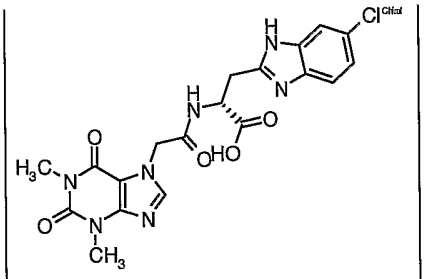
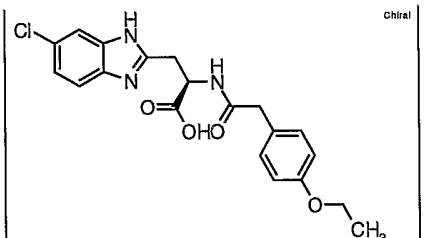
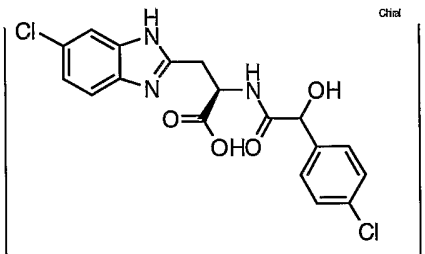
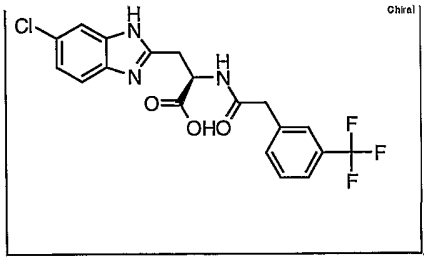
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[cyclopentyl(phenyl)acetyl]-D-alanine	425.9136	426.9136	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(1-phenylcyclopropyl)carbonyl]-D-alanine	383.8332	384.8332	10
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(2-thienylacetyl)-D-alanine	363.8236	364.8236	22
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(1,2,3,4-tetrahydronaphthalen-2-ylcarbonyl)-D-alanine	397.86	398.86	22
	N-(bicyclo[2.2.1]hept-2-ylacetyl)-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	375.8538	376.8538	22
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cyclopent-2-en-1-ylacetyl)-D-alanine	347.8002	348.8002	17

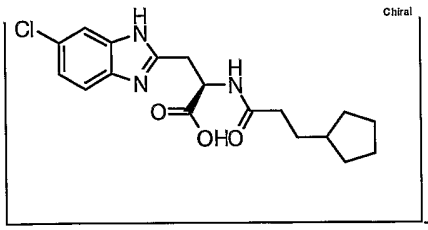
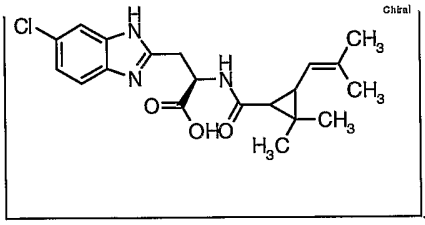
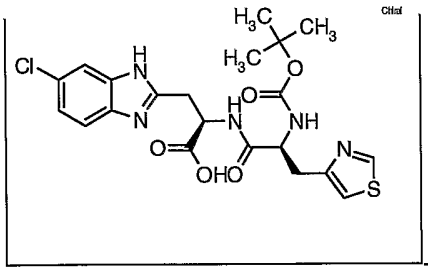
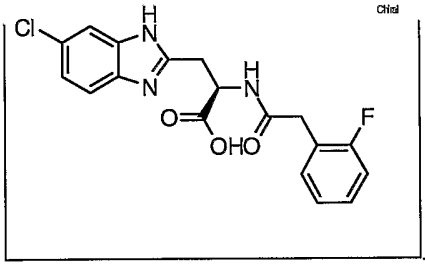
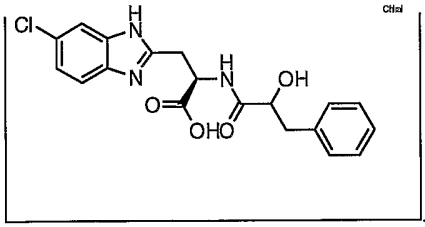
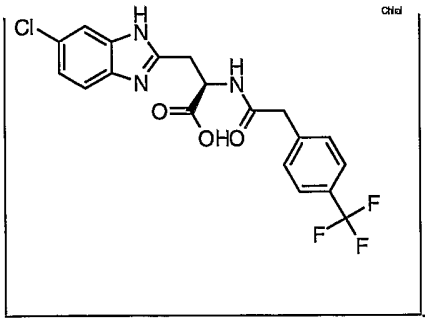
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[4-(dimethylamino)phenyl]acetyl}-D-alanine	400.8639	401.8639	5
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[2-(4-hydroxyphenoxy)propanoyl]-D-alanine	403.8202	404.8202	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2,4-dichlorophenyl)acetyl]-D-alanine	426.6856	427.6856	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(2R)-5-oxotetrahydrofuran-2-yl]carbonyl}-D-alanine	351.7446	352.7446	2
	N-{[2-(benzyloxy)phenyl]acetyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	463.9188	464.9188	27
	N-{[4-(benzyloxy)phenoxy]acetyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	479.9178	480.9178	5

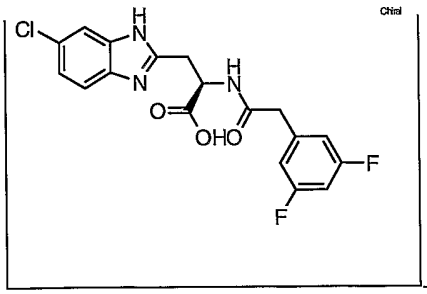
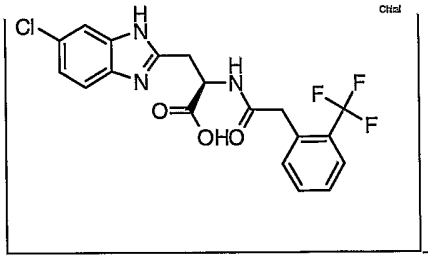
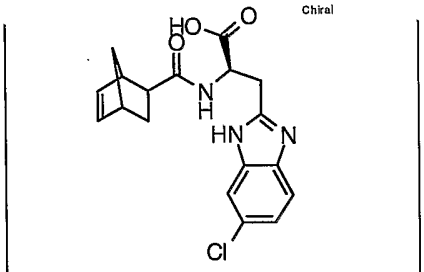
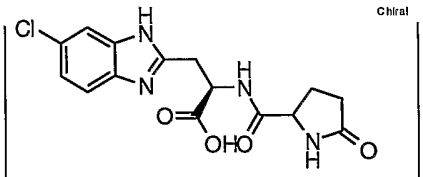
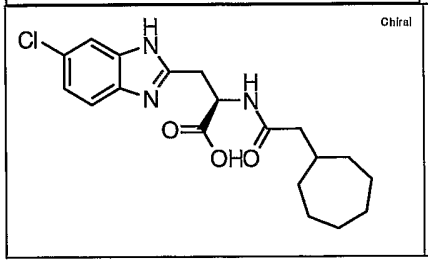
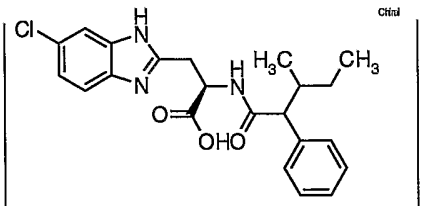
	N-(bicyclo[2.2.1]hept-2-ylcarbonyl)-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	361.827	362.827	27
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(9H-xanthen-9-ylcarbonyl)-D-alanine	447.8762	448.8762	28
	N-(tert-butoxycarbonyl)-D-tyrosyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	502.9523	503.9523	17
	N-(tert-butoxycarbonyl)-N-methyl-L-alanyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	424.8825	425.8825	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cycloheptylcarbonyl)-D-alanine	363.8428	364.8428	19
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(4-methylpentanoyl)-D-alanine	337.805	338.805	14

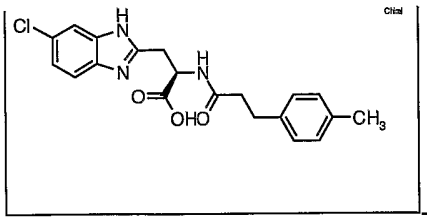
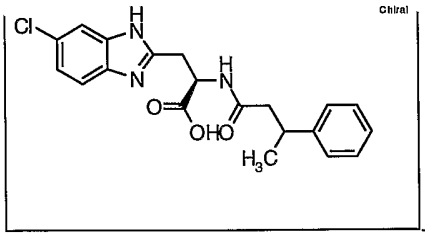
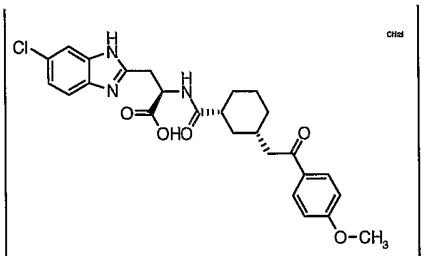
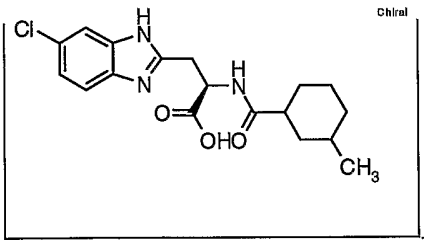
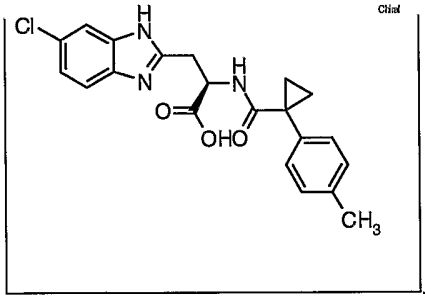
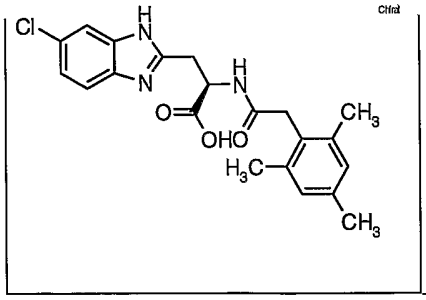
	N-{[2,4-bis(1,1-dimethylpropyl)phenoxy]acetyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	514.0624	515.0624	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2,5-dimethoxyphenyl)acetyl]-D-alanine	417.847	418.847	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-methoxyphenoxy)acetyl]-D-alanine	403.8202	404.8202	23
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-fluorophenyl)acetyl]-D-alanine	375.7855	376.7855	10
	N-[(1-acetylpiperidin-4-yl)carbonyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	392.8409	393.8409	3

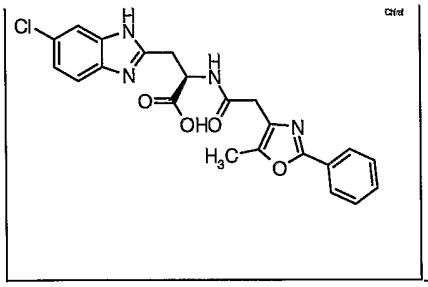
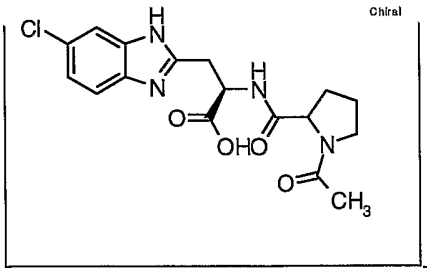
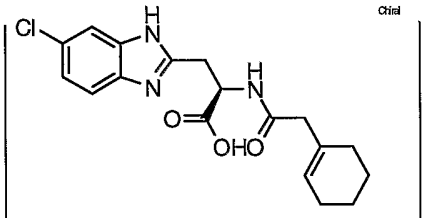
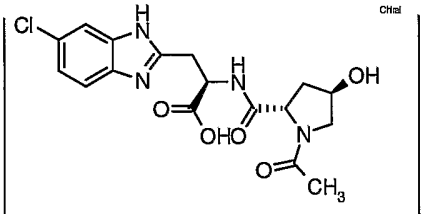
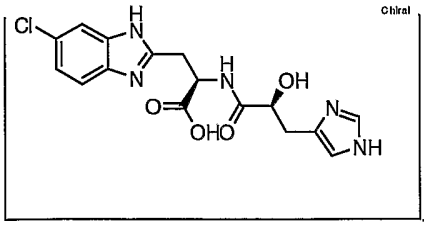
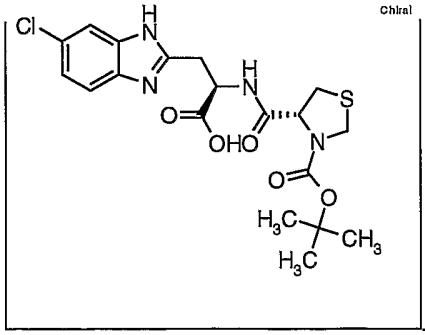
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(dicyclohexylacetyl)-D-alanine	445.9878	446.98 78	5
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(2-methylpent-4-enoyl)-D-alanine	335.7892	336.78 92	15
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[hydroxy(phenyl)acetyl]-D-alanine	373.7944	374.79 44	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(2,5-dichlorophenyl)thio]acetyl}-D-alanine	458.7516	459.75 16	18
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(3,4,5-trimethoxyphenyl)propanoyl]-D-alanine	461.8996	462.89 96	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[2-(4-isobutylphenyl)propanoyl]-D-alanine	427.9294	428.92 94	5

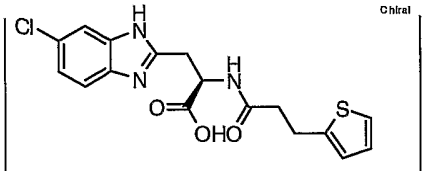
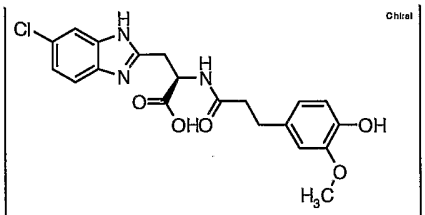
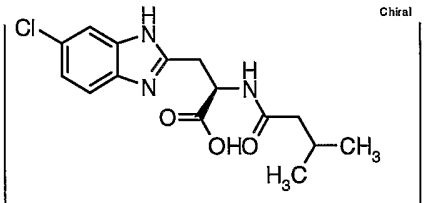
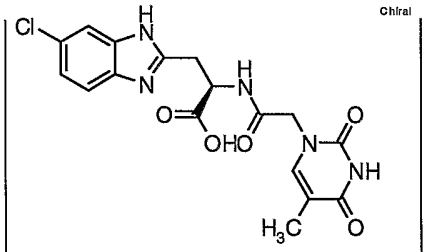
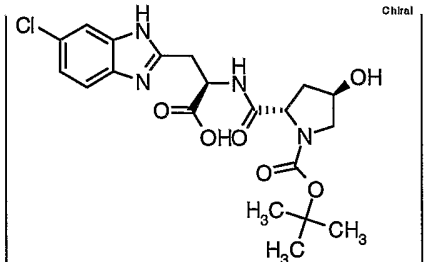
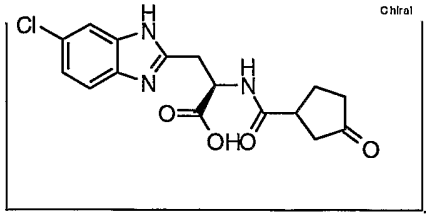
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(4-methoxyphenyl)propanoyl]-D-alanine	401.848	402.848	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)acetyl]-D-alanine	459.8482	460.8482	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-ethoxyphenyl)acetyl]-D-alanine	401.848	402.848	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-chlorophenyl)(hydroxy)acetyl]-D-alanine	408.2395	409.2395	25
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[3-(trifluoromethyl)phenyl]acetyl}-D-alanine	425.7925	426.7925	12

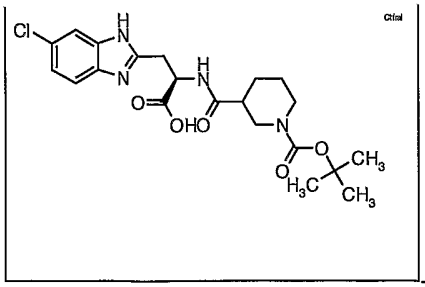
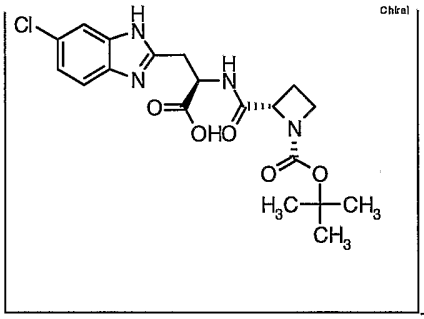
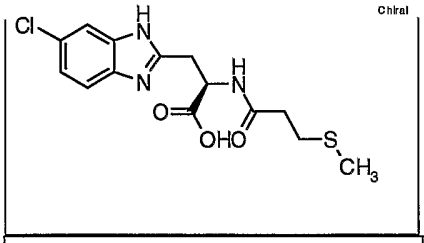
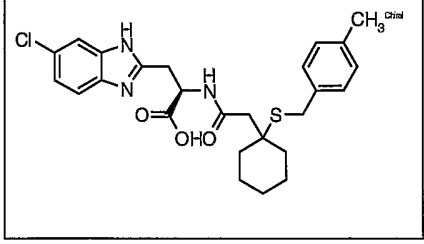
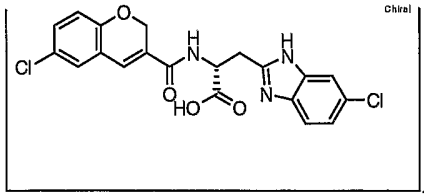
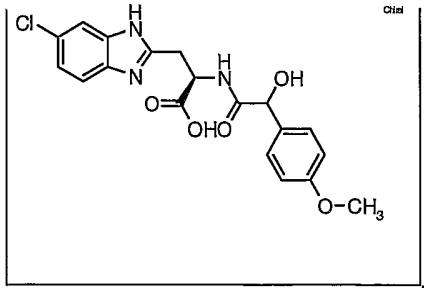
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-cyclopentylpropanoyl)-D-alanine	363.8428	364.8428	11
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]carbonyl}-D-alanine	389.8806	390.8806	23
	N-(tert-butoxycarbonyl)-3-(1,3-thiazol-4-yl)-L-alanyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	493.9696	494.9696	19
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-fluorophenyl)acetyl]-D-alanine	375.7855	376.7855	15
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(2-hydroxy-3-phenylpropanoyl)-D-alanine	387.8212	388.8212	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[4-(trifluoromethyl)phenyl]acetyl}-D-alanine	425.7925	426.7925	13

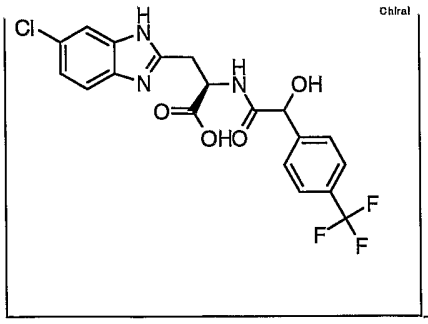
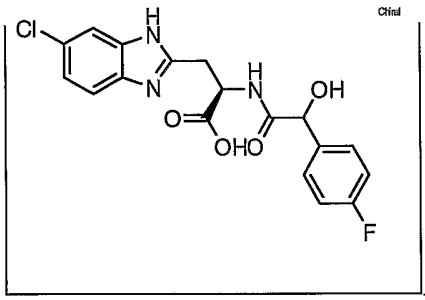
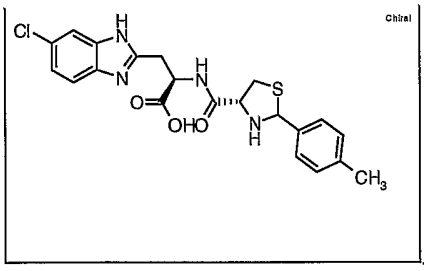
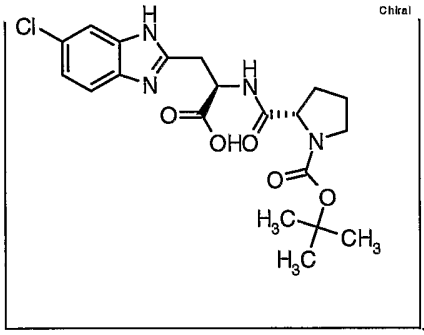
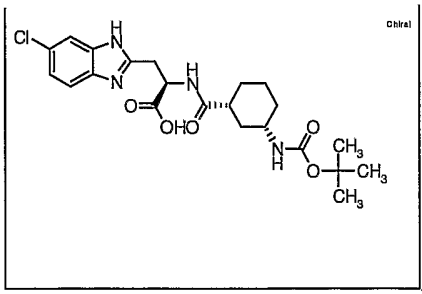
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3,5-difluorophenyl)acetyl]-D-alanine	393.7756	394.7756	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[2-(trifluoromethyl)phenyl]acetyl}-D-alanine	425.7925	426.7925	16
	N-(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	359.8112	360.8112	12
	5-oxoprolyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	350.7605	351.7605	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cycloheptylacetyl)-D-alanine	377.8696	378.8696	28
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-methyl-2-phenylpentanoyl)-D-alanine	413.9026	414.9026	14

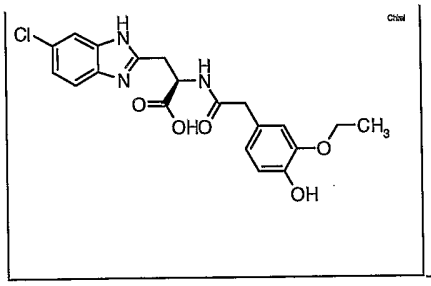
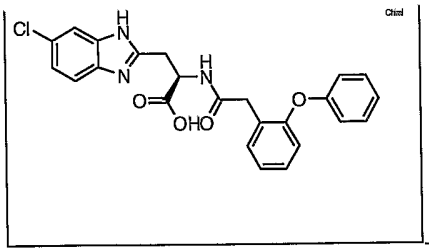
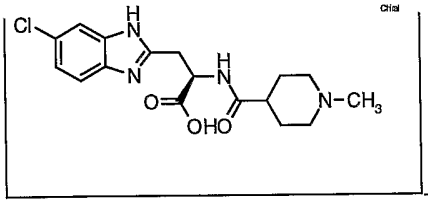
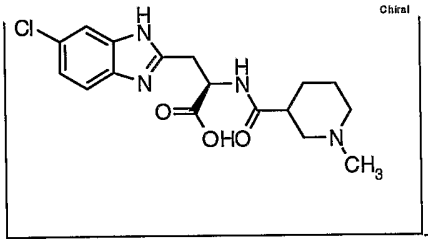
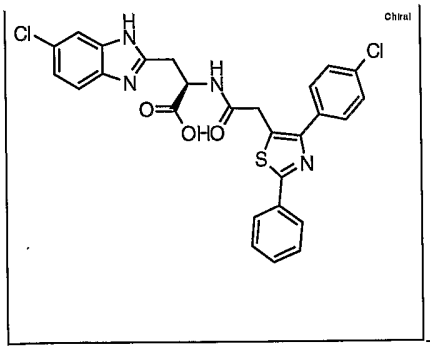
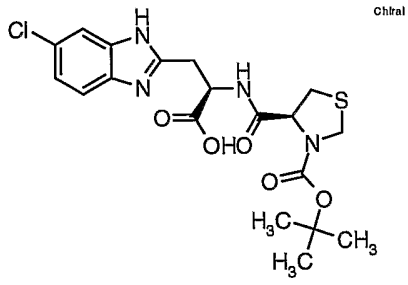
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(4-methylphenyl)propanoyl]-D-alanine	385.849	386.849	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-phenylbutanoyl)-D-alanine	385.849	386.849	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-({(1R,3S)-3-[2-(4-methoxyphenyl)-2-oxoethyl]cyclohexyl}carbonyl)-D-alanine	497.9762	498.9762	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-methylcyclohexyl)carbonyl]-D-alanine	363.8428	364.8428	17
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[1-(4-methylphenyl)cyclopropyl]carbonyl}-D-alanine	397.86	398.86	11
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(mesitylacetyl)-D-alanine	399.8758	400.8758	8

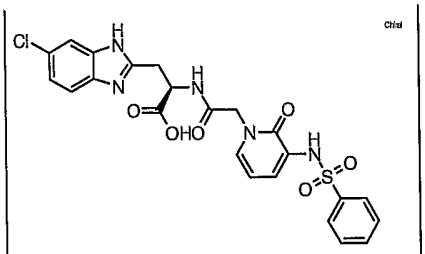
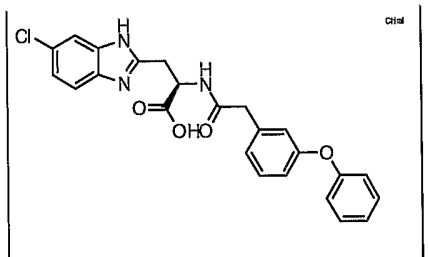
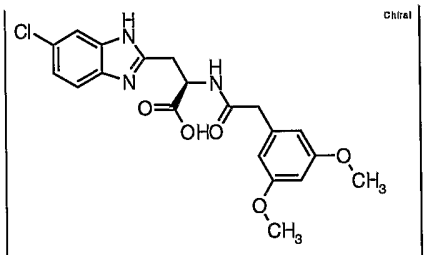
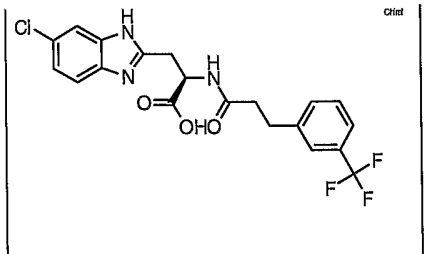
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetyl]-D-alanine	438.8691	439.8691	10
	1-acetylprolyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	378.8141	379.8141	5
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cyclohex-1-en-1-ylacetyl)-D-alanine	361.827	362.827	16
	(4R)-1-acetyl-4-hydroxy-L-prolyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	394.8131	395.8131	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2S)-2-hydroxy-3-(1H-imidazol-4-yl)propanoyl]-D-alanine	377.7864	378.7864	7
	N-{[(4R)-3-(tert-butoxycarbonyl)-1,3-thiazolidin-4-yl]carbonyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	454.9327	455.9327	10

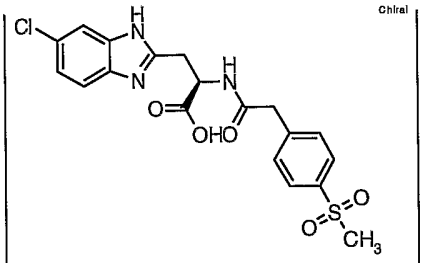
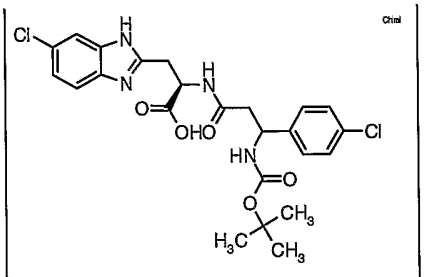
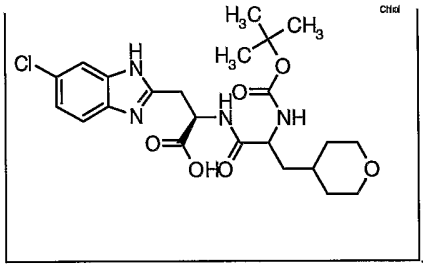
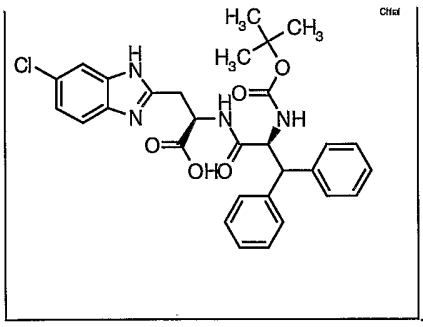
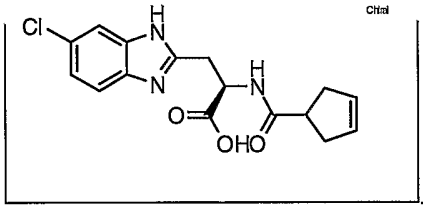
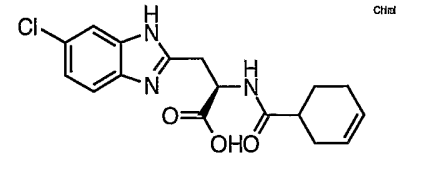
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(2-thienyl)propanoyl]-D-alanine	377.8504	378.8504	34
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(4-hydroxy-3-methoxyphenyl)propanoyl]-D-alanine	417.847	418.847	14
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-methylbutanoyl)-D-alanine	323.7782	324.7782	11
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetyl]-D-alanine	405.7964	406.7964	2
	(4R)-1-(tert-butoxycarbonyl)-4-hydroxy-L-prolyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	452.8925	453.8925	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-oxocyclopentyl)carbonyl]-D-alanine	349.7724	350.7724	7

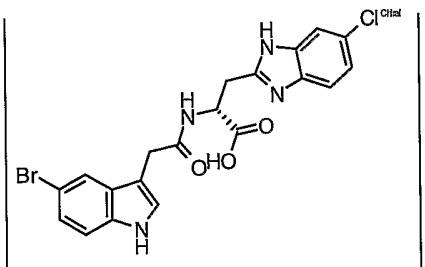
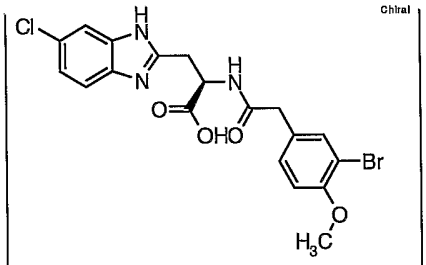
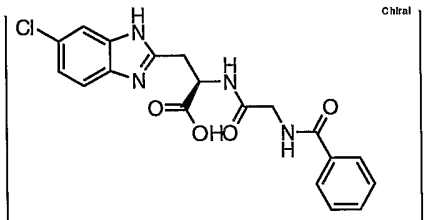
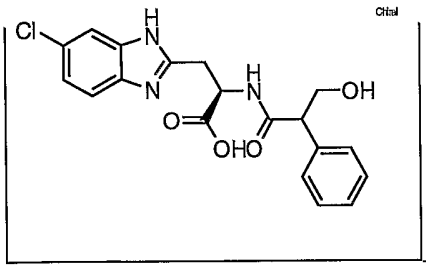
	N-{[1-(tert-butoxycarbonyl)piperidin-3-yl]carbonyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	450.9203	451.9203	7
	(2R)-2-({[(2S)-1-(tert-butoxycarbonyl)azetidin-2-yl]carbonyl}amino)-3-(6-chloro-1H-benzimidazol-2-yl)propanoic acid	422.8667	423.8667	8
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(methylthio)propanoyl]-D-alanine	341.8174	342.8174	8
	3-(6-chloro-1H-benzimidazol-2-yl)-N-({1-[(4-methylbenzyl)thio]cyclohexyl}acetyl)-D-alanine	500.06	501.06	32
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(6-chloro-2H-chromen-3-yl)carbonyl]-D-alanine	432.2615	433.2615	33
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[hydroxy(4-methoxyphenyl)acetyl]-D-alanine	403.8202	404.8202	10

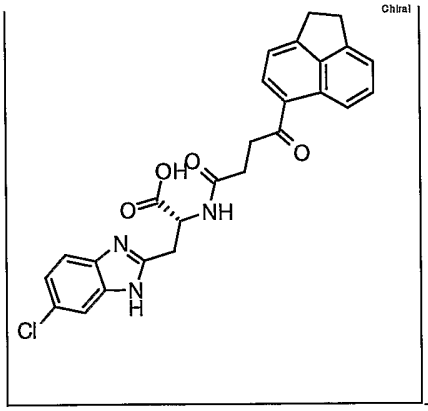
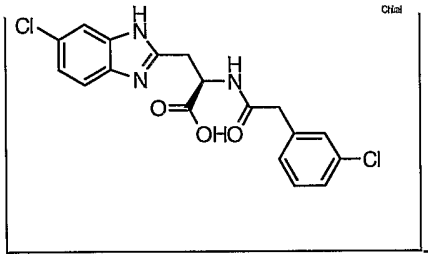
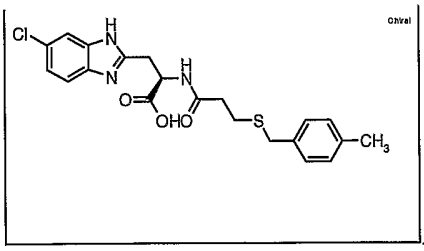
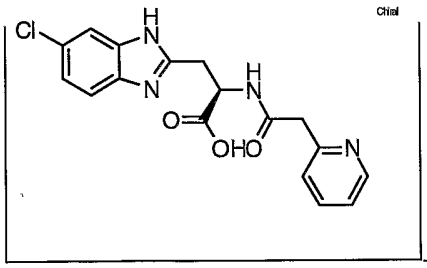
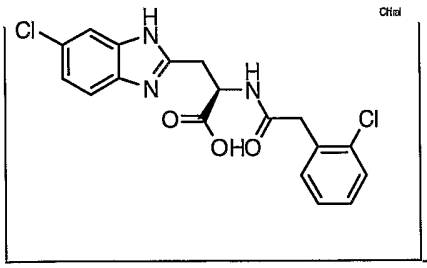
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{hydroxy[4-(trifluoromethyl)phenyl]acetyl}-D-alanine	441.7915	442.7915	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-fluorophenyl)(hydroxy)acetyl]-D-alanine	391.7845	392.7845	10
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(4R)-2-(4-methylphenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine	444.9409	445.9409	16
	1-(tert-butoxycarbonyl)-L-prolyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	436.8935	437.8935	10
	N-({(1R,3S)-3-[(tert-butoxycarbonyl)amino]cyclohexyl}carbonyl)-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	464.9471	465.9471	8

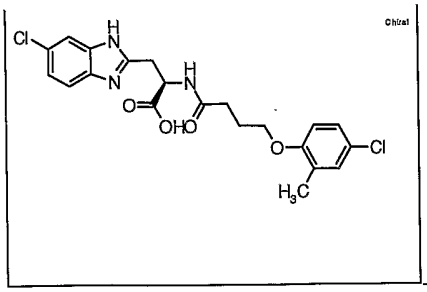
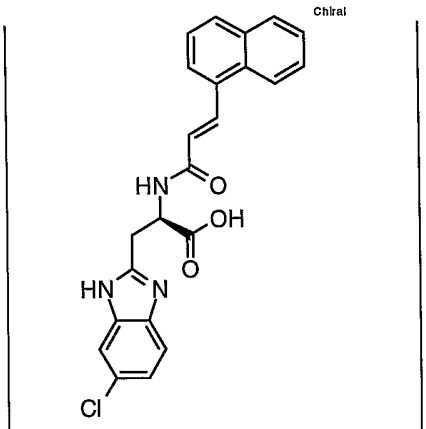
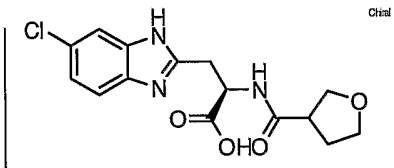
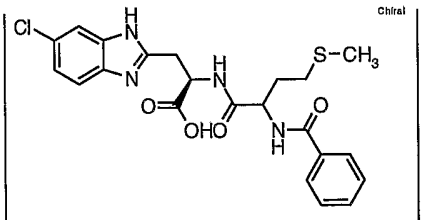
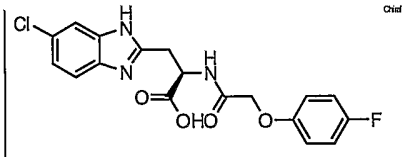
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-ethoxy-4-hydroxyphenyl)acetyl]-D-alanine	417.847	418.847	5
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-phenoxyphenyl)acetyl]-D-alanine	449.892	450.892	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(1-methylpiperidin-4-yl)carbonyl]-D-alanine	364.8309	365.8309	1
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(1-methylpiperidin-3-yl)carbonyl]-D-alanine	364.8309	365.8309	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[4-(4-chlorophenyl)-2-phenyl-1,3-thiazol-5-yl]acetyl}-D-alanine	551.452	552.452	17
	N-{[(4S)-3-(tert-butoxycarbonyl)-1,3-thiazolidin-4-yl]carbonyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	454.9327	455.9327	4

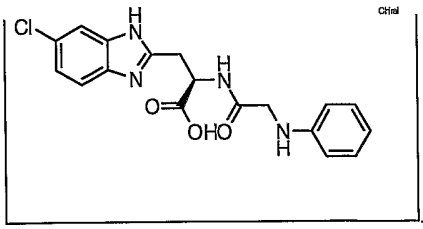
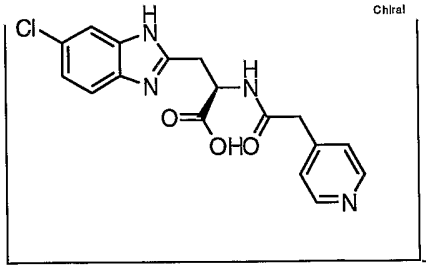
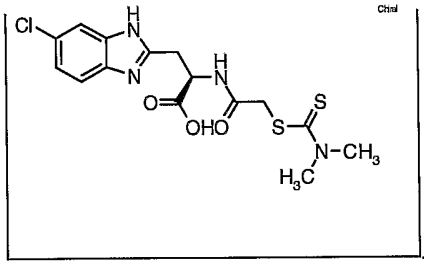
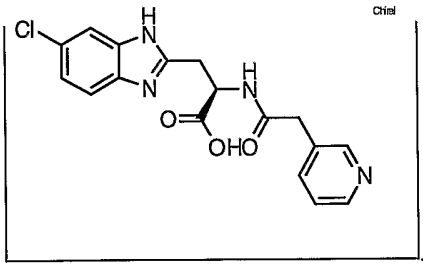
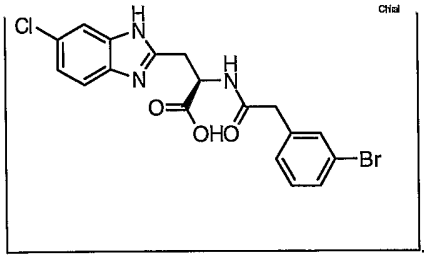
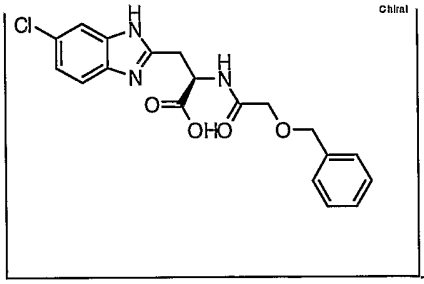
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[2-oxo-3-[(phenylsulfonyl)amino]pyridin-1(2H)-yl]acetyl}-D-alanine	529.959	530.959	14
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-phenoxyphenyl)acetyl]-D-alanine	449.892	450.892	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3,5-dimethoxyphenyl)acetyl]-D-alanine	417.847	418.847	1
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{3-[3-(trifluoromethyl)phenyl]propanoyl}-D-alanine	439.8193	440.8193	9

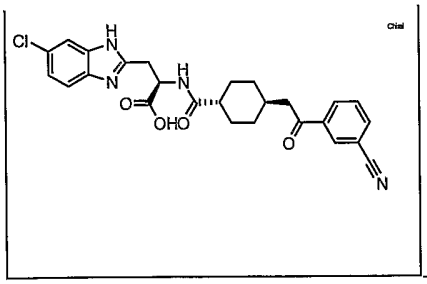
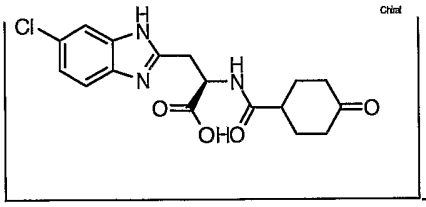
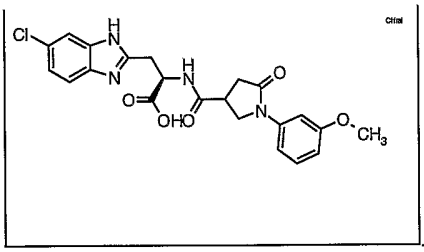
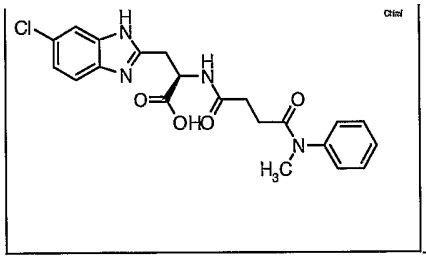
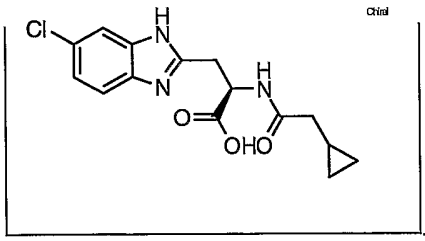
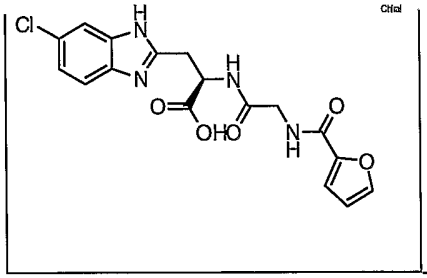
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[4-(methylsulfonyl)phenyl]acetyl}-D-alanine	435.8862	436.8862	3
	N-[3-[(tert-butoxycarbonyl)amino]-3-(4-chlorophenyl)propanoyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	521.3984	522.3984	0
	N-(tert-butoxycarbonyl)-3-(tetrahydro-2H-pyran-4-yl)alanyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	494.9729	495.9729	7
	N-(tert-butoxycarbonyl)-beta-phenyl-L-phenylalanyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	563.0509	564.0509	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cyclopent-3-en-1-ylcarbonyl)-D-alanine	333.7734	334.7734	9
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cyclohex-3-en-1-ylcarbonyl)-D-alanine	347.8002	348.8002	17

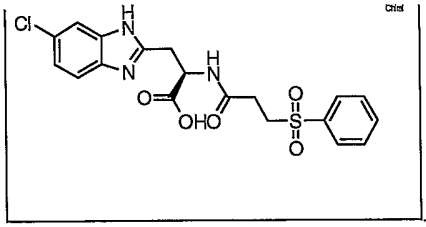
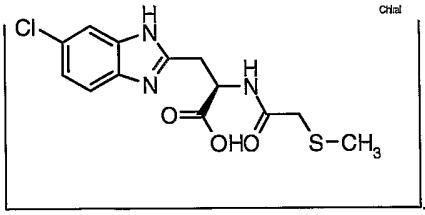
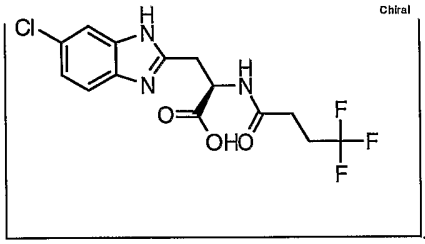
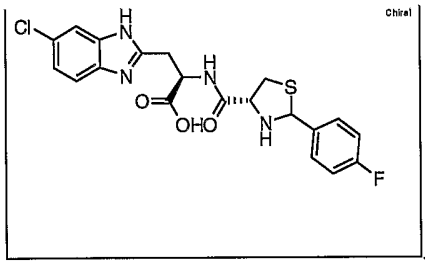
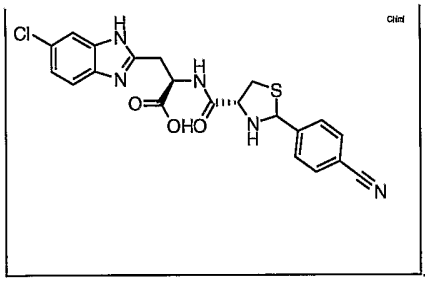
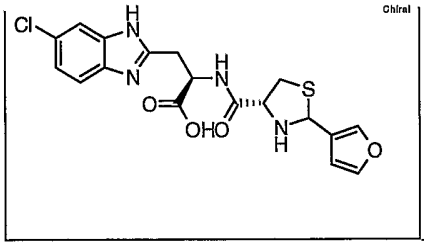
	N-[(5-bromo-1H-indol-3-yl)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	475.7284	476.7284	28
	N-[(3-bromo-4-methoxyphenyl)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	466.7173	467.7173	3
	N-benzoylglycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	400.8203	401.8203	10
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(3-hydroxy-2-phenylpropanoyl)-D-alanine	387.8212	388.8212	5

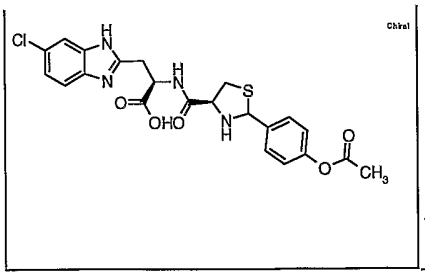
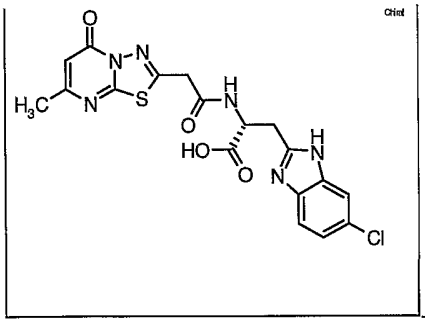
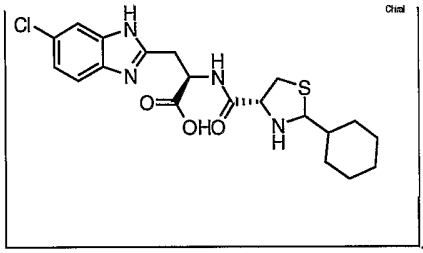
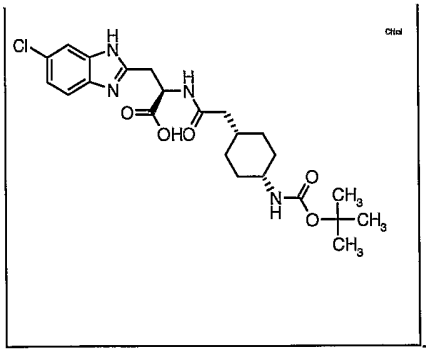
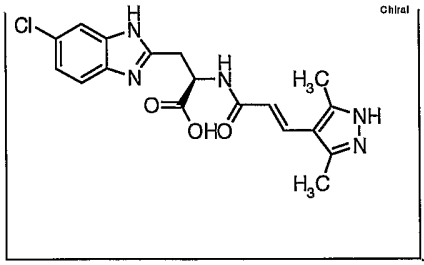
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[4-(1,2-dihydroacenaphthylen-5-yl)-4-oxobutanoyl]-D-alanine	475.9298	476.9298	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-chlorophenyl)acetyl]-D-alanine	392.2405	393.2405	5
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{3-[(4-methylbenzyl)thio]propanoyl}-D-alanine	431.9418	432.9418	19
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(pyridin-2-ylacetyl)-D-alanine	358.7835	359.7835	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-chlorophenyl)acetyl]-D-alanine	392.2405	393.2405	14

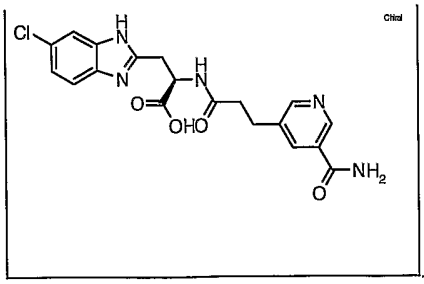
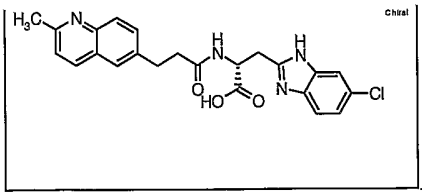
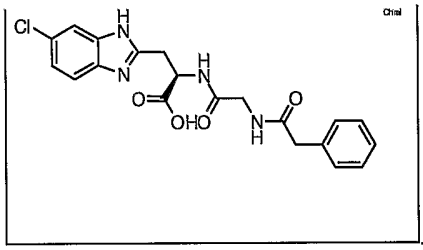
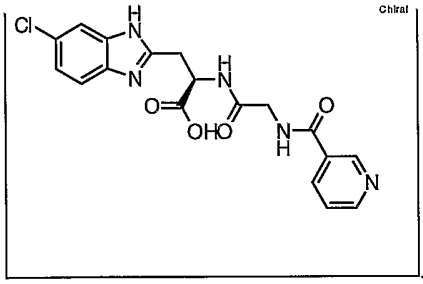
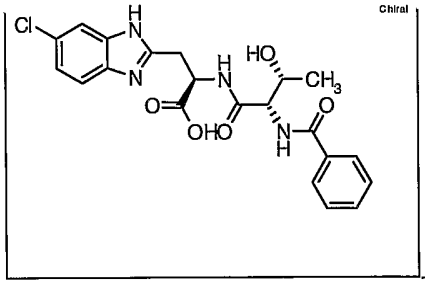
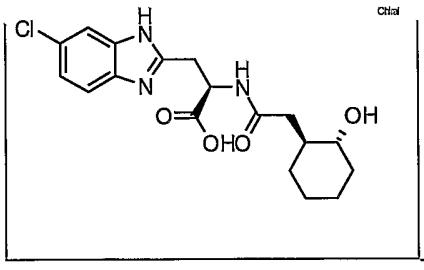
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[4-(4-chloro-2-methylphenoxy)butanoyl]-D-alanine	450.3199	451.3199	1
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2E)-3-(1-naphthyl)prop-2-enoyl]-D-alanine	419.8662	420.8662	37
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(tetrahydrofuran-3-ylcarbonyl)-D-alanine	337.7614	338.7614	10
	N-benzoylmethionyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	474.9667	475.9667	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-fluorophenoxy)acetyl]-D-alanine	391.7845	392.7845	8

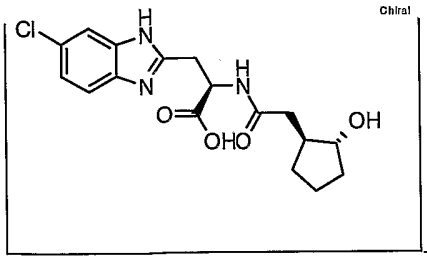
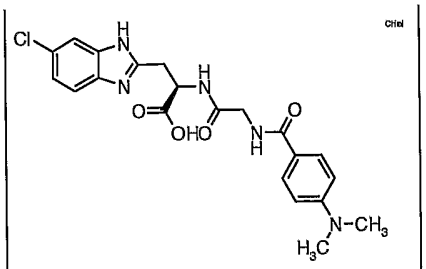
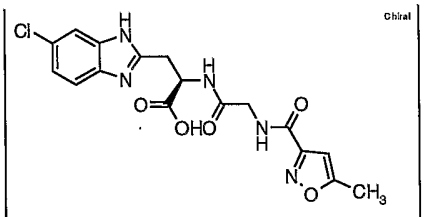
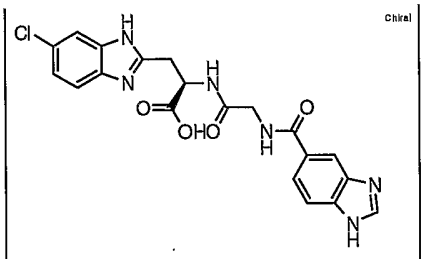
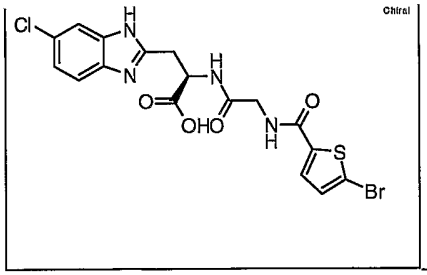
	N-phenylglycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	372.8103	373.8103	10
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(pyridin-4-ylacetyl)-D-alanine	358.7835	359.7835	1
	3-(6-chloro-1H-benzimidazol-2-yl)-N-({[(dimethylamino)carbonothioyl]thio}acetyl)-D-alanine	400.9093	401.9093	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(pyridin-3-ylacetyl)-D-alanine	358.7835	359.7835	0
	N-[(3-bromophenyl)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	436.6915	437.6915	12
	N-[(benzyloxy)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	387.8212	388.8212	14

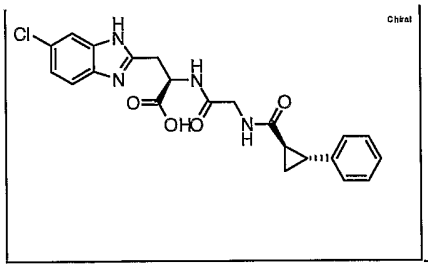
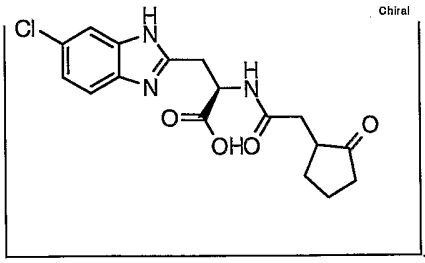
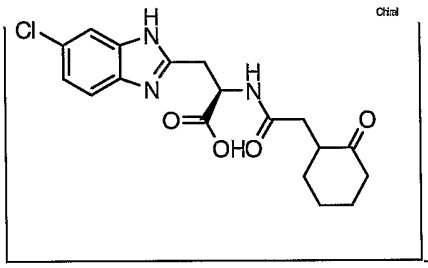
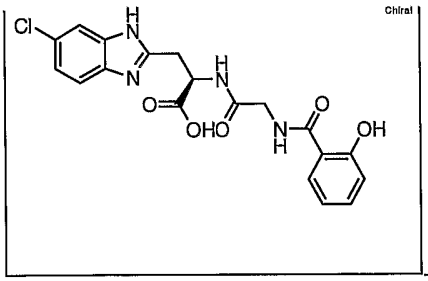
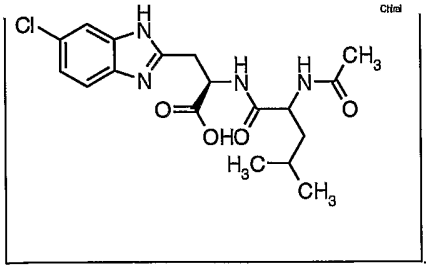
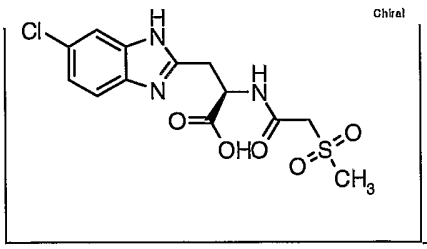
	3-(6-chloro-1H-benzimidazol-2-yl)-N-({trans-4-[2-(3-cyanophenyl)-2-oxoethyl]cyclohexyl}carbonyl)-D-alanine	492.9605	493.9605	16
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(4-oxocyclohexyl)carbonyl]-D-alanine	363.7992	364.7992	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[1-(3-methoxyphenyl)-5-oxopyrrolidin-3-yl]carbonyl}-D-alanine	456.8839	457.8839	6
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{4-[methyl(phenyl)amino]-4-oxobutanoyl}-D-alanine	428.8739	429.8739	15
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(cyclopropylacetyl)-D-alanine	321.7624	322.7624	14
	N-2-furoylglycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	390.7815	391.7815	5

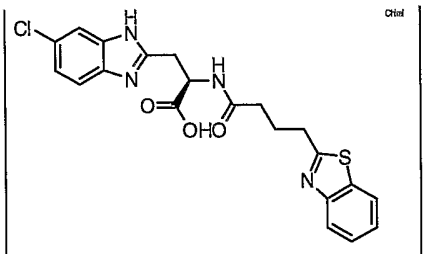
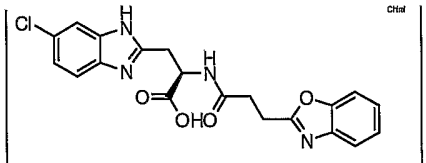
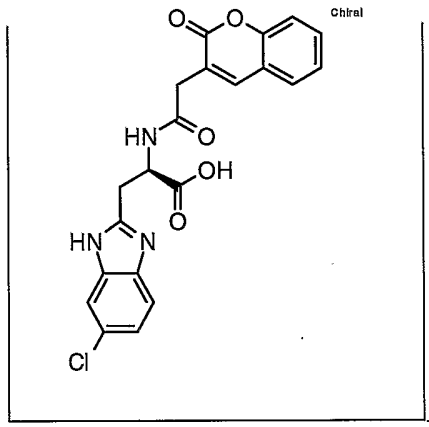
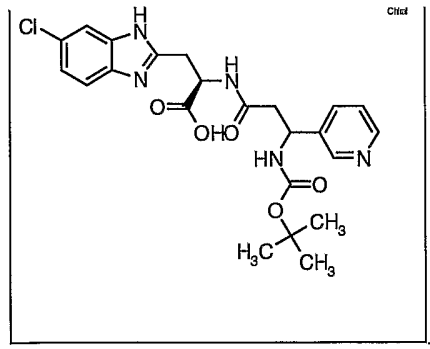
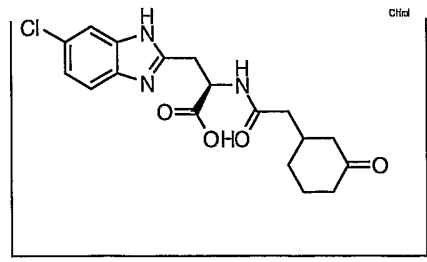
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(phenylsulfonyl)propanoyl]-D-alanine	435.8862	436.8862	13
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(methylthio)acetyl]-D-alanine	327.7906	328.7906	3
	3-(6-chloro-1H-benzimidazol-2-yl)-N-(4,4,4-trifluorobutanoyl)-D-alanine	363.7217	364.7217	3
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(4R)-2-(4-fluorophenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine	448.9042	449.9042	2
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(4R)-2-(4-cyanophenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine	455.9242	456.9242	17
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(4R)-2-(3-furyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine	420.8753	421.8753	10

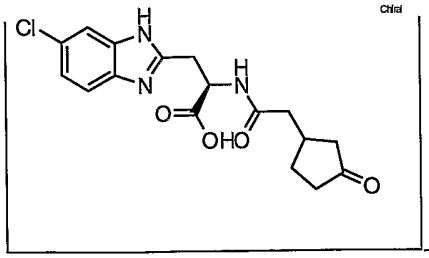
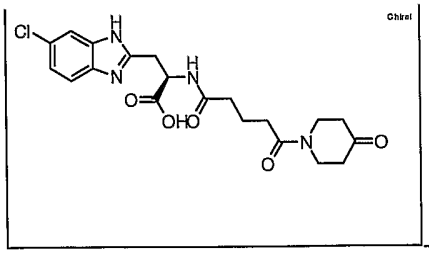
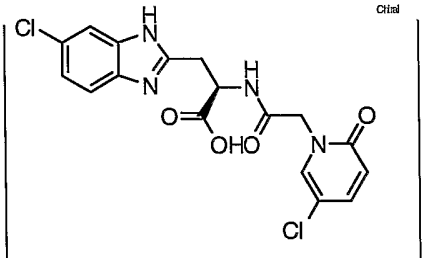
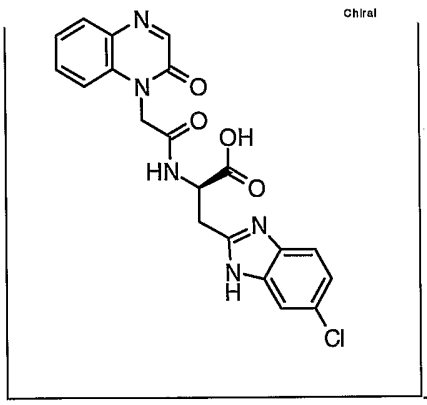
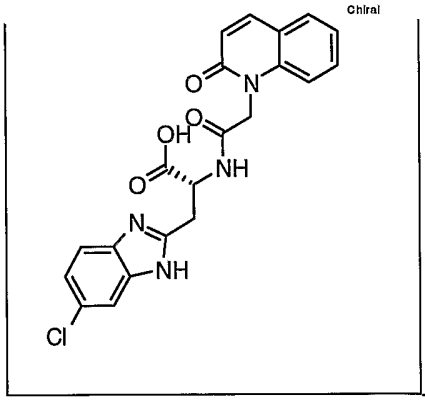
	N-({(4S)-2-[4-(acetyloxy)phenyl]-1,3-thiazolidin-4-yl}carbonyl)-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	488.9499	489.9499	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(7-methyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)acetyl]-D-alanine	446.8735	447.8735	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(4R)-2-cyclohexyl-1,3-thiazolidin-4-yl]carbonyl}-D-alanine	436.9615	437.9615	19
	N-({cis-4-[(tert-butoxycarbonyl)amino]cyclohexyl}acetyl)-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	478.9739	479.9739	9
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2E)-3-(3,5-dimethyl-1H-pyrazol-4-yl)prop-2-enoyl]-D-alanine	387.8252	388.8252	34

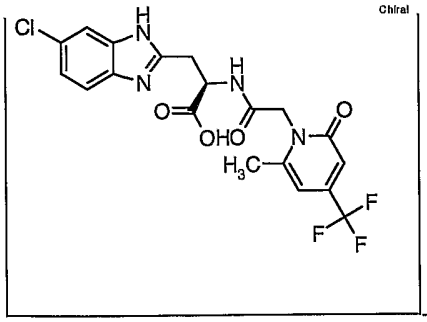
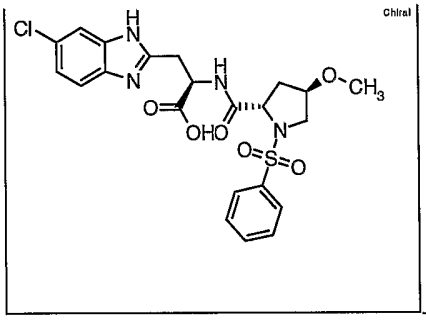
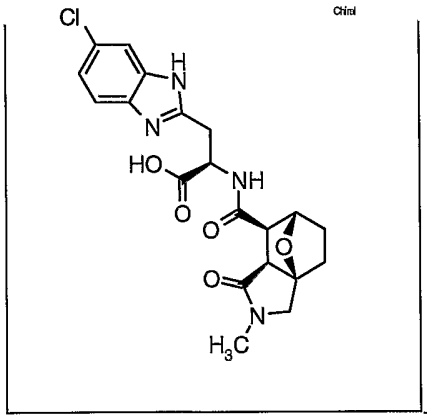
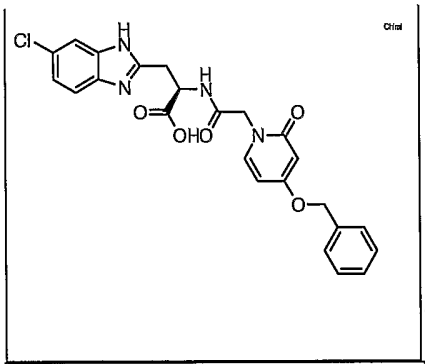
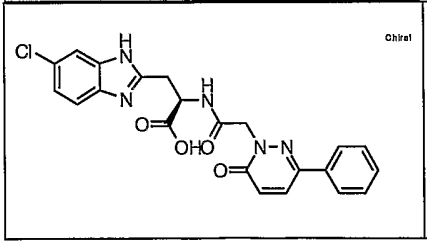
	N-{3-[5-(aminocarbonyl)pyridin-3-yl]propanoyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	415.8352	416.8352	0
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[3-(2-methylquinolin-6-yl)propanoyl]-D-alanine	436.8969	437.8969	4
	N-(phenylacetyl)glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	414.8471	415.8471	0
	N-(pyridin-3-ylcarbonyl)glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	401.8084	402.8084	0
	N-benzoyl-L-threonyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	444.8729	445.8729	11
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(1S,2R)-2-hydroxycyclohexyl]acetyl}-D-alanine	379.8418	380.8418	9

	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(1S,2R)-2-hydroxycyclopentyl]acetyl}-D-alanine	365.815	366.815	14
	N-[4-(dimethylamino)benzoyl]glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	443.8888	444.8888	5
	N-[(5-methylisoxazol-3-yl)carbonyl]glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	405.7964	406.7964	3
	N-(1H-benzimidazol-5-ylcarbonyl)glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	440.8453	441.8453	7
	N-[(5-bromo-2-thienyl)carbonyl]glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	485.7446	486.7446	6

	N-{[(1R,2R)-2-phenylcyclopropyl]carbonyl}glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	440.8849	441.8849	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-oxocyclopentyl)acetyl]-D-alanine	363.7992	364.7992	22
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-oxocyclohexyl)acetyl]-D-alanine	377.826	378.826	20
	N-(2-hydroxybenzoyl)glycyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	416.8193	417.8193	4
	N-acetylleucyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	394.8567	395.8567	14
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(methylsulfonyl)acetyl]-D-alanine	359.7886	360.7886	2

	N-[4-(1,3-benzothiazol-2-yl)butanoyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	442.9251	443.9251	21
	N-[3-(1,3-benzoxazol-2-yl)propanoyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	412.8313	413.8313	4
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-oxo-2H-chromen-3-yl)acetyl]-D-alanine	425.8264	426.8264	5
	N-{3-[(tert-butoxycarbonyl)amino]-3-pyridin-3-ylpropanoyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	487.9414	488.9414	4
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-oxocyclohexyl)acetyl]-D-alanine	377.826	378.826	7

	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(3-oxocyclopentyl)acetyl]-D-alanine	363.7992	364.7992	1
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[5-oxo-5-(4-oxopiperidin-1-yl)pentanoyl]-D-alanine	434.8777	435.8777	12
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(5-chloro-2-oxopyridin-1(2H)-yl)acetyl]-D-alanine	409.2276	410.2276	3
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-oxoquinoxalin-1(2H)-yl)acetyl]-D-alanine	425.8304	426.8304	1
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(2-oxoquinolin-1(2H)-yl)acetyl]-D-alanine	424.8423	425.8423	7

	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[6-methyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl]acetyl}-D-alanine	456.8064	457.8064	2
	(4R)-4-methoxy-1-(phenylsulfonyl)-L-prolyl-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	506.9647	507.9647	22
	3-(6-chloro-1H-benzimidazol-2-yl)-N-{[(3aR,6S,7R,7aS)-2-methyl-1-oxooctahydro-3a,6-epoxyisoindol-7-yl]carbonyl}-D-alanine	432.8619	433.8619	12
	N-{[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]acetyl}-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	480.9059	481.9059	7
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(6-oxo-3-phenylpyridazin-1(6H)-yl)acetyl]-D-alanine	451.8682	452.8682	14

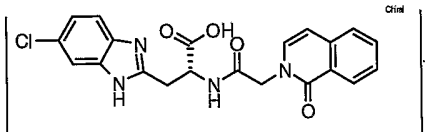
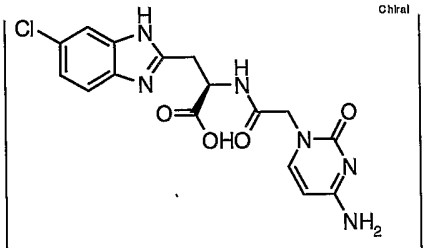
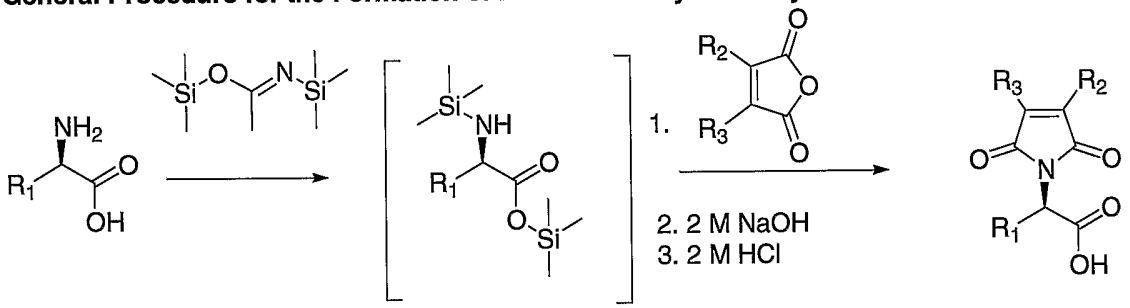
	3-(6-chloro-1H-benzimidazol-2-yl)-N-[(1-oxoisoquinolin-2(1H)-yl)acetyl]-D-alanine	424.8423	425.8423	5
	N-[(4-amino-2-oxopyrimidin-1(2H)-yl)acetyl]-3-(6-chloro-1H-benzimidazol-2-yl)-D-alanine	390.7855	391.7855	2

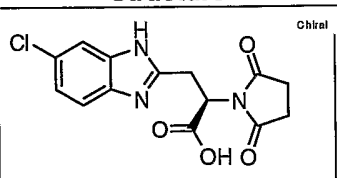
Table 5

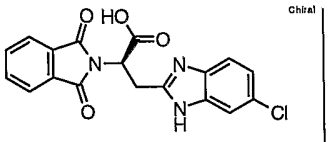
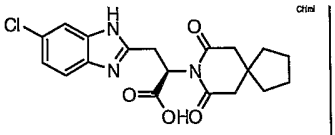
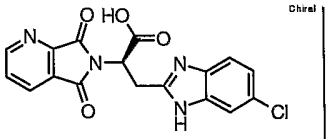
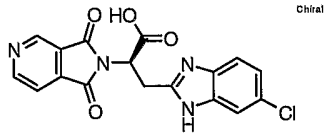
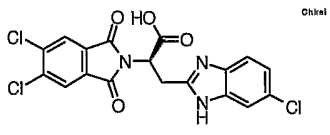
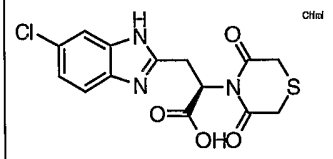
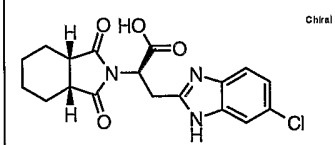
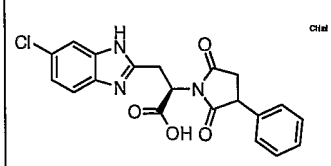
General Procedure for the Formation of Imides from Cyclic Anhydrides and Amino Acids:

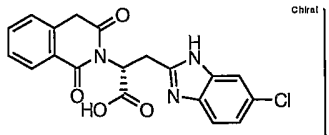
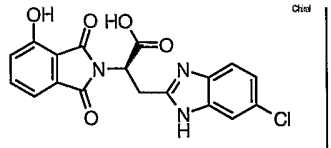
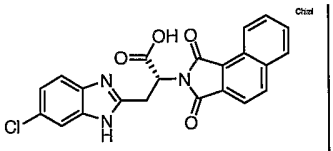
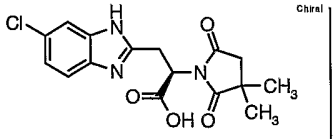
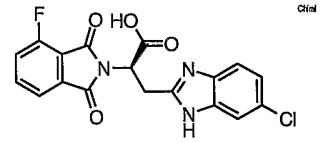
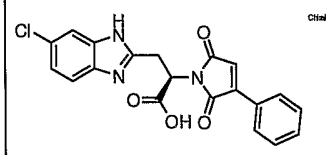
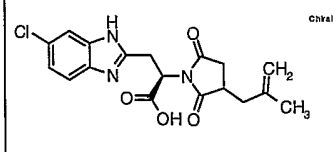


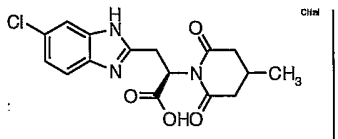
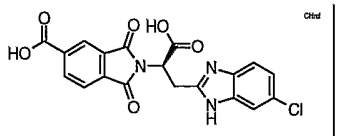
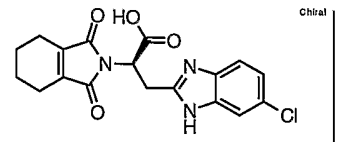
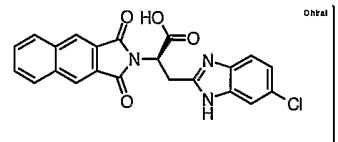
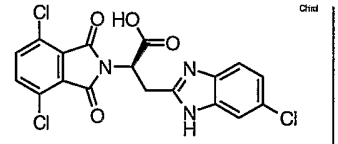
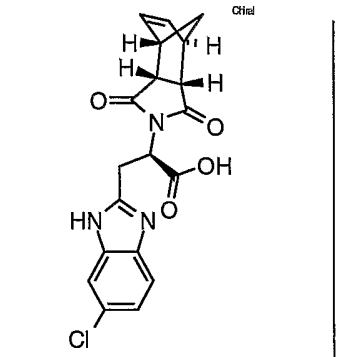
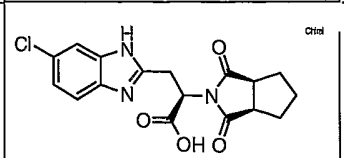
In a glovebox, each aminoacid (10 mmole) was placed into a labeled 50 mL reaction vial, and 30 mL of anhydrous NMP was added. *N,O*-bis(trimethylsilyl)acetamide (5.4 mL, 22 mmole) was added to each vial, and the reaction mixtures were allowed to stir for 16-24 h at room temperature in the glove box. The cyclic anhydrides in NMP (0.5 M, 160 µL, 0.08 mmole) were placed in the appropriate test tube, and the appropriate silylated amino acid solutions (0.2 M, 400 µL, 0.08 mmole) were added. The capped reaction mixtures were allowed to stir at room temperature for 72 h. The reactions were removed from the glovebox and heated to 80 ^{o}C for 48 h. Aqueous HCl solution (2.0 M, 200 µL, 0.4 mmole) was added to each tube, and the mixture was allowed to stir for 2 h. The solvents were removed, and the residues were reconstituted in DMSO.

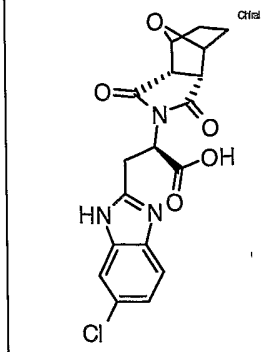
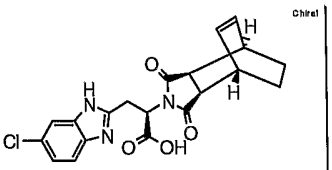
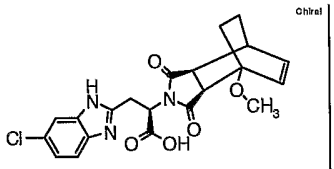
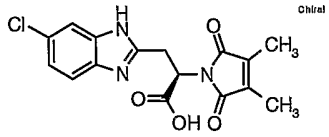
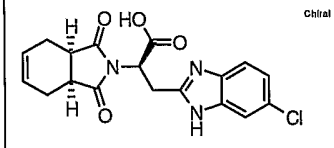
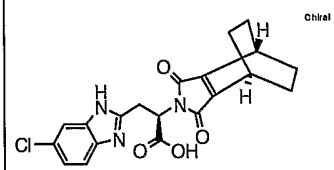
Table 5

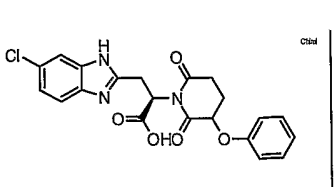
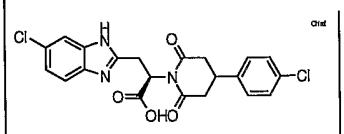
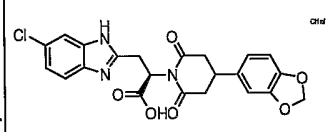
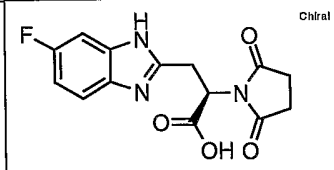
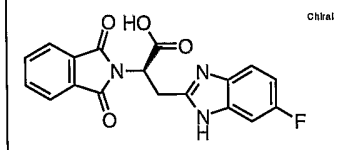
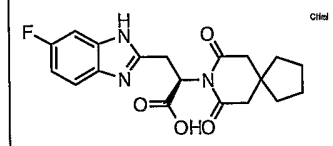
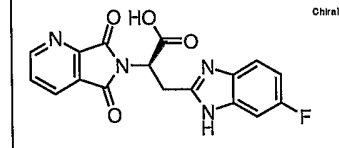
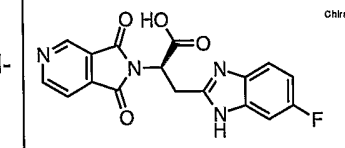
Name	Structure	MW	m/z MW + 1	% Inhibition at 10 µM
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(2,5-dioxopyrrolidin-1-yl)propanoic acid		321.719	322.719	37

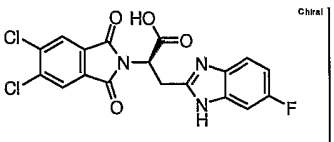
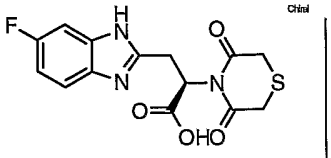
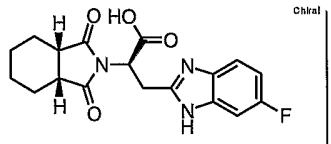
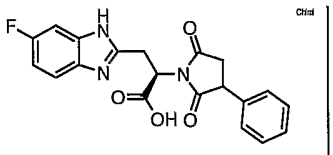
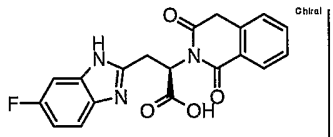
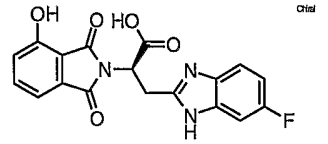
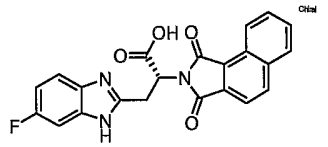
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid		369.763	370.763	55
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)propanoic acid		389.837	390.837	71
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(5,7-dioxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)propanoic acid		370.751	371.751	30
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(1,3-dioxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)propanoic acid		370.751	371.751	40
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid		438.653	439.653	86
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(3,5-dioxothiomorpholin-4-yl)propanoic acid		353.785	354.785	45
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(3aR,7aS)-1,3-dioxooctahydro-2H-isoindol-2-yl]propanoic acid		375.81	376.81	39
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(2,5-dioxo-3-phenylpyrrolidin-1-yl)propanoic acid		397.816	398.816	59

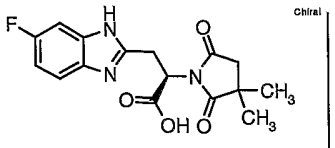
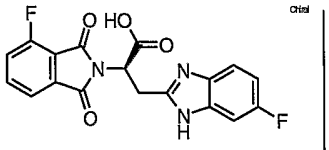
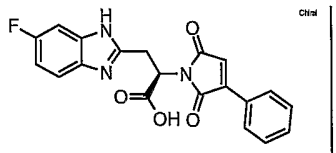
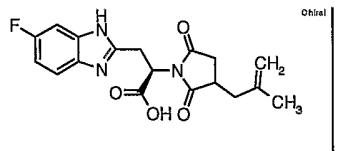
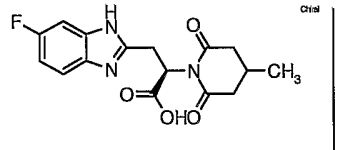
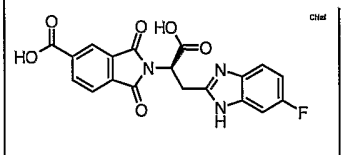
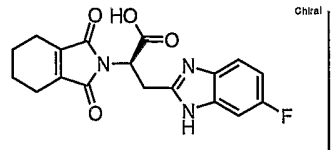
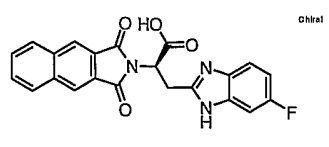
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)propanoic acid		383.79	384.79	60
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(4-hydroxy-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid		385.762	386.762	65
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(1,3-dioxo-1,3-dihydro-2H-benzo[e]isoindol-2-yl)propanoic acid		419.823	420.823	93
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(3,3-dimethyl-2,5-dioxopyrrolidin-1-yl)propanoic acid		349.772	350.772	65
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(4-fluoro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid		387.753	388.753	52
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(2,5-dioxo-3-phenyl-2,5-dihydro-1H-pyrrol-1-yl)propanoic acid		395.801	396.801	84
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[3-(2-methylprop-2-en-1-yl)-2,5-dioxopyrrolidin-1-yl]propanoic acid		375.81	376.81	55

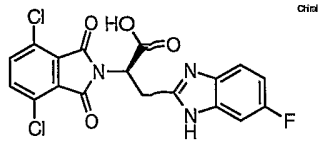
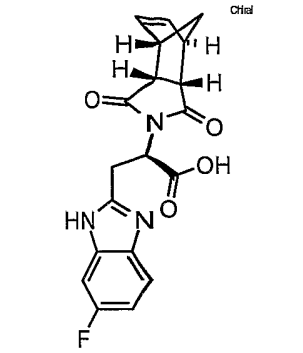
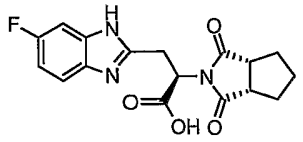
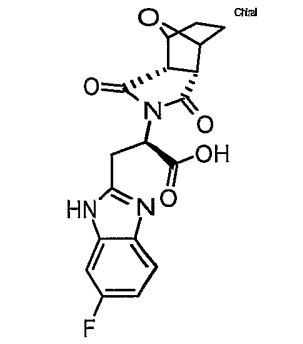
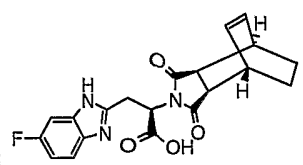
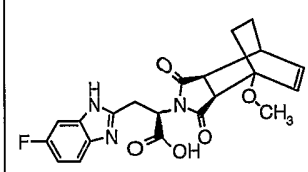
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(4-methyl-2,6-dioxopiperidin-1-yl)propanoic acid		349.772	350.772	31
2-[(1R)-1-carboxy-2-(6-chloro-1H-benzimidazol-2-yl)ethyl]-1,3-dioxoisoindoline-5-carboxylic acid		413.772	414.772	51
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(1,3-dioxo-1,3,4,5,6,7-hexahydro-2H-isoindol-2-yl)propanoic acid		373.794	374.794	59
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)propanoic acid		419.823	420.823	90
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(4,7-dichloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid		438.653	439.653	32
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl]propanoic acid		385.805	386.805	21
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(3aR,6aS)-1,3-dioxohexahydrocyclopenta[c]pyrrol-2(1H)-yl]propanoic acid		361.783	362.783	35

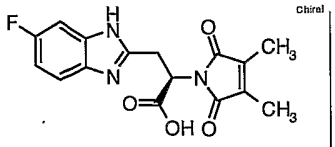
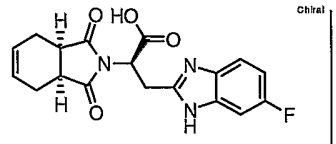
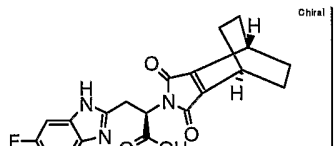
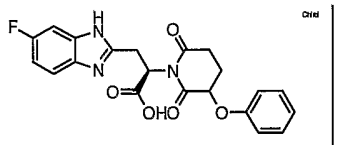
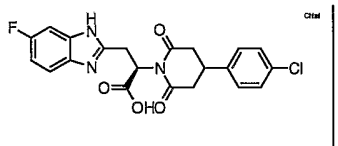
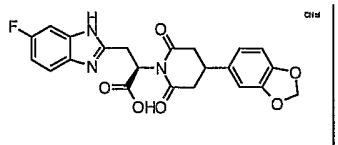
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(3aR,7aS)-1,3-dioxooctahydro-2H-4,7-epoxyisoindol-2-yl]propanoic acid		389.793	390.793	54
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-ethanoisoindol-2-yl]propanoic acid		399.832	400.832	48
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(3aS,7aS)-4-methoxy-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-ethanoisoindol-2-yl]propanoic acid		429.858	430.858	47
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(3,4-dimethyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoic acid		347.757	348.757	34
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(3aR,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl]propanoic acid		373.794	374.794	57
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[(4S,7S)-1,3-dioxo-1,3,4,5,6,7-hexahydro-2H-4,7-ethanoisoindol-2-yl]propanoic acid		399.832	400.832	87

(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-(2,6-dioxo-3-phenoxypiperidin-1-yl)propanoic acid		427.842	428.842	33
(2R)-3-(6-chloro-1H-benzimidazol-2-yl)-2-[4-(4-chlorophenyl)-2,6-dioxopiperidin-1-yl]propanoic acid		446.288	447.288	51
(2R)-2-[4-(1,3-benzodioxol-5-yl)-2,6-dioxopiperidin-1-yl]-3-(6-chloro-1H-benzimidazol-2-yl)propanoic acid		455.852	456.852	68
(2R)-2-(2,5-dioxopyrrolidin-1-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		305.264	306.264	31
(2R)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		353.308	354.308	48
(2R)-2-(7,9-dioxo-8-azaspiro[4.5]dec-8-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		373.382	374.382	69
(2R)-2-(5,7-dioxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		354.296	355.296	36
(2R)-2-(1,3-dioxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		354.296	355.296	39

(2R)-2-(5,6-dichloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		422.198	423.198	75
(2R)-2-(3,5-dioxothiomorpholin-4-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		337.33	338.33	47
(2R)-2-[(3aR,7aS)-1,3-dioxooctahydro-2H-isoindol-2-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		359.355	360.355	46
(2R)-2-(2,5-dioxo-3-phenylpyrrolidin-1-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		381.361	382.361	33
(2R)-2-(1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		367.335	368.335	65
(2R)-3-(6-fluoro-1H-benzimidazol-2-yl)-2-(4-hydroxy-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid		369.307	370.307	58
(2R)-2-(1,3-dioxo-1,3-dihydro-2H-benzo[e]isoindol-2-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		403.368	404.368	85

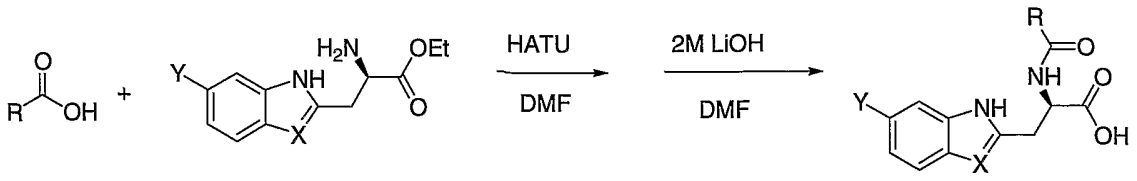
(2R)-2-(3,3-dimethyl-2,5-dioxopyrrolidin-1-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		333.317	334.317	57
(2R)-3-(6-fluoro-1H-benzimidazol-2-yl)-2-(4-fluoro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid		371.298	372.298	47
(2R)-2-(2,5-dioxo-3-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		379.346	380.346	78
(2R)-3-(6-fluoro-1H-benzimidazol-2-yl)-2-[3-(2-methylprop-2-en-1-yl)-2,5-dioxopyrrolidin-1-yl]propanoic acid		359.355	360.355	68
(2R)-3-(6-fluoro-1H-benzimidazol-2-yl)-2-(4-methyl-2,6-dioxopiperidin-1-yl)propanoic acid		333.317	334.317	40
2-[(1R)-1-carboxy-2-(6-fluoro-1H-benzimidazol-2-yl)ethyl]-1,3-dioxoisoindoline-5-carboxylic acid		397.317	398.317	42
(2R)-2-(1,3-dioxo-1,3,4,5,6,7-hexahydro-2H-isoindol-2-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		357.339	358.339	48
(2R)-2-(1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		403.368	404.368	91

(2R)-2-(4,7-dichloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		422.198	423.198	40
(2R)-2-[(3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		369.35	370.35	29
(2R)-2-[(3aR,6aS)-1,3-dioxohexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		345.328	346.328	31
(2R)-2-[(3aR,7aS)-1,3-dioxooctahydro-2H-4,7-epoxyisoindol-2-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		373.338	374.338	51
(2R)-2-[(3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-ethanoisoindol-2-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		383.377	384.377	57
(2R)-3-(6-fluoro-1H-benzimidazol-2-yl)-2-[(3aS,7aS)-4-methoxy-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-ethanoisoindol-2-yl]propanoic acid		413.403	414.403	55

(2R)-2-(3,4-dimethyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		331.302	332.302	40
(2R)-2-[(3aR,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		357.339	358.339	49
(2R)-2-[(4S,7S)-1,3-dioxo-1,3,4,5,6,7-hexahydro-2H-4,7-ethanoisoindol-2-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		383.377	384.377	81
(2R)-2-(2,6-dioxo-3-phenoxypiperidin-1-yl)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		411.387	412.387	38
(2R)-2-[4-(4-chlorophenyl)-2,6-dioxopiperidin-1-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		429.833	430.833	46
(2R)-2-[4-(1,3-benzodioxol-5-yl)-2,6-dioxopiperidin-1-yl]-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		439.397	440.397	54

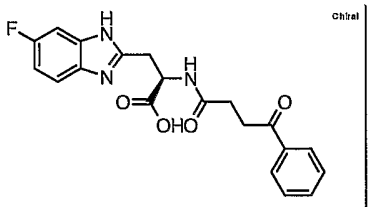
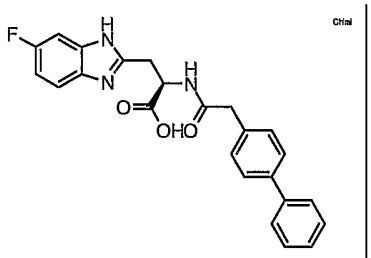
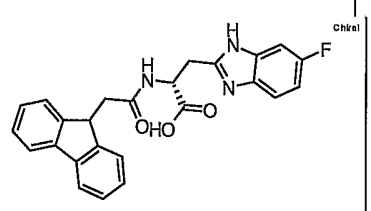
The compounds of Table 6 were made by the following general procedure:

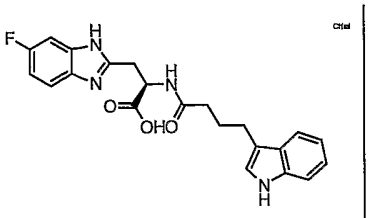
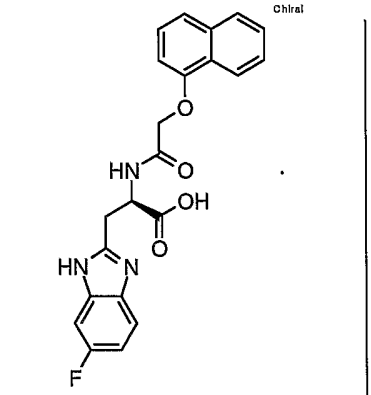
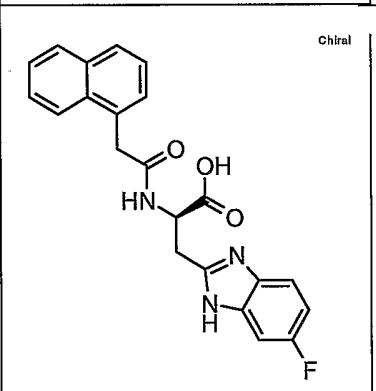
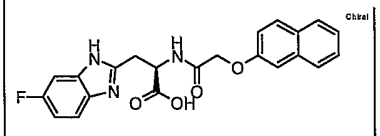
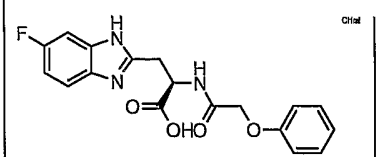
General Procedure for Amide Bond Formation with Aminoesters followed by Saponification:

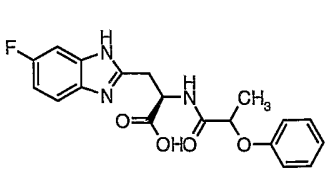
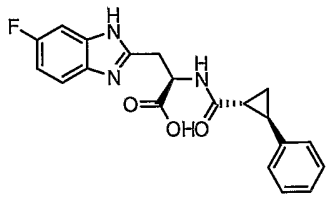
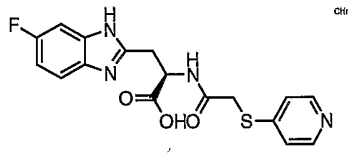
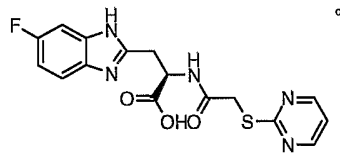
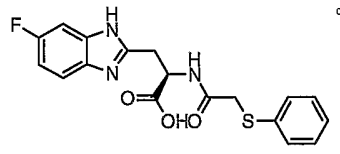
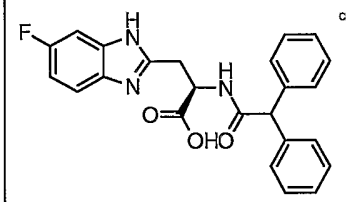
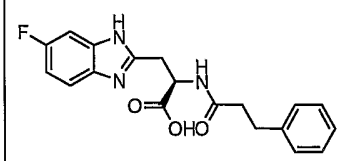


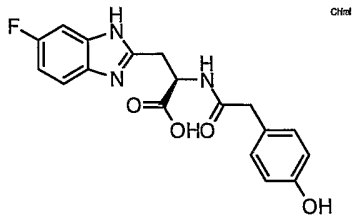
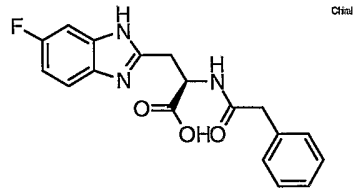
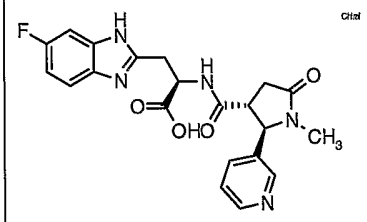
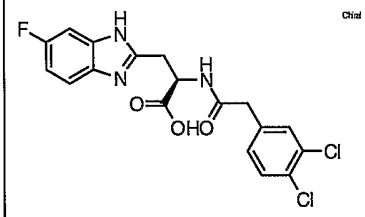
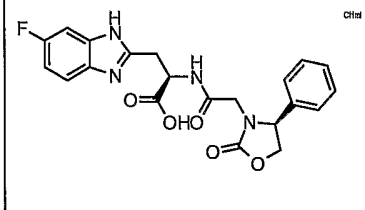
In a glovebox, a solution of the appropriate amine in DMF (0.2 M, 50 µL, 0.01 mmole), a solution of the appropriate carboxylic acid solution (0.2 M, 50 µL, 0.01 mmole), a solution of TEA (0.5 M, 20 µL, 0.01 mmole), and a solution of HATU in DMF (0.5 M, 20 µL, 0.01 mmole) were combined in a test tube, and the reactions were allowed to stir for 50 °C for 4 h. An aqueous LiOH solution (2.0 M, 50 µL, 0.10 mmole) was added to each tube, and the reactions were agitated at room temperature for 24 h. An aqueous HCl solution (1.0 M, 100 µL, 0.10 mmole) was added to each tube, and the reaction mixtures were briefly agitated. The solvents were removed, and the residues were reconstituted in DMSO.

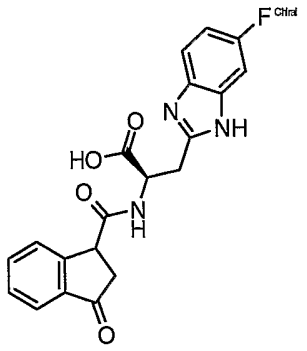
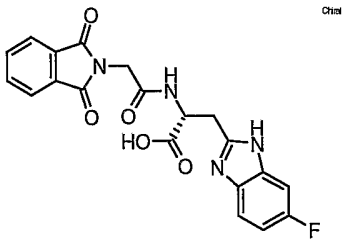
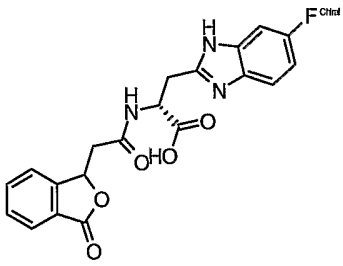
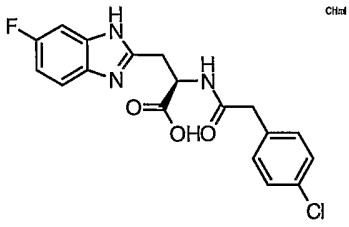
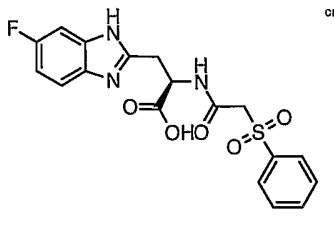
Table 6

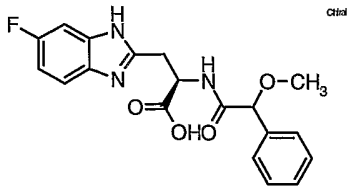
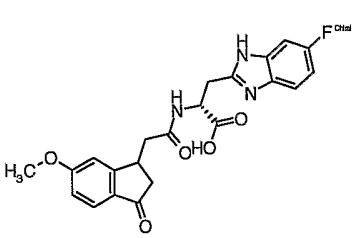
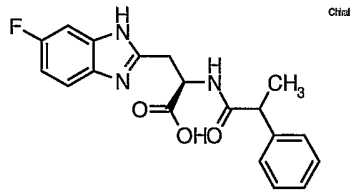
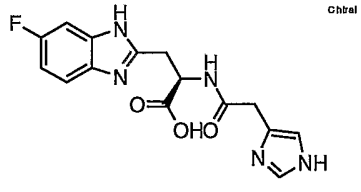
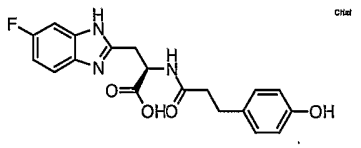
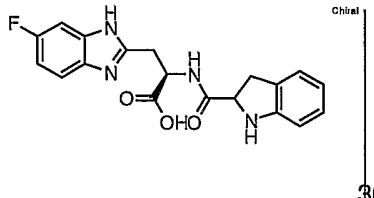
Name	Structure	MW	m/z MW + 1	% Inhibition at 10 µM
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(4-oxo-4-phenylbutanoyl)-D-alanine		383.3772	384.377	25
N-(biphenyl-4-ylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		417.438	418.438	7
N-(9H-fluoren-9-ylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		429.449	430.449	91

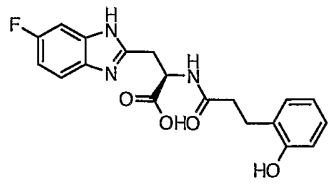
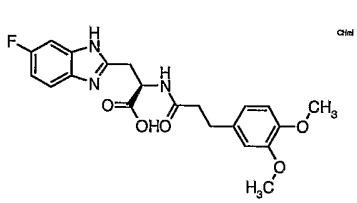
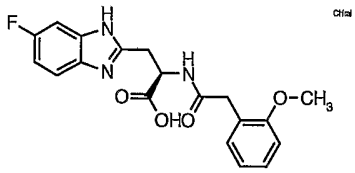
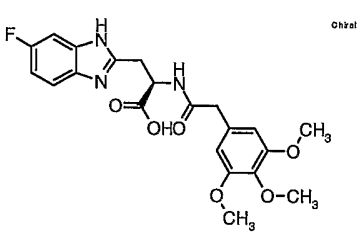
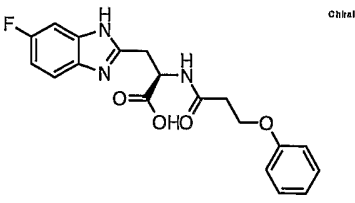
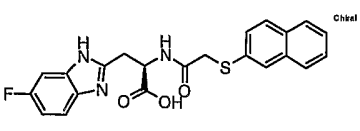
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[4-(1H-indol-3-yl)butanoyl]-D-alanine		408.4309	409.431	56
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(1-naphthyloxy)acetyl]-D-alanine		407.3992	408.399	37
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(1-naphthylacetyl)-D-alanine		391.4002	392.4	46
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-naphthyloxy)acetyl]-D-alanine		407.3992	408.399	4
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(phenoxyacetyl)-D-alanine		357.3394	358.339	29

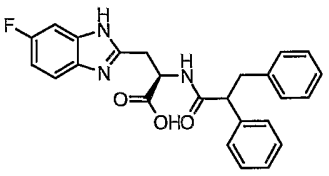
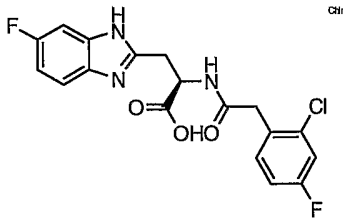
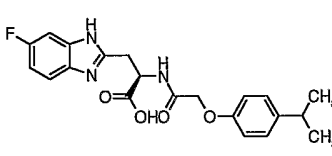
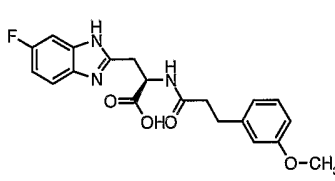
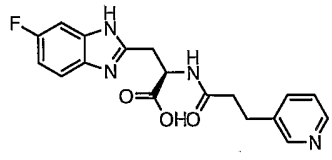
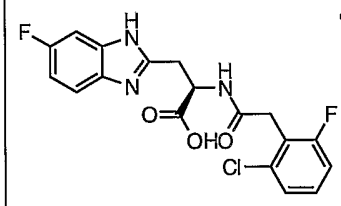
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-phenoxypropanoyl)-D-alanine		371.3662	372.366	28
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(1R,2R)-2-phenylcyclopropyl]carbonyl}-D-alanine		367.3782	368.378	29
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(pyridin-4-ylthio)acetyl]-D-alanine		374.3945	375.394	0
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(pyrimidin-2-ylthio)acetyl]-D-alanine		375.3826	376.383	0
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(phenylthio)acetyl]-D-alanine		373.4064	374.406	48
N-(diphenylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		417.438	418.438	35
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-phenylpropanoyl)-D-alanine		355.3672	356.367	45

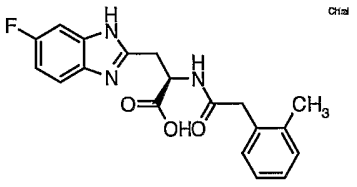
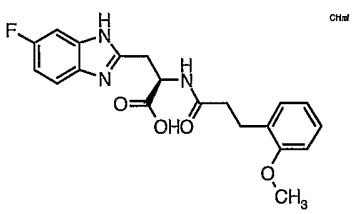
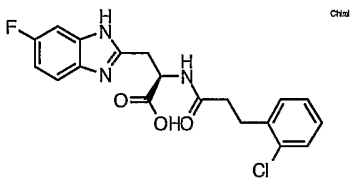
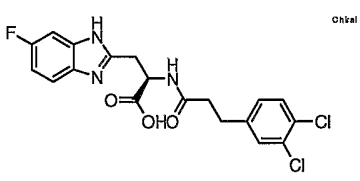
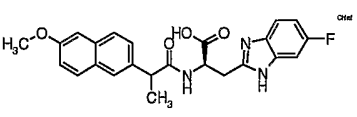
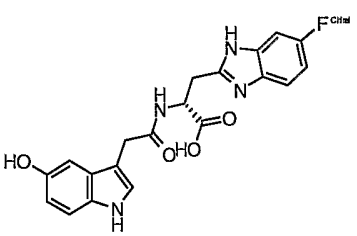
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-hydroxyphenyl)acetyl]-D-alanine		357.3394	358.339	25
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(phenylacetyl)-D-alanine		341.3404	342.34	19
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(2R,3R)-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidin-3-yl]carbonyl}-D-alanine		425.418	426.418	7
N-[(3,4-dichlorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		410.2306	411.231	20
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(4S)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]acetyl}-D-alanine		426.4021	427.402	24

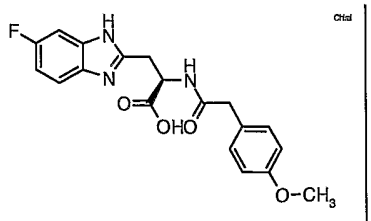
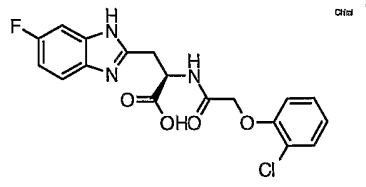
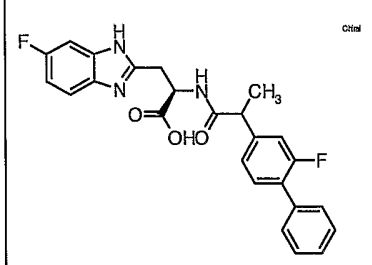
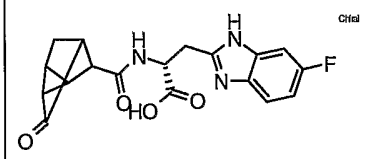
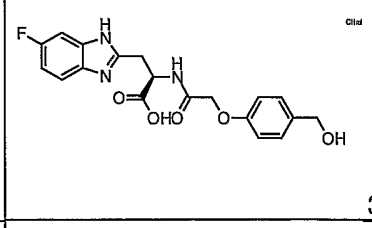
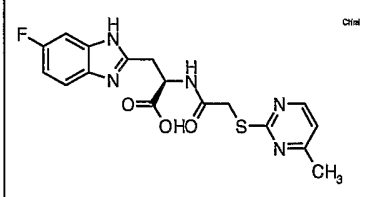
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-oxo-2,3-dihydro-1H-inden-1-yl)carbonyl]-D-alanine		381.3614	382.361	17
N-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		410.3595	411.36	4
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-oxo-1,3-dihydro-2-benzofuran-1-yl)acetyl]-D-alanine		397.3604	398.36	40
N-[(4-chlorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		375.7855	376.786	0
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(phenylsulfonyl)acetyl]-D-alanine		405.4044	406.404	29

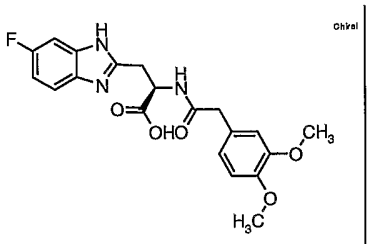
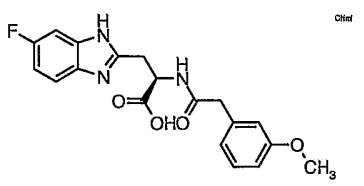
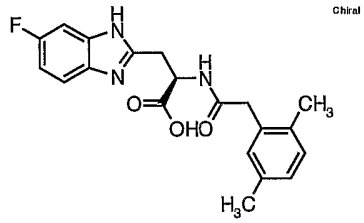
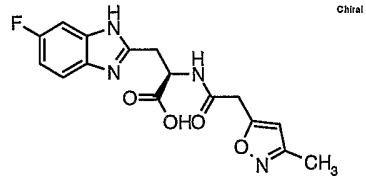
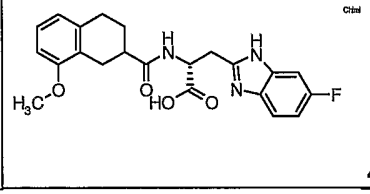
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[methoxy(phenyl)acetyl]-D-alanine		371.3662	372.366	31
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetyl]-D-alanine		425.414	426.414	73
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-phenylpropanoyl)-D-alanine		355.3672	356.367	35
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(1H-imidazol-4-ylacetyl)-D-alanine		331.3056	332.306	6
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(4-hydroxyphenyl)propanoyl]-D-alanine		371.3662	372.366	44
N-(2,3-dihydro-1H-indol-2-ylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		368.3663	369.366	73

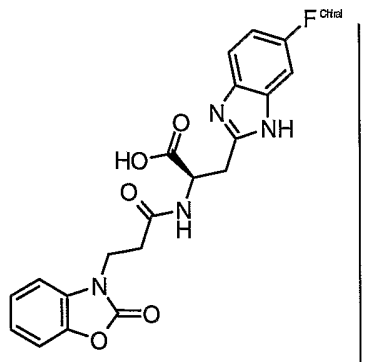
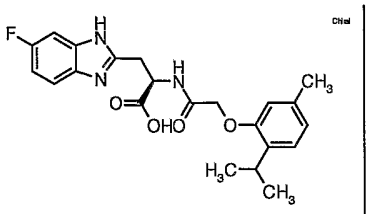
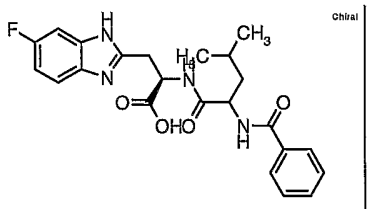
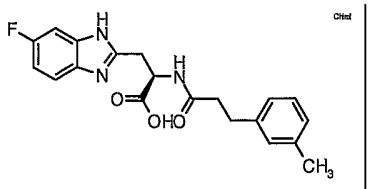
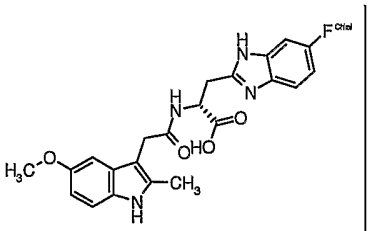
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(2-hydroxyphenyl)propanoyl]-D-alanine		371.3662	372.366	18
N-[3-(3,4-dimethoxyphenyl)propanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		415.4188	416.419	10
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-methoxyphenyl)acetyl]-D-alanine		371.3662	372.366	31
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3,4,5-trimethoxyphenyl)acetyl]-D-alanine		431.4178	432.418	0
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-phenoxypropanoyl)-D-alanine		371.3662	372.366	8
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-naphthylthio)acetyl]-D-alanine		423.4662	424.466	46

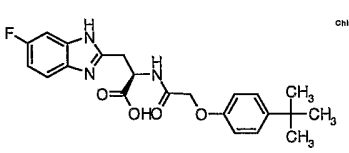
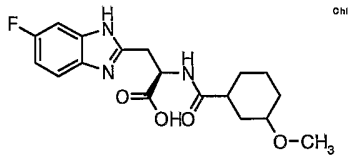
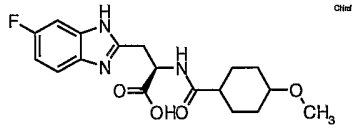
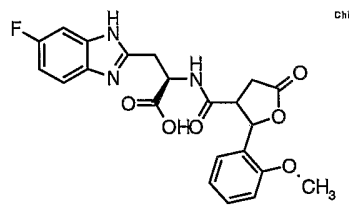
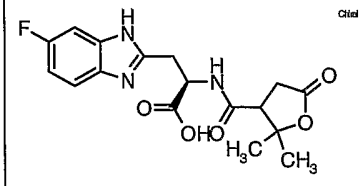
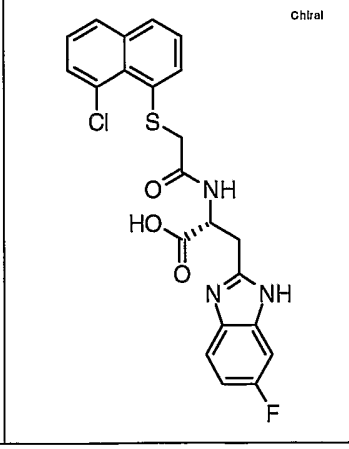
N-(2,3-diphenylpropanoyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		431.4648	432.465	29
N-[(2-chloro-4-fluorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		393.7756	394.776	44
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-isopropylphenoxy)acetyl]-D-alanine		399.4198	400.42	1
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(3-methoxyphenyl)propanoyl]-D-alanine		385.393	386.393	56
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-pyridin-3-ylpropanoyl)-D-alanine		356.3553	357.355	39
N-[(2-chloro-6-fluorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		393.7756	394.776	45

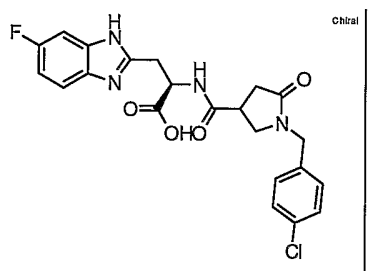
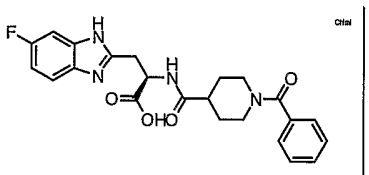
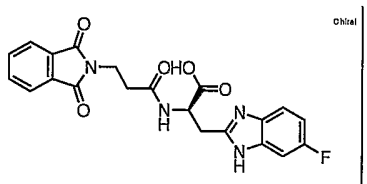
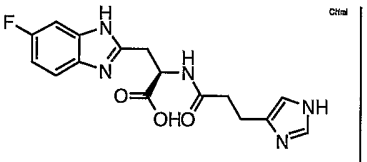
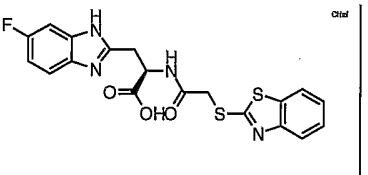
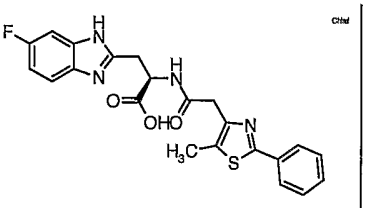
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-methylphenyl)acetyl]-D-alanine		355.3672	356.367	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(2-methoxyphenyl)propanoyl]-D-alanine		385.393	386.393	44
N-[3-(2-chlorophenyl)propanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		389.8123	390.812	30
N-[3-(3,4-dichlorophenyl)propanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		424.2574	425.257	6
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(6-methoxy-2-naphthyl)propanoyl]-D-alanine		435.4528	436.453	15
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-hydroxy-1H-indol-3-yl)acetyl]-D-alanine		396.3763	397.376	43

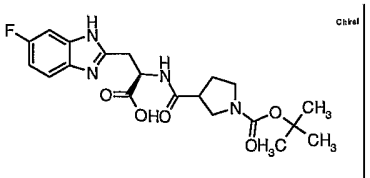
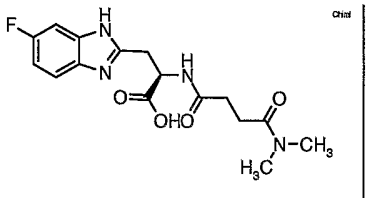
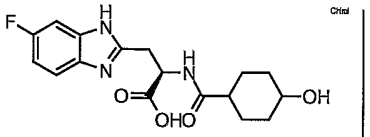
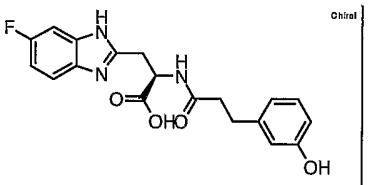
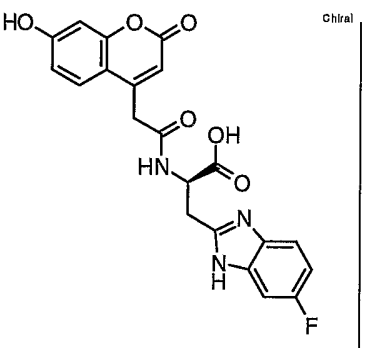
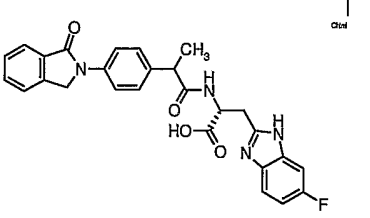
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-methoxyphenyl)acetyl]-D-alanine		371.3662	372.366	19
N-[(2-chlorophenoxy)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		391.7845	392.784	44
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(2-fluorobiphenyl-4-yl)propanoyl]-D-alanine		449.4549	450.455	25
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-oxotricyclo[2.2.1.0~2,6~]hept-3-yl)carbonyl]-D-alanine		357.3394	358.339	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[4-(hydroxymethyl)phenoxy]acetyl}-D-alanine		387.3652	388.365	20
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(4-methylpyrimidin-2-yl)thio]acetyl}-D-alanine		389.4094	390.409	0

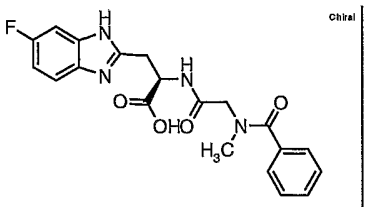
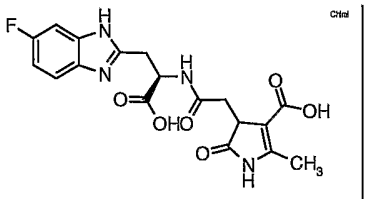
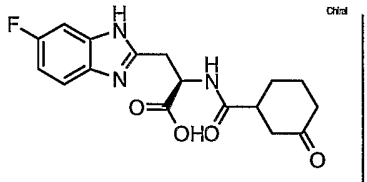
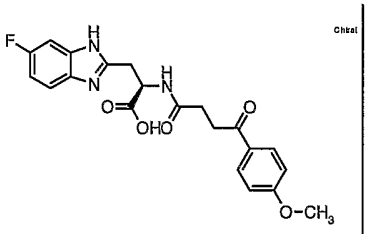
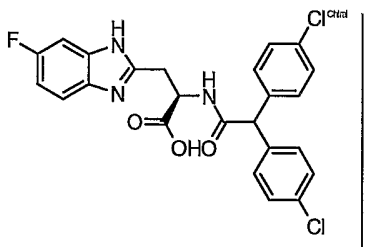
N-[(3,4-dimethoxyphenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		401.392	402.392	1
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-methoxyphenyl)acetyl]-D-alanine		371.3662	372.366	6
N-[(2,5-dimethylphenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		369.394	370.394	63
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-methylisoxazol-5-yl)acetyl]-D-alanine		346.3165	347.317	6
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)carbonyl]-D-alanine		411.4308	412.431	65

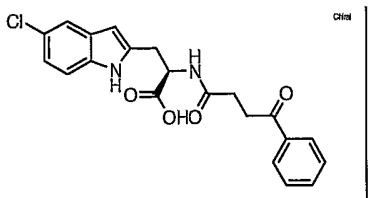
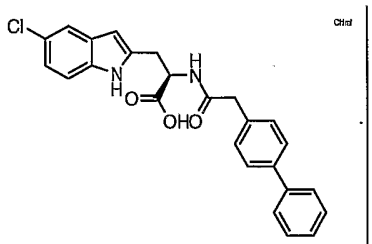
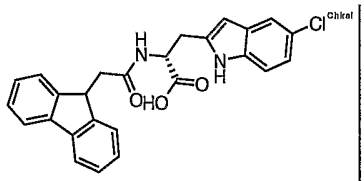
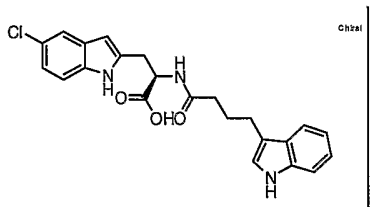
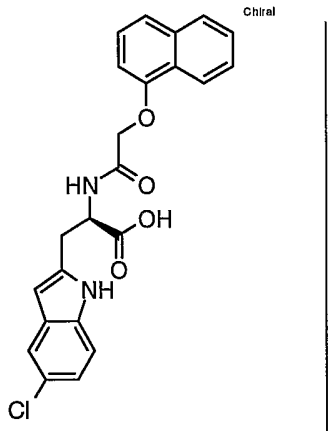
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanoyl]-D-alanine		412.3753	413.375	35
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-isopropyl-5-methylphenoxy)acetyl]-D-alanine		413.4466	414.447	73
N-benzoylleucyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		440.4725	441.473	24
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(3-methylphenyl)propanoyl]-D-alanine		369.394	370.394	58
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]-D-alanine		424.4299	425.43	27

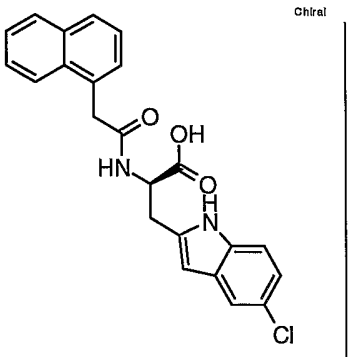
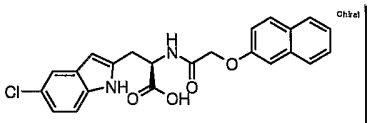
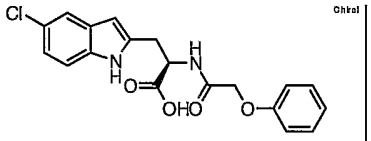
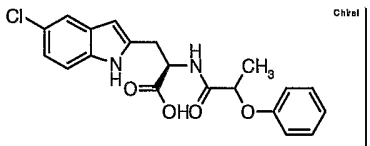
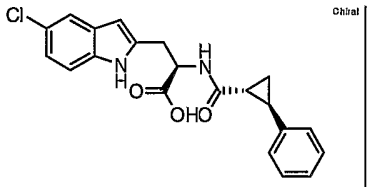
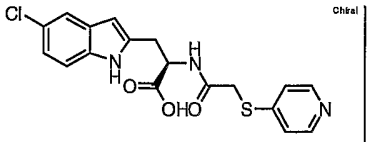
N-[(4-tert-butylphenoxy)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		413.4466	414.447	0
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-methoxycyclohexyl)carbonyl]-D-alanine		363.3868	364.387	49
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-methoxycyclohexyl)carbonyl]-D-alanine		363.3868	364.387	22
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[2-(2-methoxyphenyl)-5-oxotetrahydrofuran-3-yl]carbonyl}-D-alanine		441.413	442.413	53
N-[(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)carbonyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		363.3432	364.343	37
N-{[(8-chloro-1-naphthyl)thio]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		457.9113	458.911	7

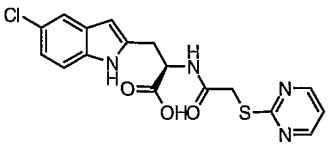
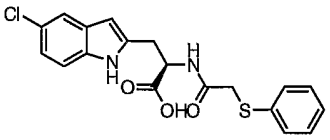
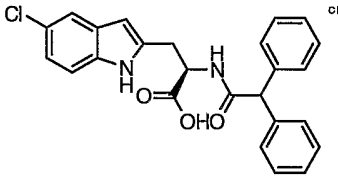
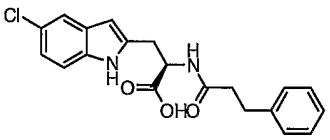
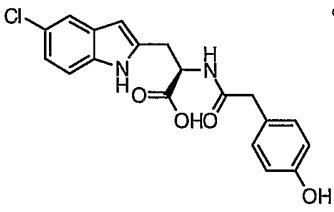
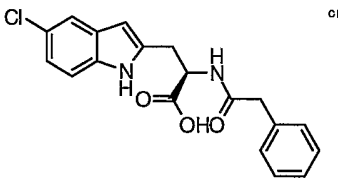
N-{[1-(4-chlorobenzyl)-5-oxopyrrolidin-3-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		458.875	459.875	20
N-[(1-benzoylpiperidin-4-yl)carbonyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		438.4567	439.457	35
N-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		424.3863	425.386	10
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(1H-imidazol-4-yl)propanoyl]-D-alanine		345.3324	346.332	10
N-[(1,3-benzothiazol-2-ylthio)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		430.4825	431.483	31
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-methyl-2-phenyl-1,3-thiazol-4-yl)acetyl]-D-alanine		438.4811	439.481	36

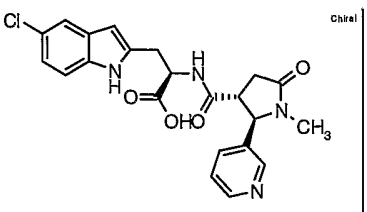
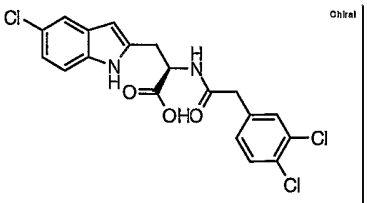
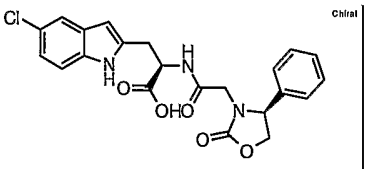
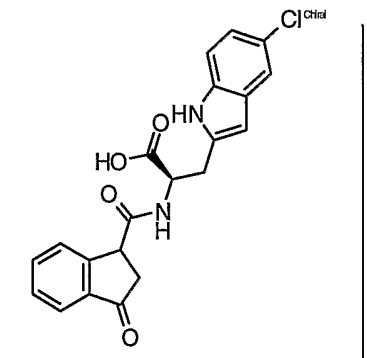
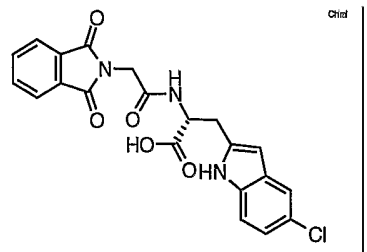
N-{[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		420.4385	421.438	24
N-[4-(dimethylamino)-4-oxobutanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		350.3481	351.348	5
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-hydroxycyclohexyl)carbonyl]-D-alanine		349.36	350.36	32
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(3-hydroxyphenyl)propanoyl]-D-alanine		371.3662	372.366	58
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(7-hydroxy-2-oxo-2H-chromen-4-yl)acetyl]-D-alanine		425.3704	426.37	12
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{2-[4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanoyl}-D-alanine		486.5007	487.501	11

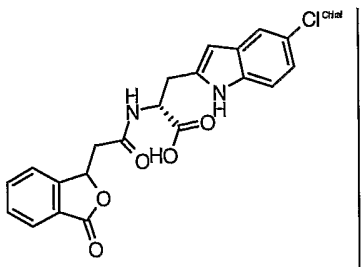
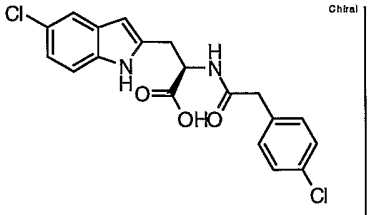
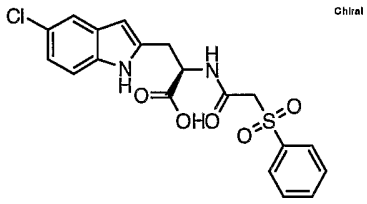
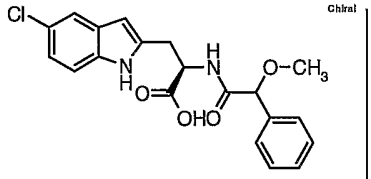
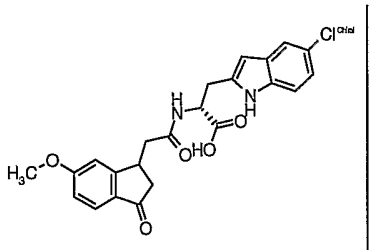
N-benzoyl-N-methylglycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		398.3921	399.392	17
4-(2-{[(1R)-1-carboxy-2-(6-fluoro-1H-benzimidazol-2-yl)ethyl]amino}-2-oxoethyl)-2-methyl-5-oxo-4,5-dihydro-1H-pyrrole-3-carboxylic acid		404.3523	405.352	34
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-oxocyclohexyl)carbonyl]-D-alanine		347.3442	348.344	17
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[4-(4-methoxyphenyl)-4-oxobutanoyl]-D-alanine		413.403	414.403	35
N-[bis(4-chlorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		486.3282	487.328	16

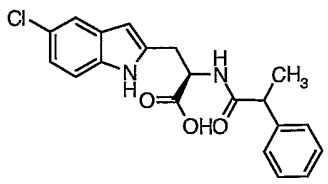
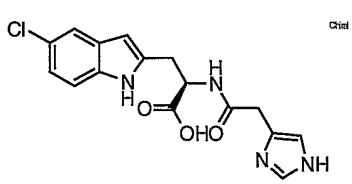
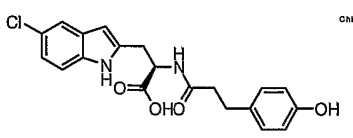
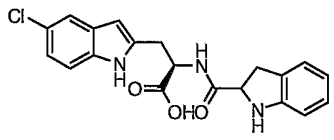
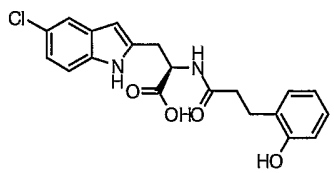
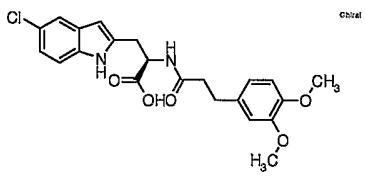
3-(5-chloro-1H-indol-2-yl)-N-(4-oxo-4-phenylbutanoyl)-D-alanine		398.8441	399.844	27
N-(biphenyl-4-ylacetyl)-3-(5-chloro-1H-indol-2-yl)-D-alanine		432.9049	433.905	46
3-(5-chloro-1H-indol-2-yl)-N-(9H-fluoren-9-ylacetyl)-D-alanine		444.9159	445.916	89
3-(5-chloro-1H-indol-2-yl)-N-[4-(1H-indol-3-yl)butanoyl]-D-alanine		423.8978	424.898	74
3-(5-chloro-1H-indol-2-yl)-N-[(1-naphthyloxy)acetyl]-D-alanine		422.8661	423.866	66

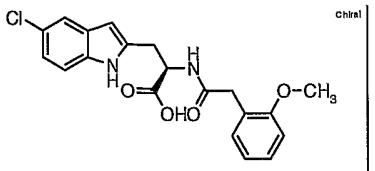
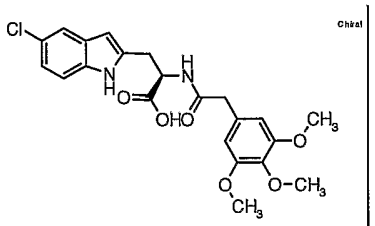
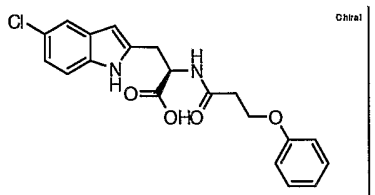
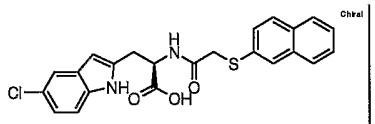
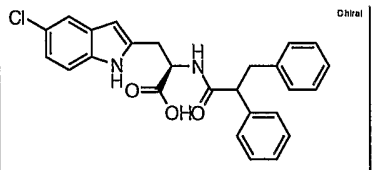
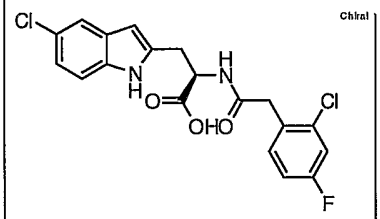
3-(5-chloro-1H-indol-2-yl)-N-(1-naphthylacetyl)-D-alanine		406.8671	407.867	56
3-(5-chloro-1H-indol-2-yl)-N-[(2-naphthyloxy)acetyl]-D-alanine		422.8661	423.866	21
3-(5-chloro-1H-indol-2-yl)-N-(phenoxyacetyl)-D-alanine		372.8063	373.806	29
3-(5-chloro-1H-indol-2-yl)-N-(2-phenoxypropanoyl)-D-alanine		386.8331	387.833	30
3-(5-chloro-1H-indol-2-yl)-N-{[(1R,2R)-2-phenylcyclopropyl]carbonyl}-D-alanine		382.8451	383.845	44
3-(5-chloro-1H-indol-2-yl)-N-[(pyridin-4-ylthio)acetyl]-D-alanine		389.8614	390.861	7

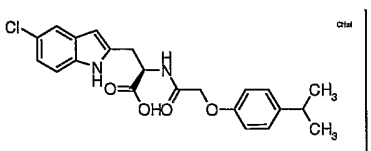
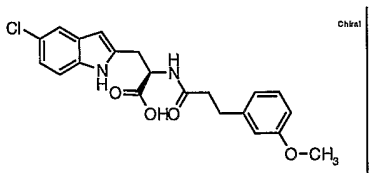
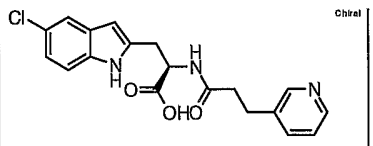
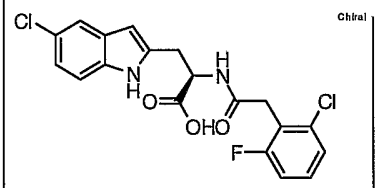
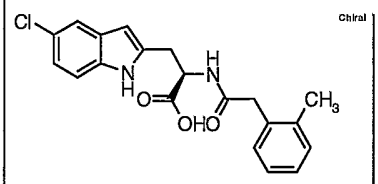
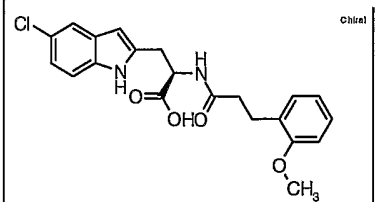
3-(5-chloro-1H-indol-2-yl)-N-[(pyrimidin-2-ylthio)acetyl]-D-alanine		390.8495	391.849	15
3-(5-chloro-1H-indol-2-yl)-N-[(phenylthio)acetyl]-D-alanine		388.8733	389.873	43
3-(5-chloro-1H-indol-2-yl)-N-(diphenylacetyl)-D-alanine		432.9049	433.905	32
3-(5-chloro-1H-indol-2-yl)-N-(3-phenylpropanoyl)-D-alanine		370.8341	371.834	45
3-(5-chloro-1H-indol-2-yl)-N-[(4-hydroxyphenyl)acetyl]-D-alanine		372.8063	373.806	29
3-(5-chloro-1H-indol-2-yl)-N-(phenylacetyl)-D-alanine		356.8073	357.807	31

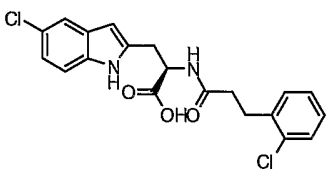
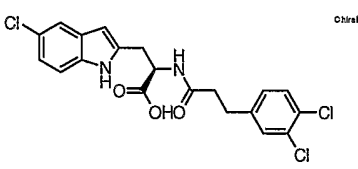
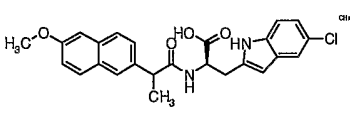
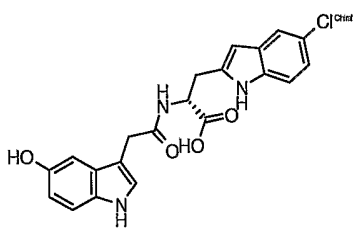
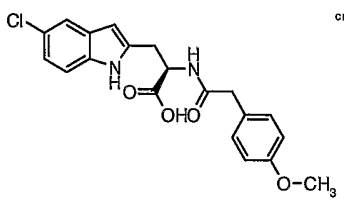
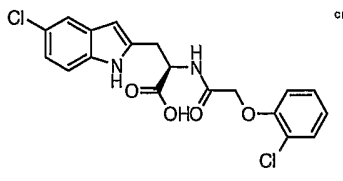
3-(5-chloro-1H-indol-2-yl)-N-{[(2R,3R)-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidin-3-yl]carbonyl}-D-alanine		440.8849	441.885	14
3-(5-chloro-1H-indol-2-yl)-N-[(3,4-dichlorophenyl)acetyl]-D-alanine		425.6975	426.697	33
3-(5-chloro-1H-indol-2-yl)-N-{[(4S)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]acetyl}-D-alanine		441.869	442.869	21
3-(5-chloro-1H-indol-2-yl)-N-[(3-oxo-2,3-dihydro-1H-inden-1-yl)carbonyl]-D-alanine		396.8283	397.828	26
3-(5-chloro-1H-indol-2-yl)-N-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyl]-D-alanine		425.8264	426.826	1

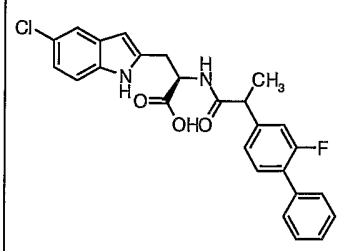
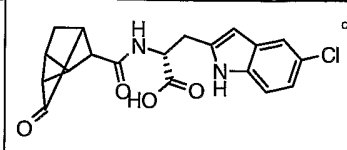
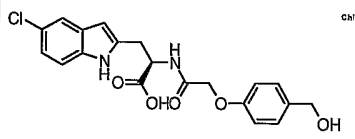
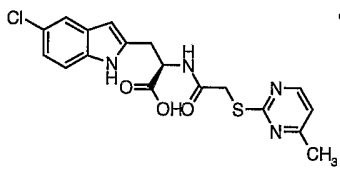
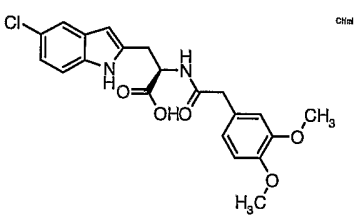
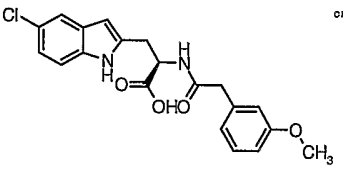
3-(5-chloro-1H-indol-2-yl)-N-[(3-oxo-1,3-dihydro-2-benzofuran-1-yl)acetyl]-D-alanine		412.8273	413.827	17
3-(5-chloro-1H-indol-2-yl)-N-[(4-chlorophenyl)acetyl]-D-alanine		391.2524	392.252	17
3-(5-chloro-1H-indol-2-yl)-N-[(phenylsulfonyl)acetyl]-D-alanine		420.8713	421.871	17
3-(5-chloro-1H-indol-2-yl)-N-[methoxy(phenyl)acetyl]-D-alanine		386.8331	387.833	38
3-(5-chloro-1H-indol-2-yl)-N-[(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetyl]-D-alanine		440.8809	441.881	77

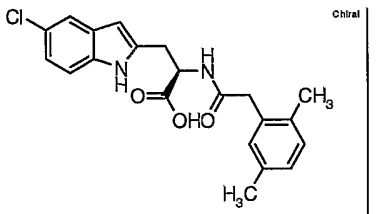
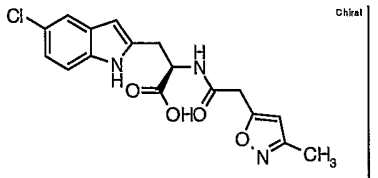
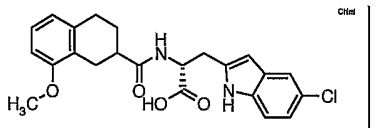
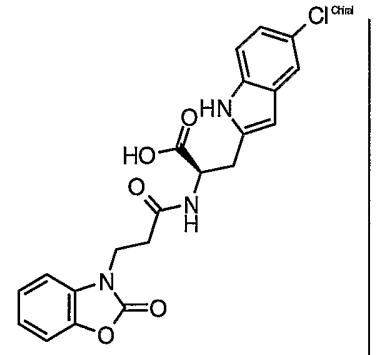
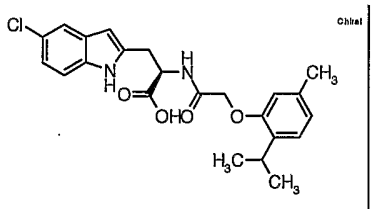
3-(5-chloro-1H-indol-2-yl)-N-(2-phenylpropanoyl)-D-alanine		370.8341	371.834	36
3-(5-chloro-1H-indol-2-yl)-N-(1H-imidazol-4-ylacetyl)-D-alanine		346.7725	347.772	10
3-(5-chloro-1H-indol-2-yl)-N-[3-(4-hydroxyphenyl)propanoyl]-D-alanine		386.8331	387.833	48
3-(5-chloro-1H-indol-2-yl)-N-(2,3-dihydro-1H-indol-2-ylcarbonyl)-D-alanine		383.8332	384.833	30
3-(5-chloro-1H-indol-2-yl)-N-[3-(2-hydroxyphenyl)propanoyl]-D-alanine		386.8331	387.833	45
3-(5-chloro-1H-indol-2-yl)-N-[3-(3,4-dimethoxyphenyl)propanoyl]-D-alanine		430.8857	431.886	29

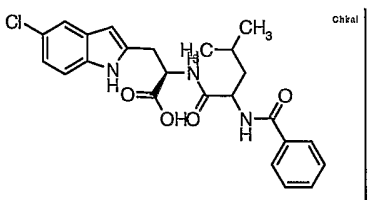
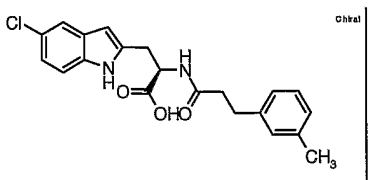
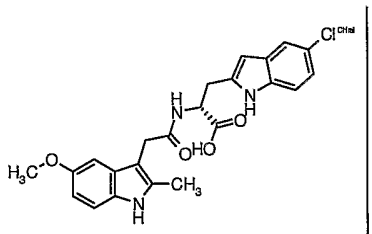
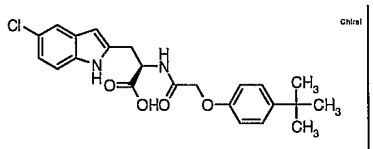
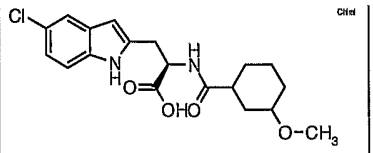
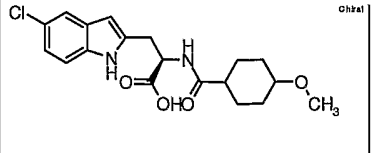
3-(5-chloro-1H-indol-2-yl)-N-[(2-methoxyphenyl)acetyl]-D-alanine		386.8331	387.833	25
3-(5-chloro-1H-indol-2-yl)-N-[(3,4,5-trimethoxyphenyl)acetyl]-D-alanine		446.8847	447.885	6
3-(5-chloro-1H-indol-2-yl)-N-(3-phenoxypropanoyl)-D-alanine		386.8331	387.833	13
3-(5-chloro-1H-indol-2-yl)-N-[(2-naphthylthio)acetyl]-D-alanine		438.9331	439.933	50
3-(5-chloro-1H-indol-2-yl)-N-(2,3-diphenylpropanoyl)-D-alanine		446.9317	447.932	56
N-[(2-chloro-4-fluorophenyl)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		409.2425	410.243	43

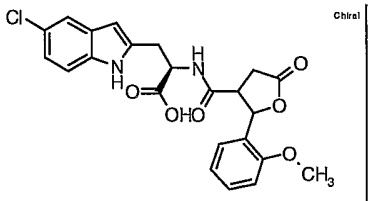
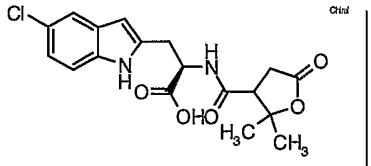
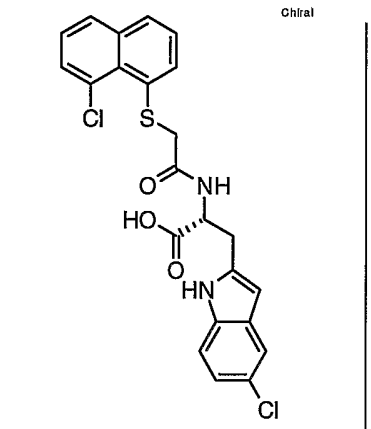
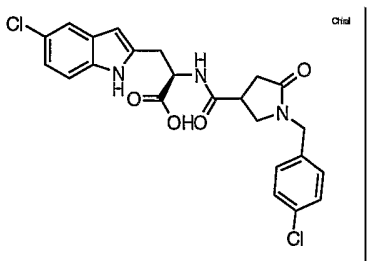
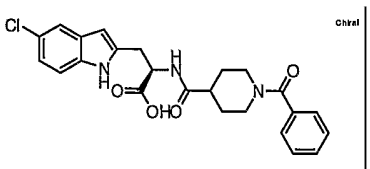
3-(5-chloro-1H-indol-2-yl)-N-[(4-isopropylphenoxy)acetyl]-D-alanine		414.8867	415.887	25
3-(5-chloro-1H-indol-2-yl)-N-[3-(3-methoxyphenyl)propanoyl]-D-alanine		400.8599	401.86	68
3-(5-chloro-1H-indol-2-yl)-N-(3-pyridin-3-ylpropanoyl)-D-alanine		371.8222	372.822	46
N-[(2-chloro-6-fluorophenyl)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		409.2425	410.243	35
3-(5-chloro-1H-indol-2-yl)-N-[(2-methylphenyl)acetyl]-D-alanine		370.8341	371.834	23
3-(5-chloro-1H-indol-2-yl)-N-[3-(2-methoxyphenyl)propanoyl]-D-alanine		400.8599	401.86	46

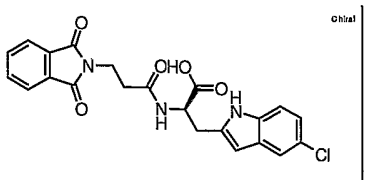
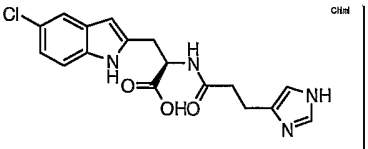
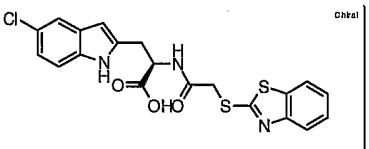
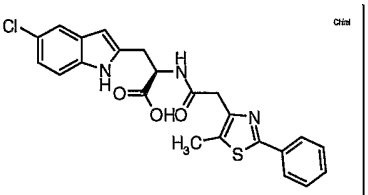
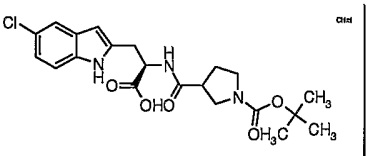
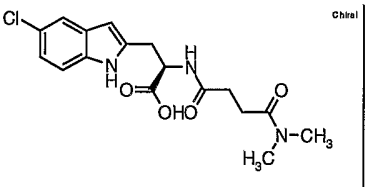
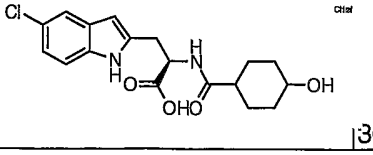
3-(5-chloro-1H-indol-2-yl)-N-[3-(2-chlorophenyl)propanoyl]-D-alanine		405.2792	406.279	50
3-(5-chloro-1H-indol-2-yl)-N-[3-(3,4-dichlorophenyl)propanoyl]-D-alanine		439.7243	440.724	43
3-(5-chloro-1H-indol-2-yl)-N-[2-(6-methoxy-2-naphthyl)propanoyl]-D-alanine		450.9197	451.92	12
3-(5-chloro-1H-indol-2-yl)-N-[(5-hydroxy-1H-indol-3-yl)acetyl]-D-alanine		411.8432	412.843	24
3-(5-chloro-1H-indol-2-yl)-N-[(4-methoxyphenyl)acetyl]-D-alanine		386.8331	387.833	54
3-(5-chloro-1H-indol-2-yl)-N-[(2-chlorophenoxy)acetyl]-D-alanine		407.2514	408.251	54

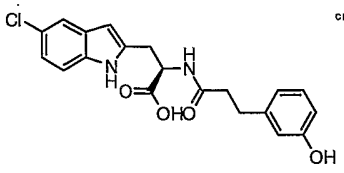
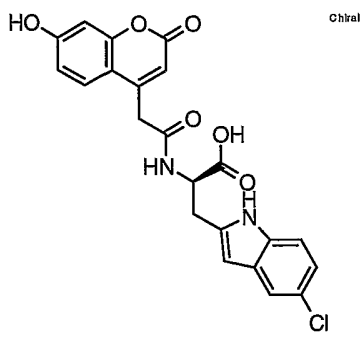
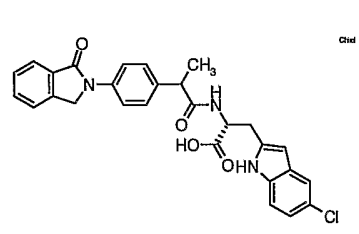
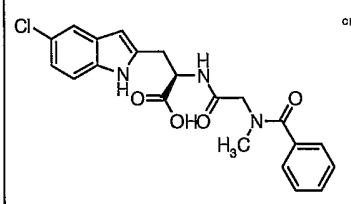
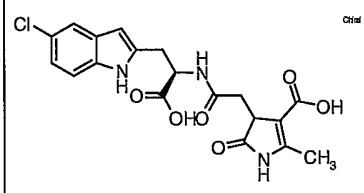
3-(5-chloro-1H-indol-2-yl)-N-[2-(2-fluorobiphenyl-4-yl)propanoyl]-D-alanine		464.9218	465.922	31
3-(5-chloro-1H-indol-2-yl)-N-[(5-oxotricyclo[2.2.1.0~2,6~]hept-3-yl)carbonyl]-D-alanine		372.8063	373.806	48
3-(5-chloro-1H-indol-2-yl)-N-{[4-(hydroxymethyl)phenoxy]acetyl}-D-alanine		402.8321	403.832	21
3-(5-chloro-1H-indol-2-yl)-N-{[(4-methylpyrimidin-2-yl)thio]acetyl}-D-alanine		404.8763	405.876	0
3-(5-chloro-1H-indol-2-yl)-N-[(3,4-dimethoxyphenyl)acetyl]-D-alanine		416.8589	417.859	7
3-(5-chloro-1H-indol-2-yl)-N-[(3-methoxyphenyl)acetyl]-D-alanine		386.8331	387.833	34

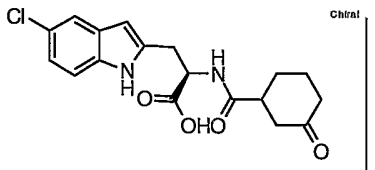
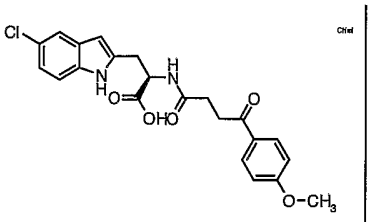
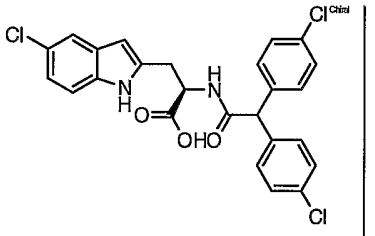
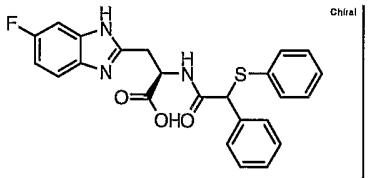
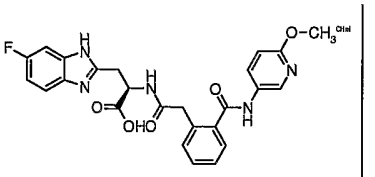
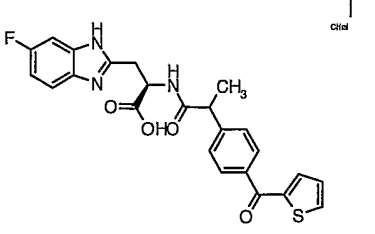
3-(5-chloro-1H-indol-2-yl)-N-[(2,5-dimethylphenyl)acetyl]-D-alanine		384.8609	385.861	41
3-(5-chloro-1H-indol-2-yl)-N-[(3-methylisoxazol-5-yl)acetyl]-D-alanine		361.7834	362.783	15
3-(5-chloro-1H-indol-2-yl)-N-[(8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)carbonyl]-D-alanine		426.8977	427.898	58
3-(5-chloro-1H-indol-2-yl)-N-[3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanoyl]-D-alanine		427.8422	428.842	41
3-(5-chloro-1H-indol-2-yl)-N-[(2-isopropyl-5-methylphenoxy)acetyl]-D-alanine		428.9135	429.914	58

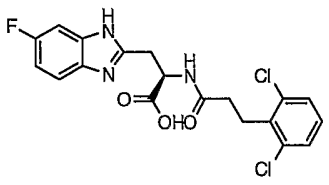
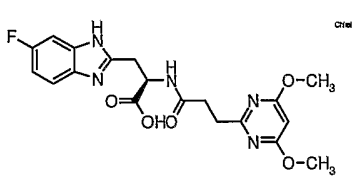
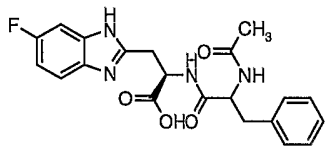
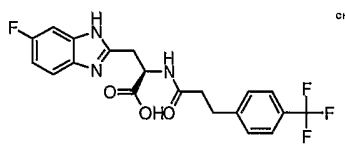
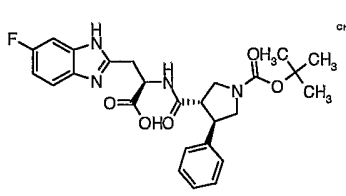
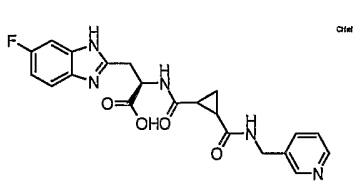
N-benzoylleucyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		455.9394	456.939	16
3-(5-chloro-1H-indol-2-yl)-N-[3-(3-methylphenyl)propanoyl]-D-alanine		384.8609	385.861	61
3-(5-chloro-1H-indol-2-yl)-N-[(5-methoxy-2-methyl-1H-indol-3-yl)acetyl]-D-alanine		439.8968	440.897	22
N-[(4-tert-butylphenoxy)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		428.9135	429.914	15
3-(5-chloro-1H-indol-2-yl)-N-[(3-methoxycyclohexyl)carbonyl]-D-alanine		378.8537	379.854	21
3-(5-chloro-1H-indol-2-yl)-N-[(4-methoxycyclohexyl)carbonyl]-D-alanine		378.8537	379.854	20

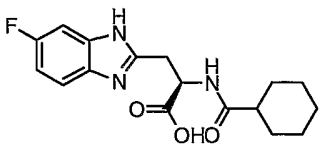
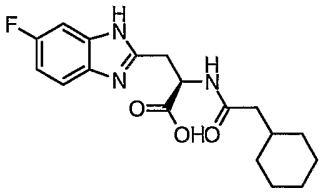
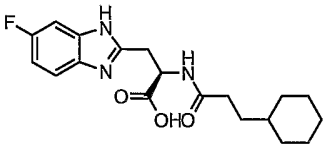
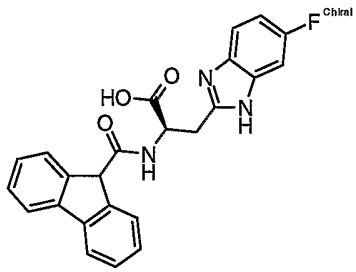
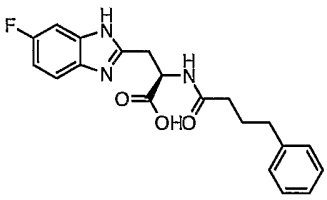
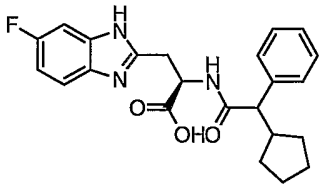
3-(5-chloro-1H-indol-2-yl)-N-{[2-(2-methoxyphenyl)-5-oxotetrahydrofuran-3-yl]carbonyl}-D-alanine		456.8799	457.88	40
3-(5-chloro-1H-indol-2-yl)-N-[(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)carbonyl]-D-alanine		378.8101	379.81	20
3-(5-chloro-1H-indol-2-yl)-N-{[(8-chloro-1-naphthyl)thio]acetyl}-D-alanine		473.3782	474.378	42
N-{[1-(4-chlorobenzyl)-5-oxopyrrolidin-3-yl]carbonyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		474.3419	475.342	40
N-[(1-benzoylpiperidin-4-yl)carbonyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		453.9236	454.924	41

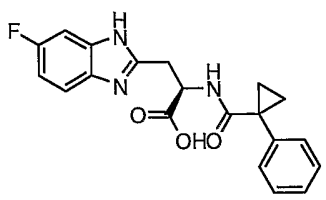
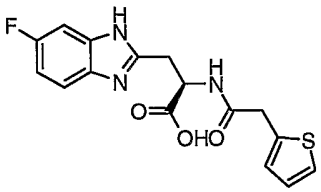
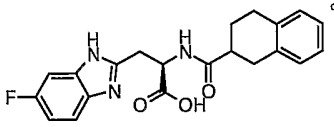
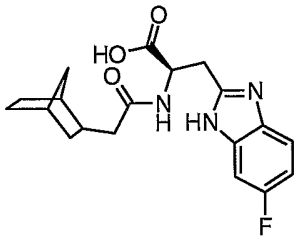
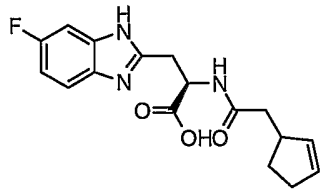
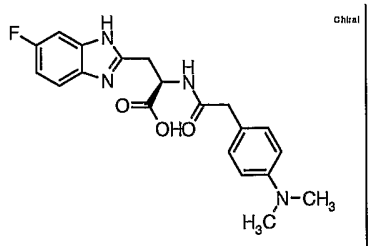
3-(5-chloro-1H-indol-2-yl)-N-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoyl]-D-alanine		439.8532	440.853	12
3-(5-chloro-1H-indol-2-yl)-N-[3-(1H-imidazol-4-yl)propanoyl]-D-alanine		360.7993	361.799	8
N-[(1,3-benzothiazol-2-ylthio)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		445.9494	446.949	16
3-(5-chloro-1H-indol-2-yl)-N-[(5-methyl-2-phenyl-1,3-thiazol-4-yl)acetyl]-D-alanine		453.948	454.948	31
N-{[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]carbonyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		435.9054	436.905	32
3-(5-chloro-1H-indol-2-yl)-N-[4-(dimethylamino)-4-oxobutanoyl]-D-alanine		365.815	366.815	14
3-(5-chloro-1H-indol-2-yl)-N-[(4-hydroxycyclohexyl)carbonyl]-D-alanine		364.8269	365.827	33

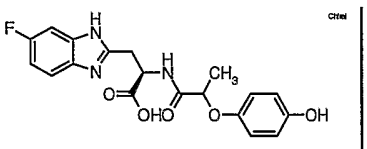
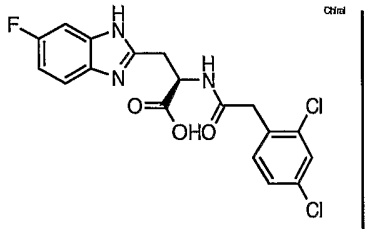
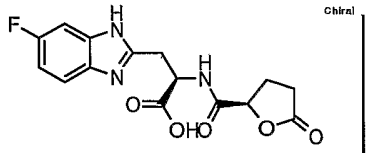
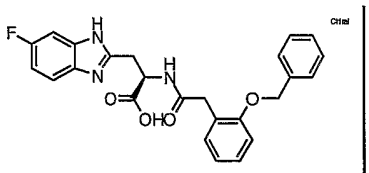
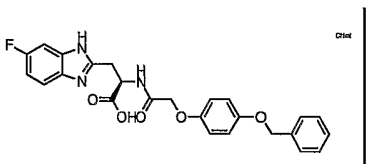
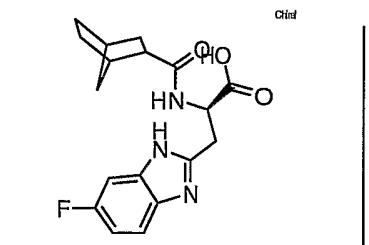
3-(5-chloro-1H-indol-2-yl)-N-[3-(3-hydroxyphenyl)propanoyl]-D-alanine		386.8331	387.833	53
3-(5-chloro-1H-indol-2-yl)-N-[(7-hydroxy-2-oxo-2H-chromen-4-yl)acetyl]-D-alanine		440.8373	441.837	30
3-(5-chloro-1H-indol-2-yl)-N-{2-[4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanoyl}-D-alanine		501.9676	502.968	17
N-benzoyl-N-methylglycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		413.859	414.859	12
4-(2-{[(1R)-1-carboxy-2-(5-chloro-1H-indol-2-yl)ethyl]amino}-2-oxoethyl)-2-methyl-5-oxo-4,5-dihydro-1H-pyrrole-3-carboxylic acid		419.8192	420.819	33

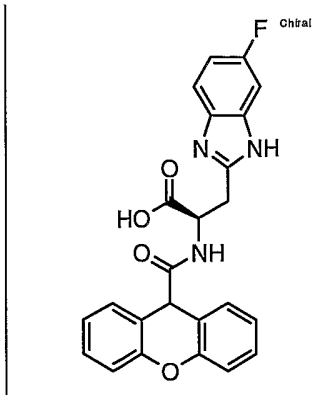
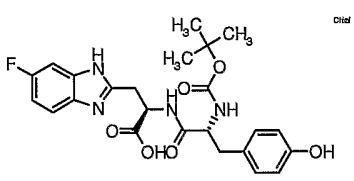
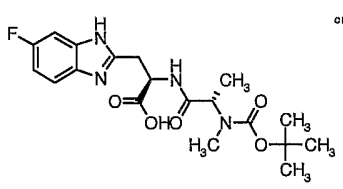
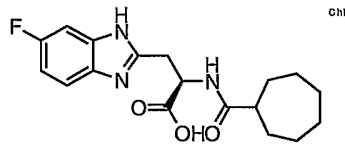
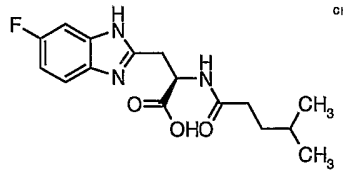
3-(5-chloro-1H-indol-2-yl)-N-[(3-oxocyclohexyl)carbonyl]-D-alanine		362.8111	363.811	15
3-(5-chloro-1H-indol-2-yl)-N-[4-(4-methoxyphenyl)-4-oxobutanoyl]-D-alanine		428.8699	429.87	38
N-[bis(4-chlorophenyl)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		501.7951	502.795	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[phenyl(phenylthio)acetyl]-D-alanine		449.504	450.504	52
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-{[(6-methoxypyridin-3-yl)amino]carbonyl}phenyl)acetyl]-D-alanine		491.4768	492.477	11
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{2-[4-(2-thienylcarbonyl)phenyl]propanoyl}-D-alanine		465.503	466.503	12

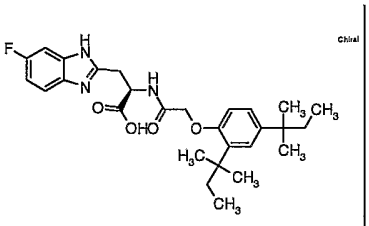
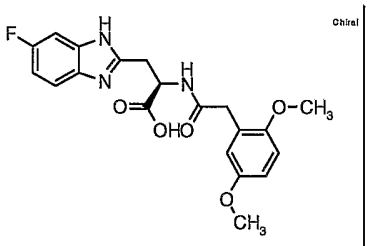
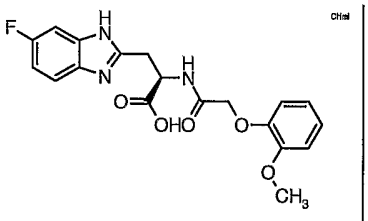
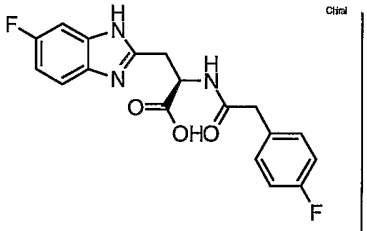
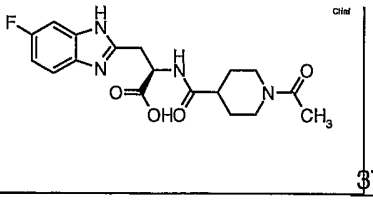
N-[3-(2,6-dichlorophenyl)propanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		424.2574	425.257	35
N-[3-(4,6-dimethoxypyrimidin-2-yl)propanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		417.395	418.395	29
N-acetylphenylalanyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		412.4189	413.419	45
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{3-[4-(trifluoromethyl)phenyl]propanoyl}-D-alanine		423.3643	424.364	13
N-{[(3S,4R)-1-(tert-butoxycarbonyl)-4-phenylpyrrolidin-3-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		496.5361	497.536	14
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-{[(pyridin-3-ylmethyl)amino]carbonyl}cyclopropyl)carbonyl]-D-alanine		425.418	426.418	15

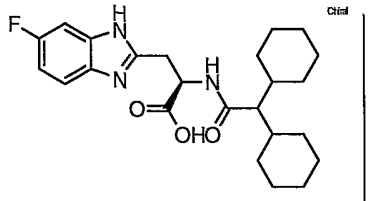
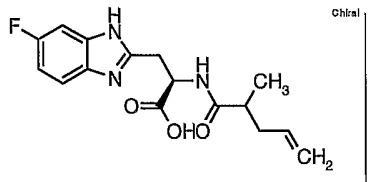
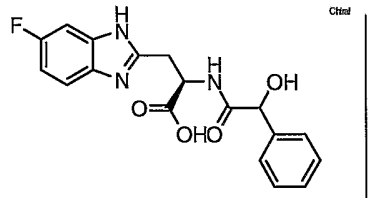
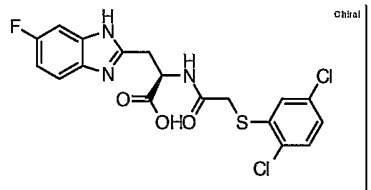
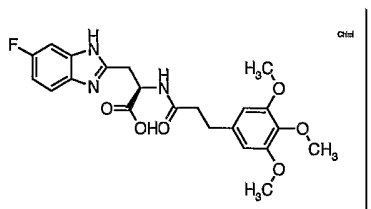
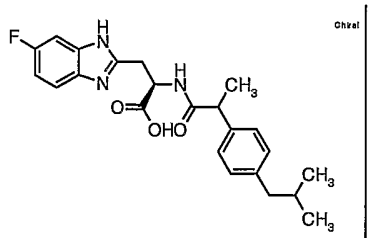
N-(cyclohexylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		333.361	334.361	37
N-(cyclohexylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		347.3878	348.388	43
N-(3-cyclohexylpropanoyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		361.4146	362.415	33
N-(9H-fluoren-9-ylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		415.4222	416.422	12
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(4-phenylbutanoyl)-D-alanine		369.394	370.394	37
N-[cyclopentyl(phenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		409.4586	410.459	40

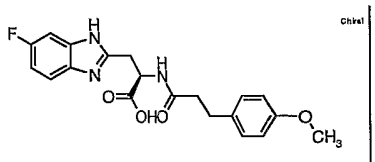
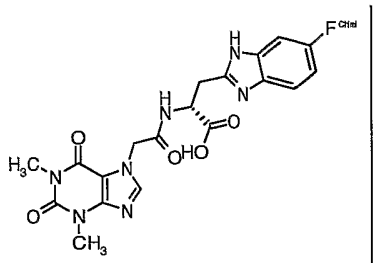
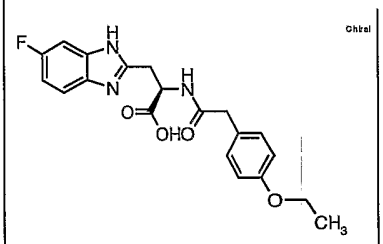
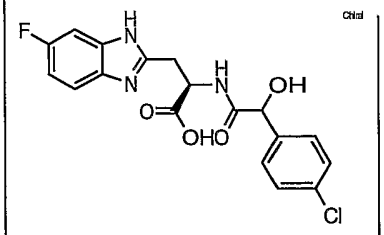
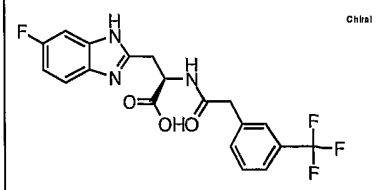
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(1-phenylcyclopropyl)carbonyl]-D-alanine		367.3782	368.378	17
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-thienylacetyl)-D-alanine		347.3686	348.369	22
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(1,2,3,4-tetrahydronaphthalen-2-ylcarbonyl)-D-alanine		381.405	382.405	57
N-(bicyclo[2.2.1]hept-2-ylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		359.3988	360.399	53
N-(cyclopent-2-en-1-ylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		331.3452	332.345	42
N-{[4-(dimethylamino)phenyl]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		384.4089	385.409	8

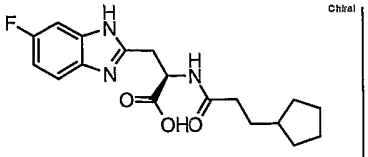
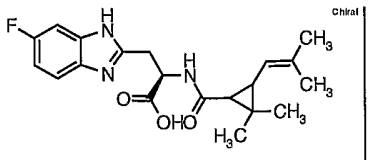
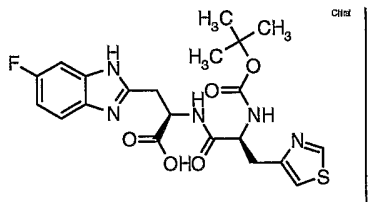
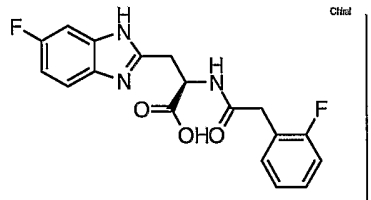
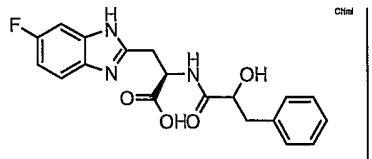
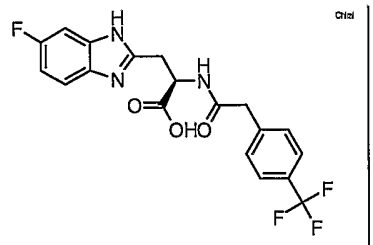
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(4-hydroxyphenoxy)propanoyl]-D-alanine		387.3652	388.365	3
N-[(2,4-dichlorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		410.2306	411.231	25
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(2R)-5-oxotetrahydrofuran-2-yl]carbonyl}-D-alanine		335.2896	336.29	0
N-{[2-(benzyloxy)phenyl]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		447.4638	448.464	55
N-{[4-(benzyloxy)phenoxy]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		463.4628	464.463	6
N-(bicyclo[2.2.1]hept-2-ylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		345.372	346.372	68

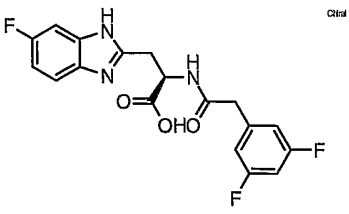
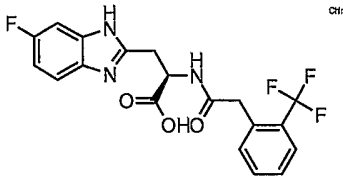
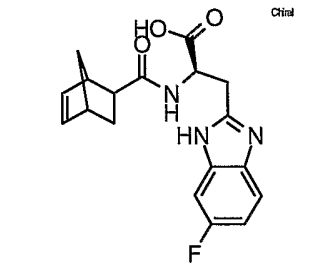
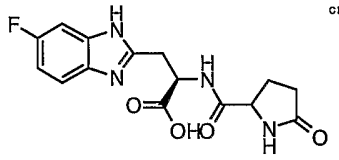
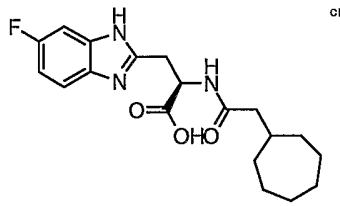
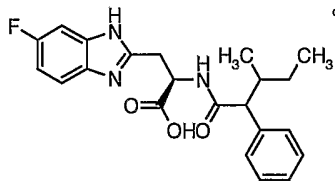
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(9H-xanthen-9-ylcarbonyl)-D-alanine		431.4212	432.421	14
N-(tert-butoxycarbonyl)-D-tyrosyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		486.4973	487.497	28
N-(tert-butoxycarbonyl)-N-methyl-L-alanyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		408.4275	409.428	23
N-(cycloheptylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		347.3878	348.388	50
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(4-methylpentanoyl)-D-alanine		321.35	322.35	30

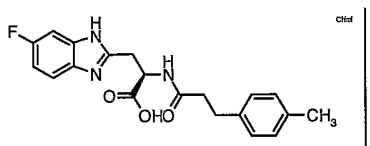
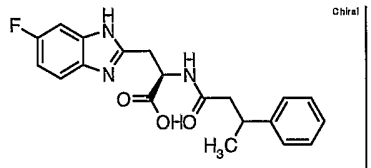
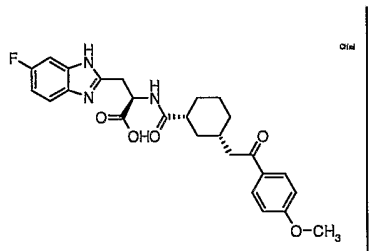
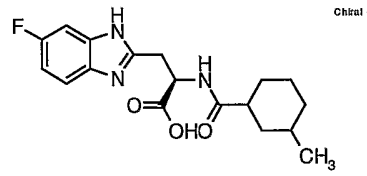
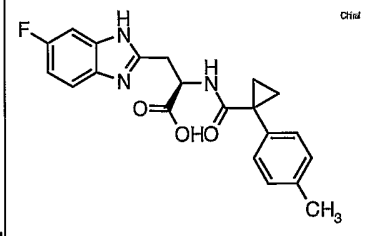
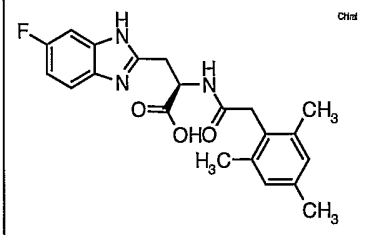
N-{[2,4-bis(1,1-dimethylpropyl)phenoxy]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		497.6074	498.607	47
N-[(2,5-dimethoxyphenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		401.392	402.392	8
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-methoxyphenoxy)acetyl]-D-alanine		387.3652	388.365	63
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-fluorophenyl)acetyl]-D-alanine		359.3305	360.33	19
N-[(1-acetylpiperidin-4-yl)carbonyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		376.3859	377.386	15

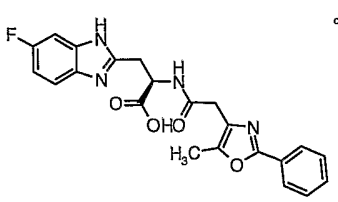
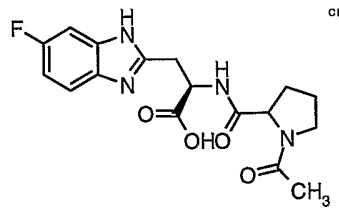
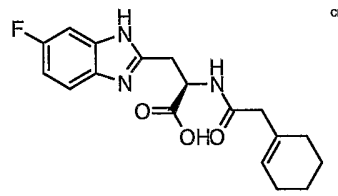
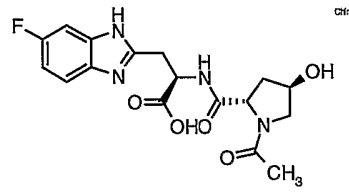
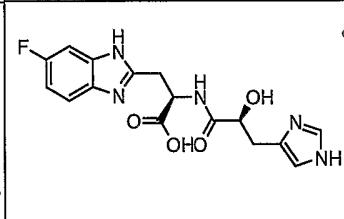
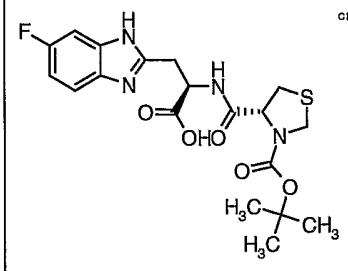
N-(dicyclohexylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		429.5328	430.533	13
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-methylpent-4-enoyl)-D-alanine		319.3342	320.334	40
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[hydroxy(phenyl)acetyl]-D-alanine		357.3394	358.339	30
N-{[(2,5-dichlorophenyl)thio]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		442.2966	443.297	28
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(3,4,5-trimethoxyphenyl)propanoyl]-D-alanine		445.4446	446.445	55
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[2-(4-isobutylphenyl)propanoyl]-D-alanine		411.4744	412.474	10

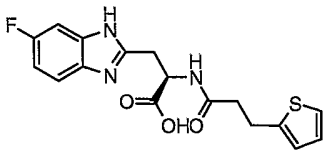
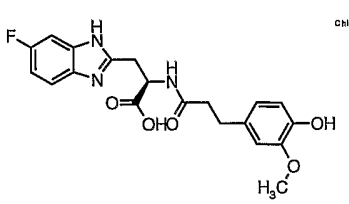
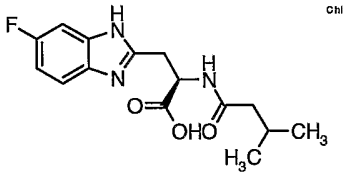
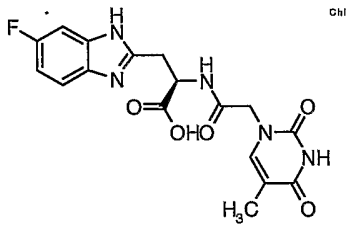
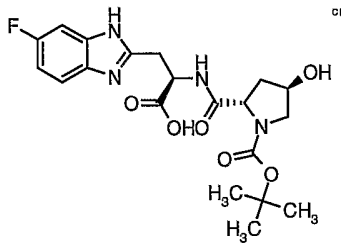
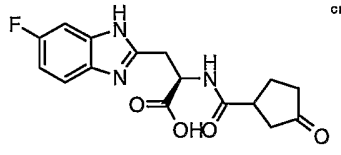
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(4-methoxyphenyl)propanoyl]-D-alanine		385.393	386.393	25
N-[(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		443.3932	444.393	0
N-[(4-ethoxyphenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		385.393	386.393	1
N-[(4-chlorophenyl)(hydroxy)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		391.7845	392.784	39
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[3-(trifluoromethyl)phenyl]acetyl}-D-alanine		409.3375	410.337	27

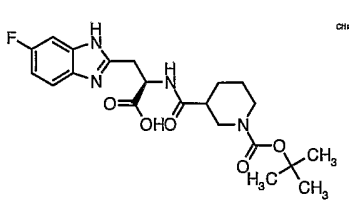
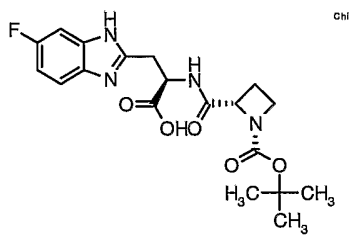
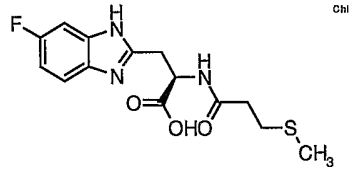
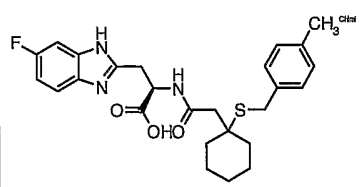
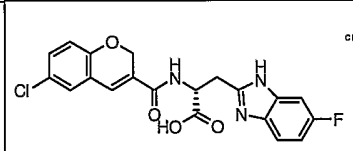
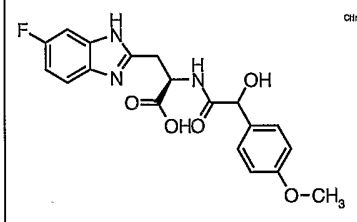
N-(3-cyclopentylpropanoyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		347.3878	348.388	22
N-{[2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		373.4256	374.426	48
N-(tert-butoxycarbonyl)-3-(1,3-thiazol-4-yl)-L-alanyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		477.5146	478.515	42
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-fluorophenyl)acetyl]-D-alanine		359.3305	360.33	36
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(2-hydroxy-3-phenylpropanoyl)-D-alanine		371.3662	372.366	0
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[4-(trifluoromethyl)phenyl]acetyl}-D-alanine		409.3375	410.337	5

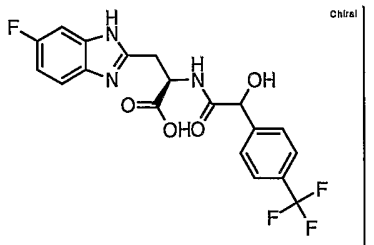
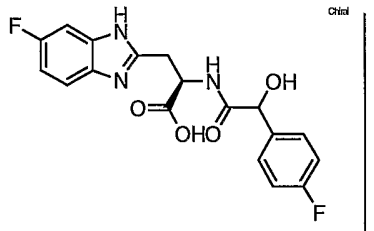
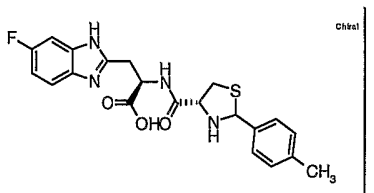
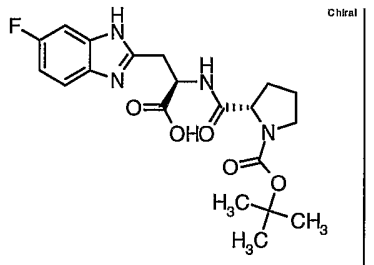
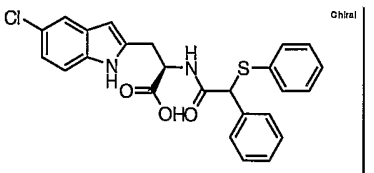
N-[(3,5-difluorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		377.3206	378.321	13
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[2-(trifluoromethyl)phenyl]acetyl}-D-alanine		409.3375	410.337	42
N-(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		343.3562	344.356	39
5-oxoprolyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		334.3055	335.305	3
N-(cycloheptylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		361.4146	362.415	56
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-methyl-2-phenylpentanoyl)-D-alanine		397.4476	398.448	28

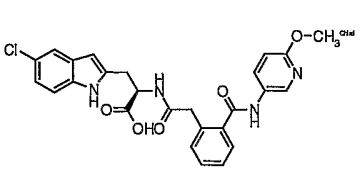
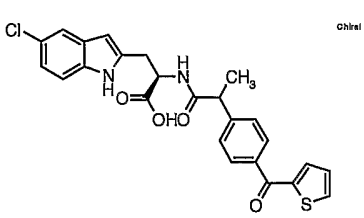
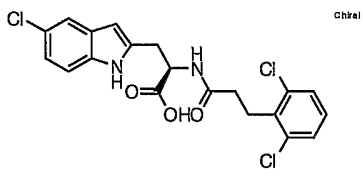
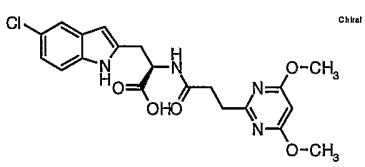
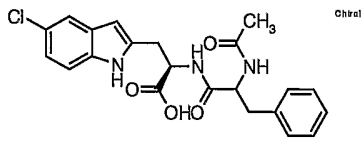
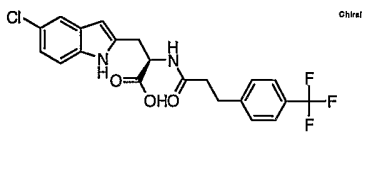
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(4-methylphenyl)propanoyl]-D-alanine		369.394	370.394	23
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-phenylbutanoyl)-D-alanine		369.394	370.394	55
3-(6-fluoro-1H-benzimidazol-2-yl)-N-({(1R,3S)-3-[2-(4-methoxyphenyl)-2-oxoethyl]cyclohexyl}carbonyl)-D-alanine		481.5212	482.521	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-methylcyclohexyl)carbonyl]-D-alanine		347.3878	348.388	47
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[1-(4-methylphenyl)cyclopropyl]carbonyl}-D-alanine		381.405	382.405	33
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(mesitylacetyl)-D-alanine		383.4208	384.421	22

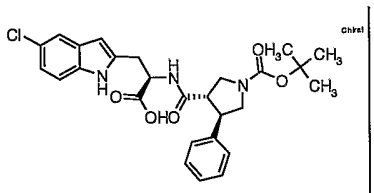
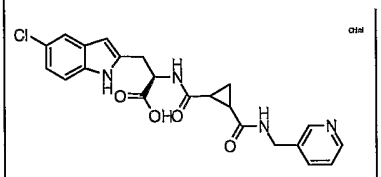
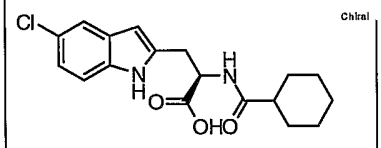
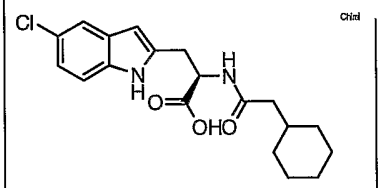
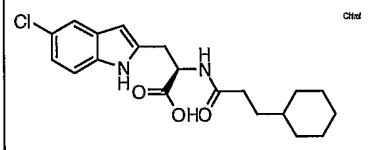
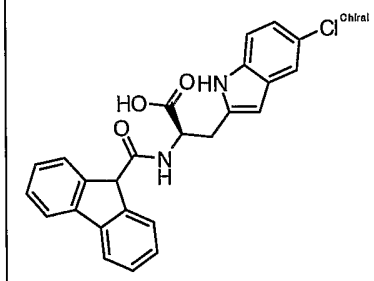
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetyl]-D-alanine		422.4141	423.414	30
1-acetylprolyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		362.3591	363.359	15
N-(cyclohex-1-en-1-ylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		345.372	346.372	21
(4R)-1-acetyl-4-hydroxy-L-prolyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		378.3581	379.358	20
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2S)-2-hydroxy-3-(1H-imidazol-4-yl)propanoyl]-D-alanine		361.3314	362.331	2
N-{[(4R)-3-(tert-butoxycarbonyl)-1,3-thiazolidin-4-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		438.4777	439.478	36

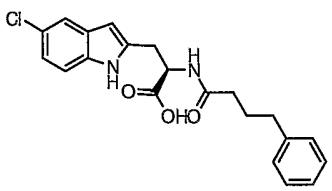
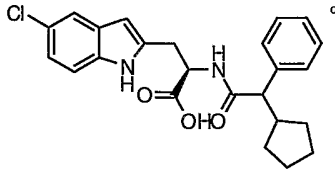
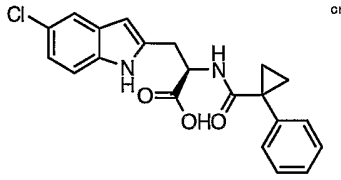
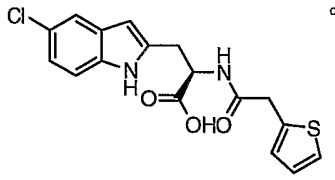
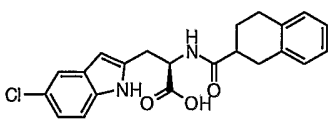
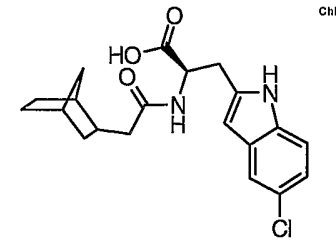
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(2-thienyl)propanoyl]-D-alanine		361.3954	362.395	51
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(4-hydroxy-3-methoxyphenyl)propanoyl]-D-alanine		401.392	402.392	33
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-methylbutanoyl)-D-alanine		307.3232	308.323	29
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetyl]-D-alanine		389.3414	390.341	1
(4R)-1-(tert-butoxycarbonyl)-4-hydroxy-L-prolyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		436.4375	437.438	21
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-oxocyclopentyl)carbonyl]-D-alanine		333.3174	334.317	35

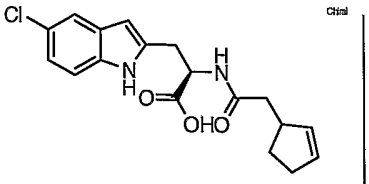
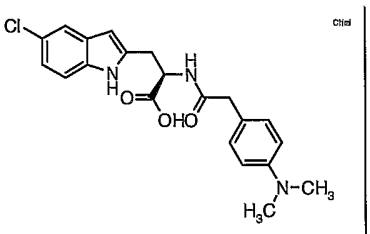
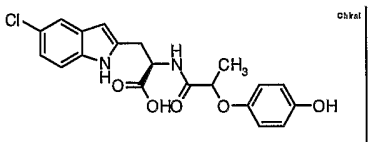
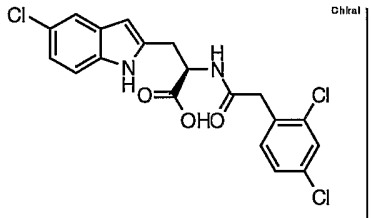
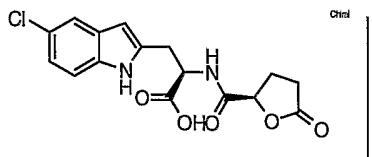
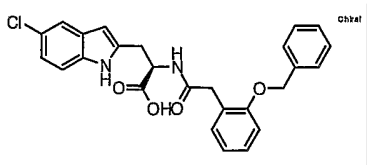
N-{[1-(tert-butoxycarbonyl)piperidin-3-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		434.4653	435.465	27
(2R)-2-({[(2S)-1-(tert-butoxycarbonyl)azetidin-2-yl]carbonyl}amino)-3-(6-fluoro-1H-benzimidazol-2-yl)propanoic acid		406.4117	407.412	26
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(methylthio)propanoyl]-D-alanine		325.3624	326.362	41
3-(6-fluoro-1H-benzimidazol-2-yl)-N-({1-[(4-methylbenzyl)thio]cyclohexyl}acetyl)-D-alanine		483.605	484.605	78
N-[(6-chloro-2H-chromen-3-yl)carbonyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		415.8065	416.807	68
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[hydroxy(4-methoxyphenyl)acetyl]-D-alanine		387.3652	388.365	14

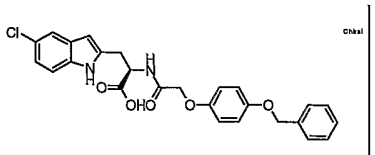
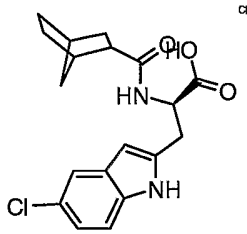
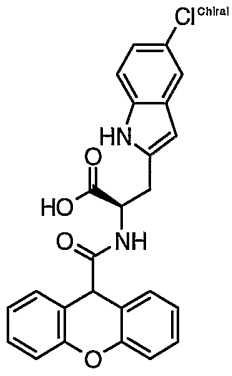
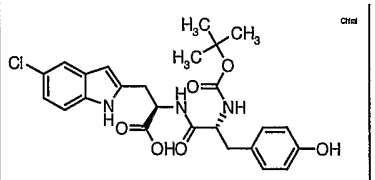
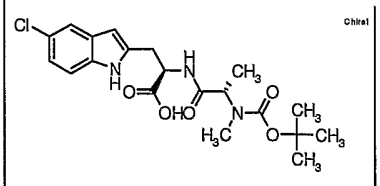
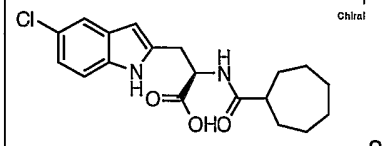
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{hydroxy[4-(trifluoromethyl)phenyl]acetyl}-D-alanine		425.3365	426.337	2
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-fluorophenyl)(hydroxy)acetyl]-D-alanine		375.3295	376.33	39
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(4R)-2-(4-methylphenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		428.4859	429.486	31
1-(tert-butoxycarbonyl)-L-prolyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		420.4385	421.438	38
3-(5-chloro-1H-indol-2-yl)-N-[phenyl(phenylthio)acetyl]-D-alanine		464.9709	465.971	36

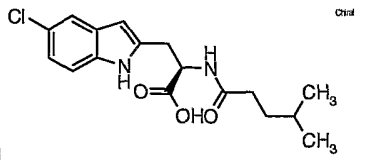
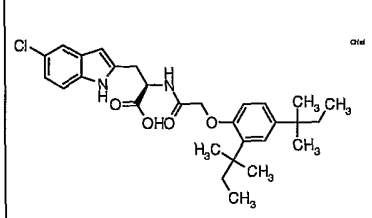
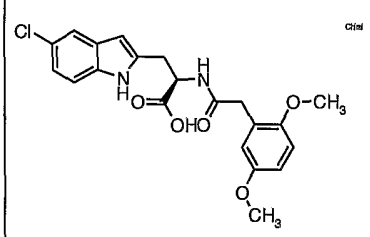
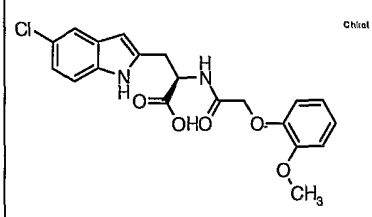
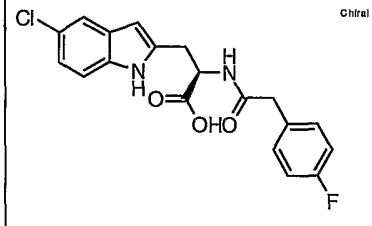
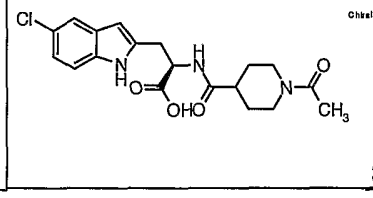
3-(5-chloro-1H-indol-2-yl)-N-[(2-{[(6-methoxypyridin-3-yl)amino]carbonyl}phenyl)acetyl]-D-alanine		506.9437	507.944	27
3-(5-chloro-1H-indol-2-yl)-N-{2-[4-(2-thienylcarbonyl)phenyl]propanoyl}-D-alanine		480.9699	481.97	28
3-(5-chloro-1H-indol-2-yl)-N-[3-(2,6-dichlorophenyl)propanoyl]-D-alanine		439.7243	440.724	65
3-(5-chloro-1H-indol-2-yl)-N-[3-(4,6-dimethoxypyrimidin-2-yl)propanoyl]-D-alanine		432.8619	433.862	14
N-acetylphenylalanyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		427.8858	428.886	33
3-(5-chloro-1H-indol-2-yl)-N-{3-[4-(trifluoromethyl)phenyl]propanoyl}-D-alanine		438.8312	439.831	33

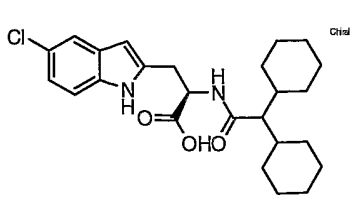
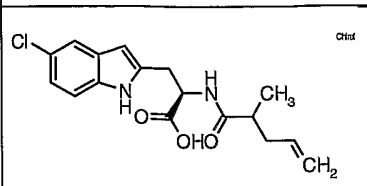
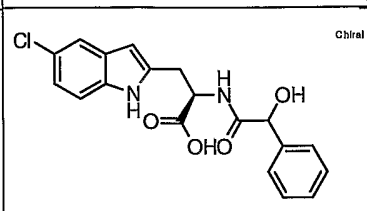
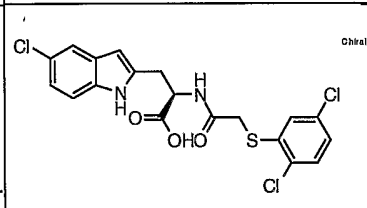
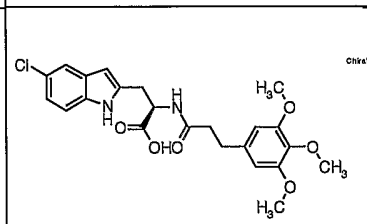
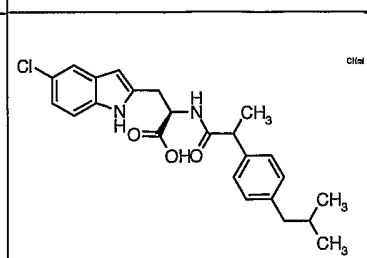
N-{[(3S,4R)-1-(tert-butoxycarbonyl)-4-phenylpyrrolidin-3-yl]carbonyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		512.003	513.003	37
3-(5-chloro-1H-indol-2-yl)-N-[(2-{[(pyridin-3-ylmethyl)amino]carbonyl}cyclopropyl)carbonyl]-D-alanine		440.8849	441.885	12
3-(5-chloro-1H-indol-2-yl)-N-(cyclohexylcarbonyl)-D-alanine		348.8279	349.828	16
3-(5-chloro-1H-indol-2-yl)-N-(cyclohexylacetyl)-D-alanine		362.8547	363.855	59
3-(5-chloro-1H-indol-2-yl)-N-(3-cyclohexylpropanoyl)-D-alanine		376.8815	377.882	37
3-(5-chloro-1H-indol-2-yl)-N-(9H-fluoren-9-ylcarbonyl)-D-alanine		430.8891	431.889	27

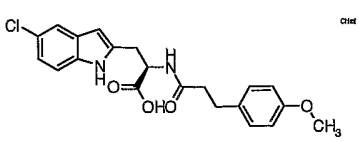
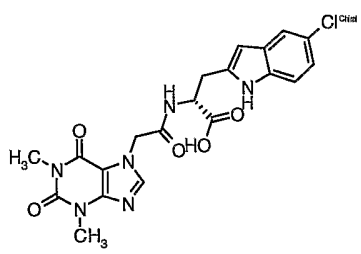
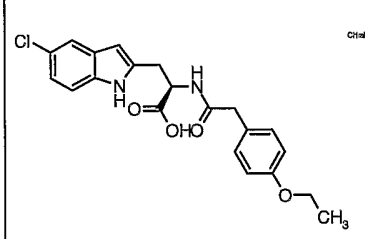
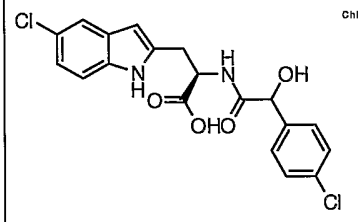
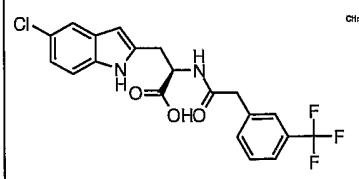
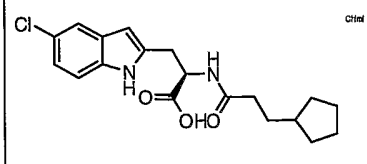
3-(5-chloro-1H-indol-2-yl)-N-(4-phenylbutanoyl)-D-alanine		384.8609	385.861	31
3-(5-chloro-1H-indol-2-yl)-N-[cyclopentyl(phenyl)acetyl]-D-alanine		424.9255	425.926	65
3-(5-chloro-1H-indol-2-yl)-N-[(1-phenylcyclopropyl)carbonyl]-D-alanine		382.8451	383.845	25
3-(5-chloro-1H-indol-2-yl)-N-(2-thienylacetyl)-D-alanine		362.8355	363.836	23
3-(5-chloro-1H-indol-2-yl)-N-(1,2,3,4-tetrahydronaphthalen-2-ylcarbonyl)-D-alanine		396.8719	397.872	64
N-(bicyclo[2.2.1]hept-2-ylacetyl)-3-(5-chloro-1H-indol-2-yl)-D-alanine		374.8657	375.866	33

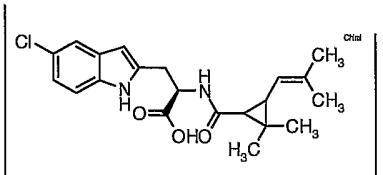
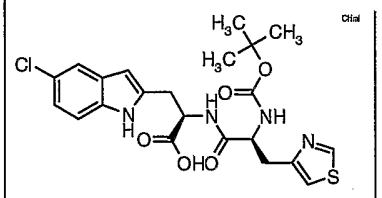
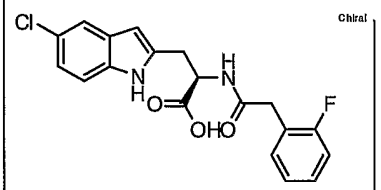
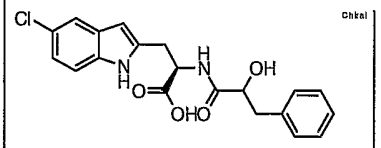
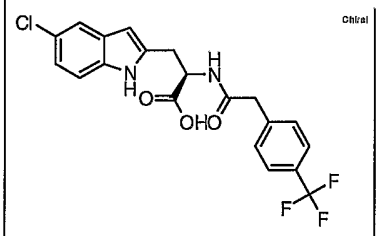
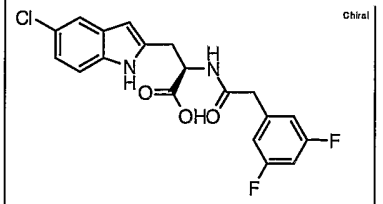
3-(5-chloro-1H-indol-2-yl)-N-(cyclopent-2-en-1-ylacetyl)-D-alanine		346.8121	347.812	46
3-(5-chloro-1H-indol-2-yl)-N-{[4-(dimethylamino)phenyl]acetyl}-D-alanine		399.8758	400.876	6
3-(5-chloro-1H-indol-2-yl)-N-[2-(4-hydroxyphenoxy)propanoyl]-D-alanine		402.8321	403.832	15
3-(5-chloro-1H-indol-2-yl)-N-[(2,4-dichlorophenyl)acetyl]-D-alanine		425.6975	426.697	24
3-(5-chloro-1H-indol-2-yl)-N-{[(2R)-5-oxotetrahydrofuran-2-yl]carbonyl}-D-alanine		350.7565	351.757	0
N-{[2-(benzyloxy)phenyl]acetyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		462.9307	463.931	43

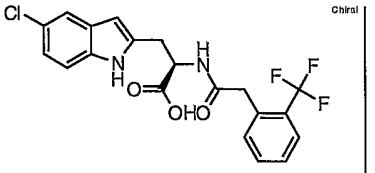
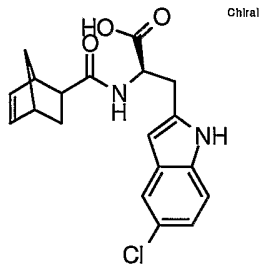
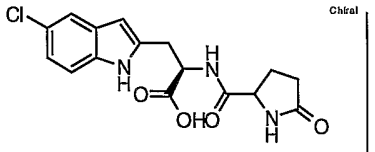
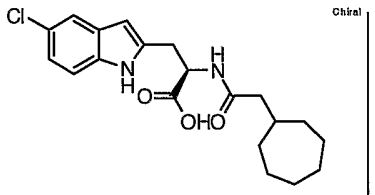
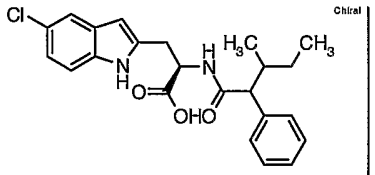
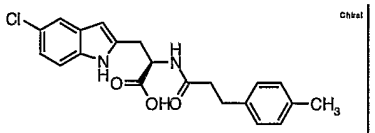
N-{[4-(benzyloxy)phenoxy]acetyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		478.9297	479.93	35
N-(bicyclo[2.2.1]hept-2-ylcarbonyl)-3-(5-chloro-1H-indol-2-yl)-D-alanine		360.8389	361.839	41
3-(5-chloro-1H-indol-2-yl)-N-(9H-xanthen-9-ylcarbonyl)-D-alanine		446.8881	447.888	25
N-(tert-butoxycarbonyl)-D-tyrosyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		501.9642	502.964	22
N-(tert-butoxycarbonyl)-N-methyl-L-alanyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		423.8944	424.894	25
3-(5-chloro-1H-indol-2-yl)-N-(cycloheptylcarbonyl)-D-alanine		362.8547	363.855	49

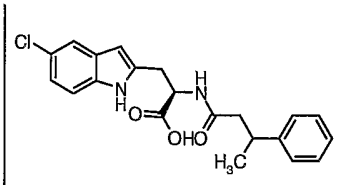
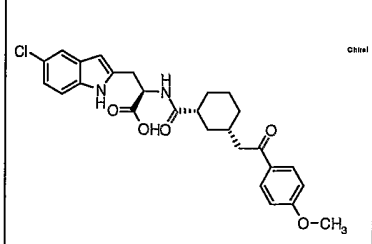
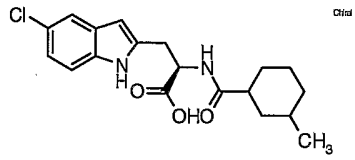
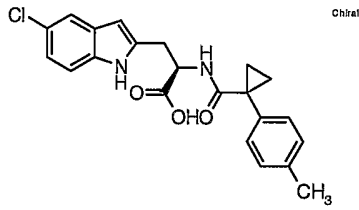
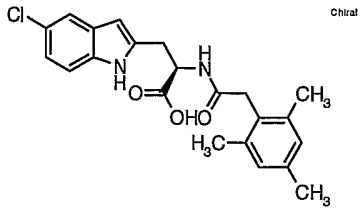
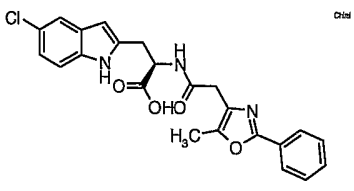
3-(5-chloro-1H-indol-2-yl)-N-(4-methylpentanoyl)-D-alanine		336.8169	337.817	35
N-{[2,4-bis(1,1-dimethylpropyl)phenoxy]acetyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		513.0743	514.074	39
3-(5-chloro-1H-indol-2-yl)-N-[(2,5-dimethoxyphenyl)acetyl]-D-alanine		416.8589	417.859	18
3-(5-chloro-1H-indol-2-yl)-N-[(2-methoxyphenoxy)acetyl]-D-alanine		402.8321	403.832	9
3-(5-chloro-1H-indol-2-yl)-N-[(4-fluorophenyl)acetyl]-D-alanine		374.7974	375.797	23
N-[(1-acetylpiperidin-4-yl)carbonyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		391.8528	392.853	18

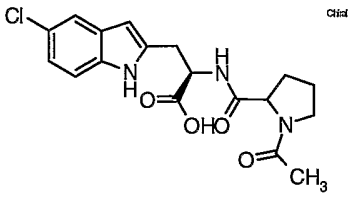
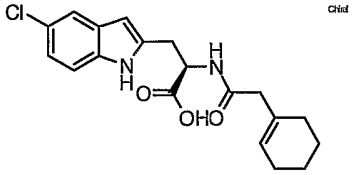
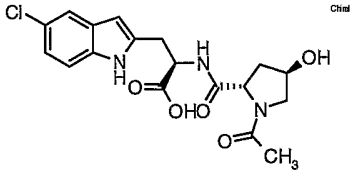
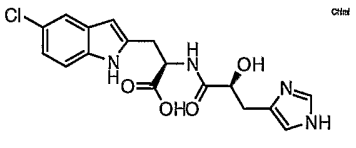
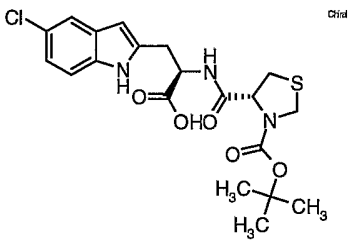
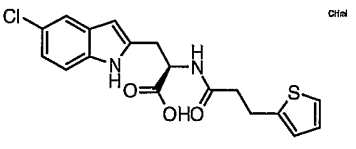
3-(5-chloro-1H-indol-2-yl)-N-(dicyclohexylacetyl)-D-alanine		444.9997	446	7
3-(5-chloro-1H-indol-2-yl)-N-(2-methylpent-4-enoyl)-D-alanine		334.8011	335.801	37
3-(5-chloro-1H-indol-2-yl)-N-[hydroxy(phenyl)acetyl]-D-alanine		372.8063	373.806	20
3-(5-chloro-1H-indol-2-yl)-N-{[(2,5-dichlorophenyl)thio]acetyl}-D-alanine		457.7635	458.764	60
3-(5-chloro-1H-indol-2-yl)-N-[3-(3,4,5-trimethoxyphenyl)propanoyl]-D-alanine		460.9115	461.911	47
3-(5-chloro-1H-indol-2-yl)-N-[2-(4-isobutylphenyl)propanoyl]-D-alanine		426.9413	427.941	8

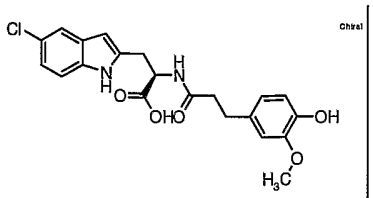
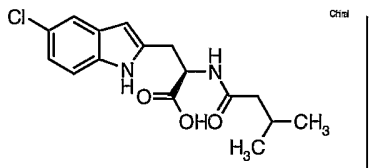
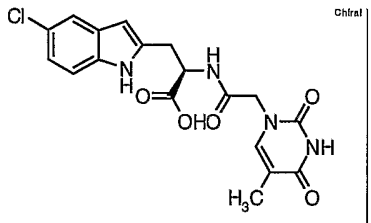
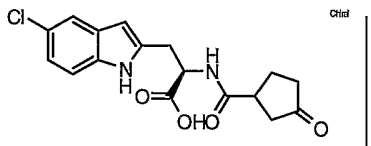
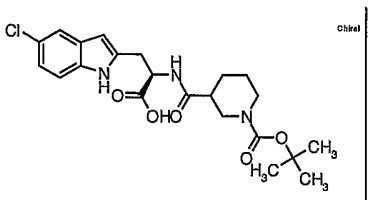
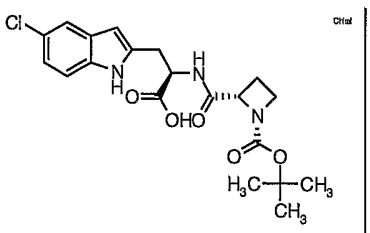
3-(5-chloro-1H-indol-2-yl)-N-[3-(4-methoxyphenyl)propanoyl]-D-alanine		400.8599	401.86	51
3-(5-chloro-1H-indol-2-yl)-N-[(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)acetyl]-D-alanine		458.8601	459.86	0
3-(5-chloro-1H-indol-2-yl)-N-[(4-ethoxyphenyl)acetyl]-D-alanine		400.8599	401.86	29
3-(5-chloro-1H-indol-2-yl)-N-[(4-chlorophenyl)(hydroxy)acetyl]-D-alanine		407.2514	408.251	47
3-(5-chloro-1H-indol-2-yl)-N-{[3-(trifluoromethyl)phenyl]acetyl}-D-alanine		424.8044	425.804	28
3-(5-chloro-1H-indol-2-yl)-N-(3-cyclopentylpropanoyl)-D-alanine		362.8547	363.855	24

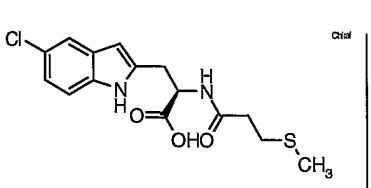
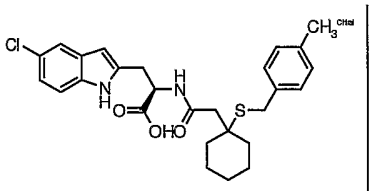
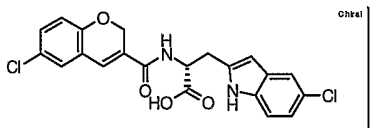
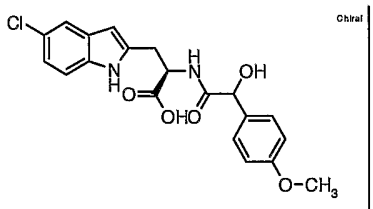
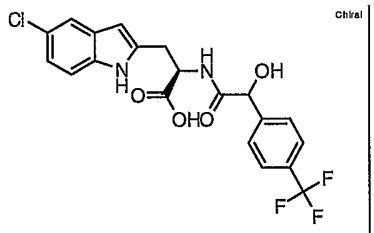
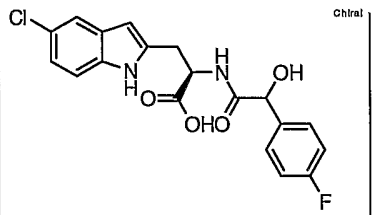
3-(5-chloro-1H-indol-2-yl)-N-{[2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]carbonyl}-D-alanine		388.8925	389.892	42
N-(tert-butoxycarbonyl)-3-(1,3-thiazol-4-yl)-L-alanyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		492.9815	493.981	34
3-(5-chloro-1H-indol-2-yl)-N-[(2-fluorophenyl)acetyl]-D-alanine		374.7974	375.797	37
3-(5-chloro-1H-indol-2-yl)-N-(2-hydroxy-3-phenylpropanoyl)-D-alanine		386.8331	387.833	39
3-(5-chloro-1H-indol-2-yl)-N-{[4-(trifluoromethyl)phenyl]acetyl}-D-alanine		424.8044	425.804	13
3-(5-chloro-1H-indol-2-yl)-N-[(3,5-difluorophenyl)acetyl]-D-alanine		392.7875	393.788	0

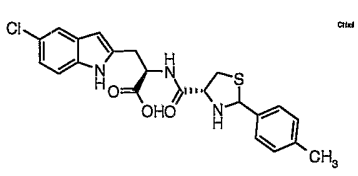
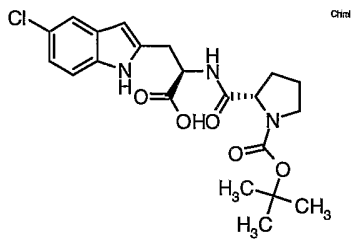
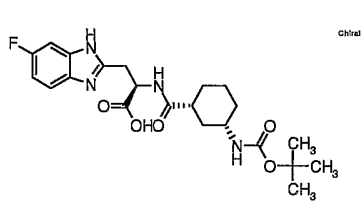
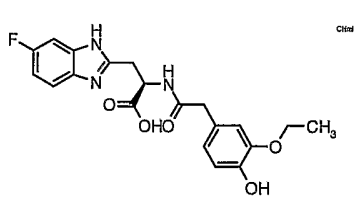
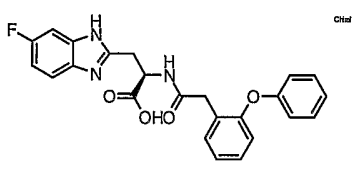
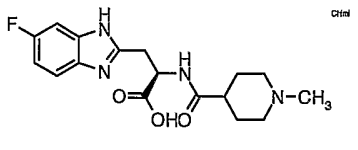
3-(5-chloro-1H-indol-2-yl)-N-{[2-(trifluoromethyl)phenyl]acetyl}-D-alanine		424.8044	425.804	38
N-(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-3-(5-chloro-1H-indol-2-yl)-D-alanine		358.8231	359.823	33
5-oxoprolyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		349.7724	350.772	0
3-(5-chloro-1H-indol-2-yl)-N-(cycloheptylacetyl)-D-alanine		376.8815	377.882	43
3-(5-chloro-1H-indol-2-yl)-N-(3-methyl-2-phenylpentanoyl)-D-alanine		412.9145	413.914	52
3-(5-chloro-1H-indol-2-yl)-N-[3-(4-methylphenyl)propanoyl]-D-alanine		384.8609	385.861	47

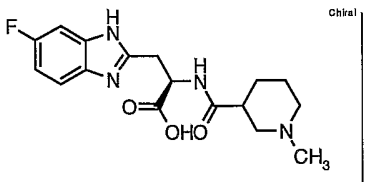
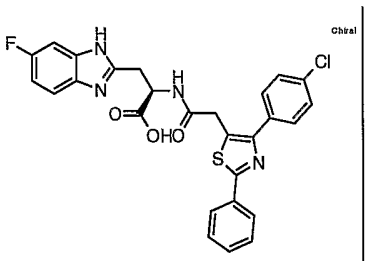
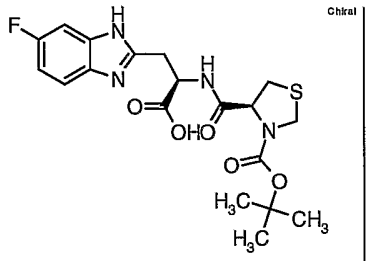
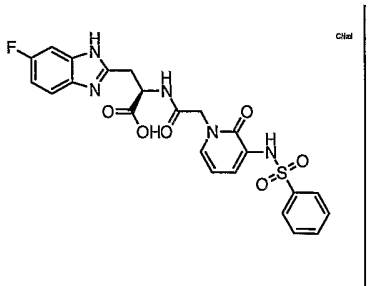
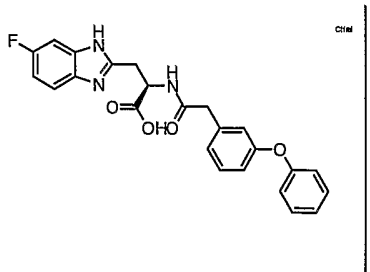
3-(5-chloro-1H-indol-2-yl)-N-(3-phenylbutanoyl)-D-alanine		384.8609	385.861	60
3-(5-chloro-1H-indol-2-yl)-N-({(1R,3S)-3-[2-(4-methoxyphenyl)-2-oxoethyl]cyclohexyl}carbonyl)-D-alanine		496.9881	497.988	18
3-(5-chloro-1H-indol-2-yl)-N-[(3-methylcyclohexyl)carbonyl]-D-alanine		362.8547	363.855	47
3-(5-chloro-1H-indol-2-yl)-N-{[1-(4-methylphenyl)cyclopropyl]carbonyl}-D-alanine		396.8719	397.872	11
3-(5-chloro-1H-indol-2-yl)-N-(mesitylacetyl)-D-alanine		398.8877	399.888	3
3-(5-chloro-1H-indol-2-yl)-N-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetyl]-D-alanine		437.881	438.881	11

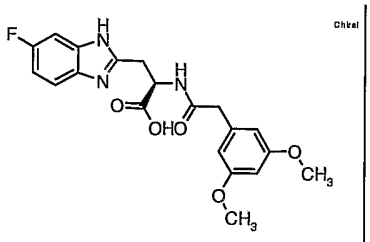
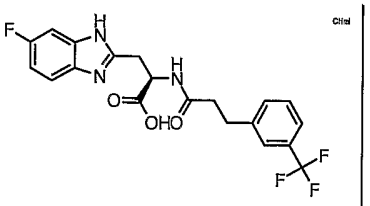
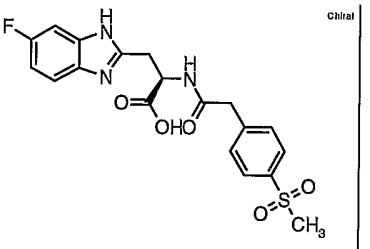
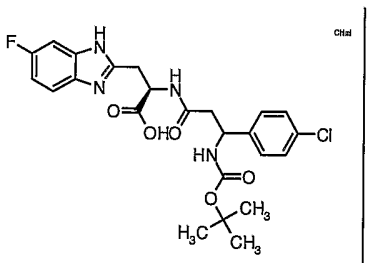
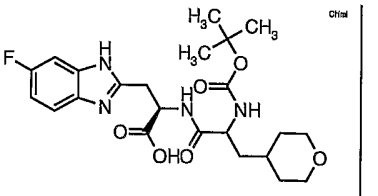
1-acetylprolyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		377.826	378.826	13
3-(5-chloro-1H-indol-2-yl)-N-(cyclohex-1-en-1-ylacetyl)-D-alanine		360.8389	361.839	45
(4R)-1-acetyl-4-hydroxy-L-prolyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		393.825	394.825	13
3-(5-chloro-1H-indol-2-yl)-N-[(2S)-2-hydroxy-3-(1H-imidazol-4-yl)propanoyl]-D-alanine		376.7983	377.798	0
N-{[(4R)-3-(tert-butoxycarbonyl)-1,3-thiazolidin-4-yl]carbonyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		453.9446	454.945	25
3-(5-chloro-1H-indol-2-yl)-N-[3-(2-thienyl)propanoyl]-D-alanine		376.8623	377.862	50

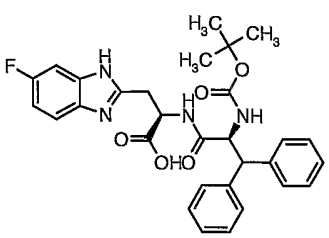
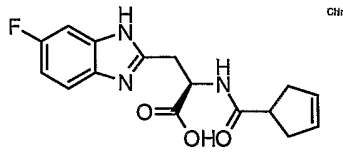
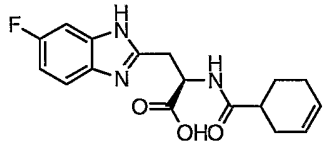
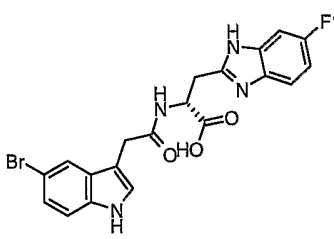
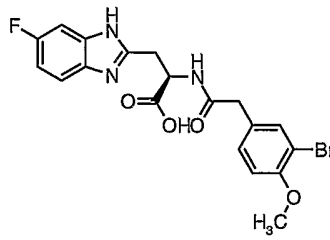
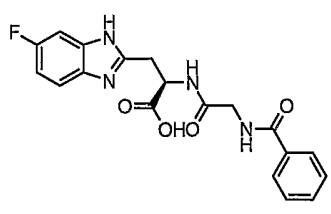
3-(5-chloro-1H-indol-2-yl)-N-[3-(4-hydroxy-3-methoxyphenyl)propanoyl]-D-alanine		416.8589	417.859	43
3-(5-chloro-1H-indol-2-yl)-N-(3-methylbutanoyl)-D-alanine		322.7901	323.79	38
3-(5-chloro-1H-indol-2-yl)-N-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetyl]-D-alanine		404.8083	405.808	1
3-(5-chloro-1H-indol-2-yl)-N-[(3-oxocyclopentyl)carbonyl]-D-alanine		348.7843	349.784	20
N-{[1-(tert-butoxycarbonyl)piperidin-3-yl]carbonyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		449.9322	450.932	22
(2R)-2-({[(2S)-1-(tert-butoxycarbonyl)azetidin-2-yl]carbonyl}amino)-3-(5-chloro-1H-indol-2-yl)propanoic acid		421.8786	422.879	17

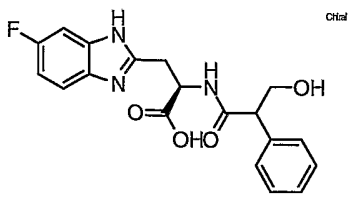
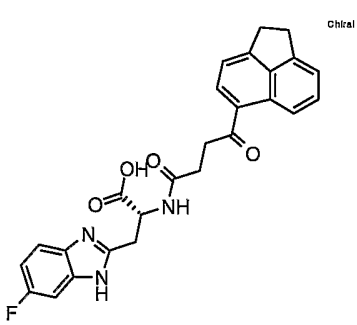
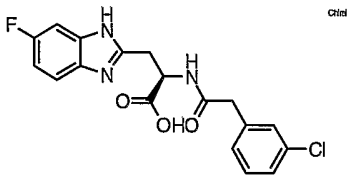
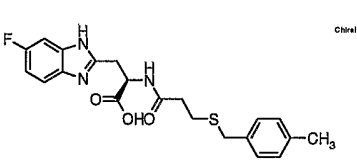
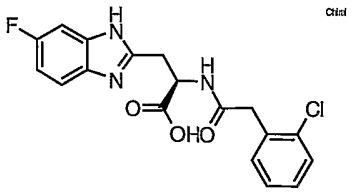
3-(5-chloro-1H-indol-2-yl)-N-[3-(methylthio)propanoyl]-D-alanine		340.8293	341.829	28
3-(5-chloro-1H-indol-2-yl)-N-({1-[(4-methylbenzyl)thio]cyclohexyl}acetyl)-D-alanine		499.0719	500.072	78
N-[(6-chloro-2H-chromen-3-yl)carbonyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		431.2734	432.273	86
3-(5-chloro-1H-indol-2-yl)-N-[hydroxy(4-methoxyphenyl)acetyl]-D-alanine		402.8321	403.832	16
3-(5-chloro-1H-indol-2-yl)-N-{hydroxy[4-(trifluoromethyl)phenyl]acetyl}-D-alanine		440.8034	441.803	10
3-(5-chloro-1H-indol-2-yl)-N-[(4-fluorophenyl)(hydroxy)acetyl]-D-alanine		390.7964	391.796	20

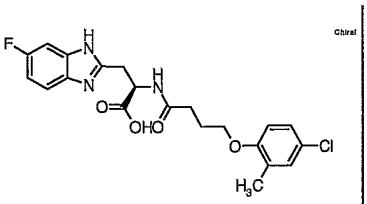
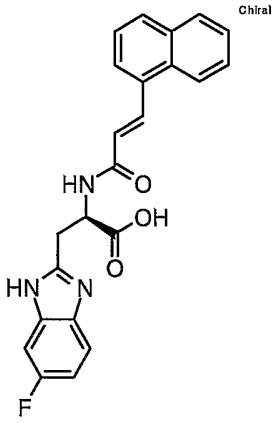
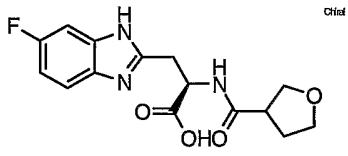
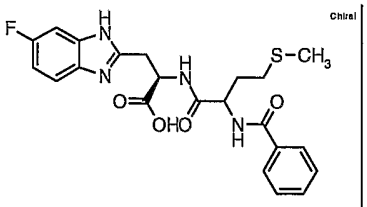
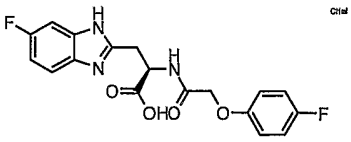
3-(5-chloro-1H-indol-2-yl)-N-{[(4R)-2-(4-methylphenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		443.9528	444.953	27
1-(tert-butoxycarbonyl)-L-prolyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		435.9054	436.905	43
N-({(1R,3S)-3-[(tert-butoxycarbonyl)amino]cyclohexyl}carbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		448.4921	449.492	15
N-[(3-ethoxy-4-hydroxyphenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		401.392	402.392	6
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-phenoxyphenyl)acetyl]-D-alanine		433.437	434.437	8
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(1-methylpiperidin-4-yl)carbonyl]-D-alanine		348.3759	349.376	0

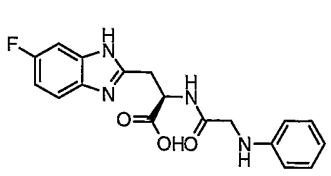
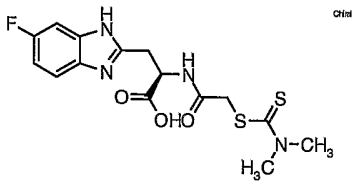
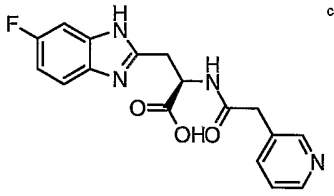
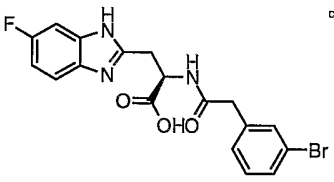
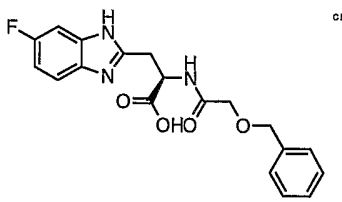
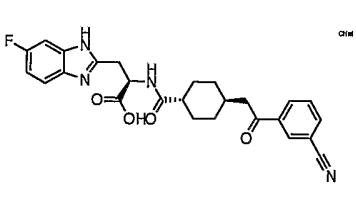
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(1-methylpiperidin-3-yl)carbonyl]-D-alanine		348.3759	349.376	0
N-{[4-(4-chlorophenyl)-2-phenyl-1,3-thiazol-5-yl]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		534.997	535.997	63
N-{[(4S)-3-(tert-butoxycarbonyl)-1,3-thiazolidin-4-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		438.4777	439.478	29
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[2-oxo-3-[(phenylsulfonyl)amino]pyridin-1(2H)-yl]acetyl}-D-alanine		513.504	514.504	15
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-phenoxyphenyl)acetyl]-D-alanine		433.437	434.437	18

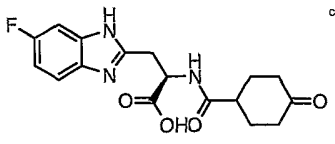
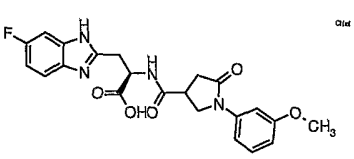
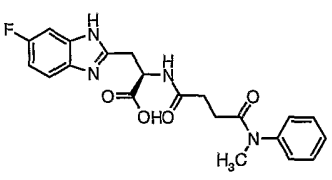
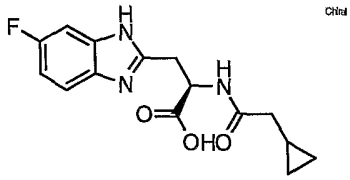
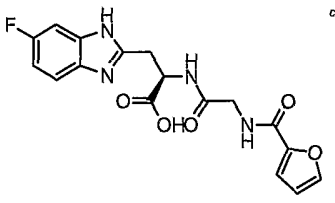
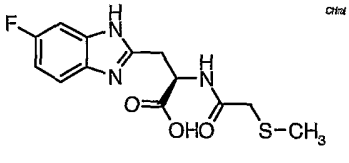
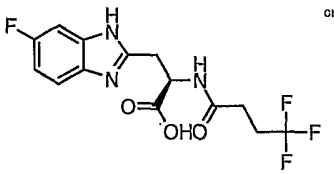
N-[(3,5-dimethoxyphenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		401.392	402.392	11
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{3-[3-(trifluoromethyl)phenyl]propanoyl}-D-alanine		423.3643	424.364	25
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[4-(methylsulfonyl)phenyl]acetyl}-D-alanine		419.4312	420.431	0
N-[3-[(tert-butoxycarbonyl)amino]-3-(4-chlorophenyl)propanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		504.9434	505.943	3
N-(tert-butoxycarbonyl)-3-(tetrahydro-2H-pyran-4-yl)alanyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		478.5179	479.518	12

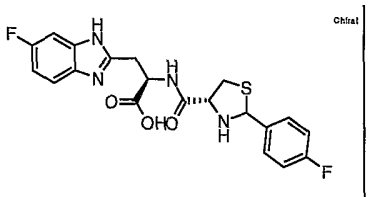
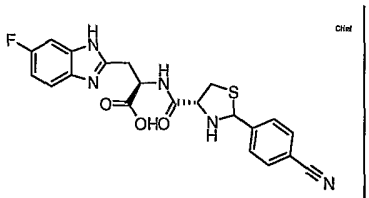
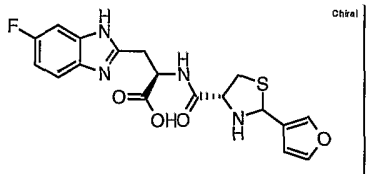
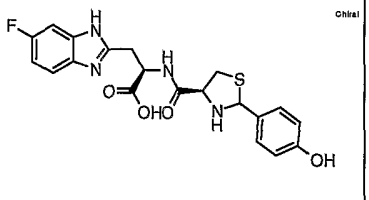
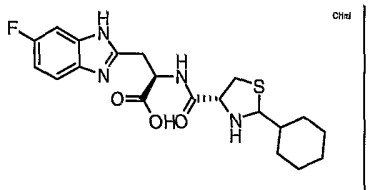
N-(tert-butoxycarbonyl)-beta-phenyl-L-phenylalanyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		546.5959	547.596	29
N-(cyclopent-3-en-1-ylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		317.3184	318.318	35
N-(cyclohex-3-en-1-ylcarbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		331.3452	332.345	33
N-[(5-bromo-1H-indol-3-yl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		459.2734	460.273	26
N-[(3-bromo-4-methoxyphenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		450.2623	451.262	17
N-benzoylglycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		384.3653	385.365	13

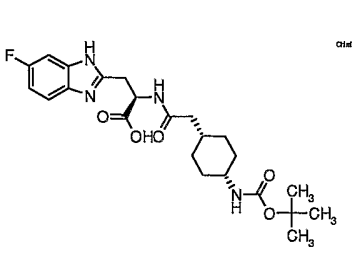
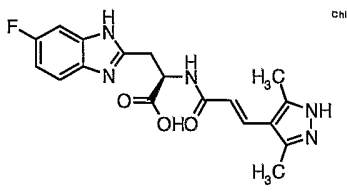
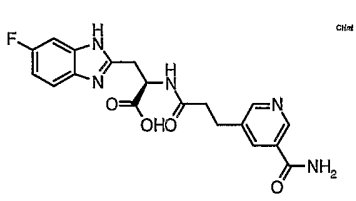
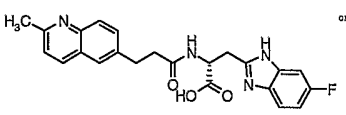
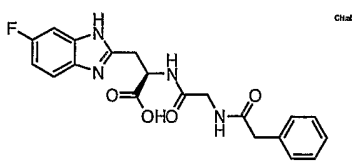
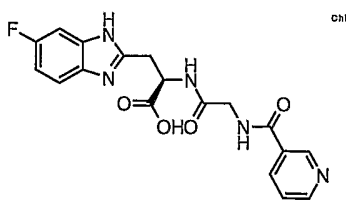
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(3-hydroxy-2-phenylpropanoyl)-D-alanine		371.3662	372.366	33
N-[4-(1,2-dihydroacenaphthylen-5-yl)-4-oxobutanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		459.4748	460.475	20
N-[(3-chlorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		375.7855	376.786	15
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{3-[(4-methylbenzyl)thio]propanoyl}-D-alanine		415.4868	416.487	45
N-[(2-chlorophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		375.7855	376.786	46

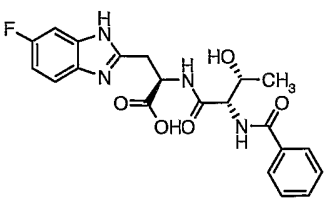
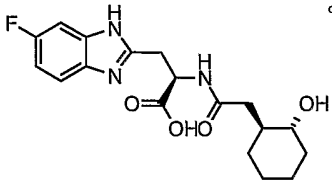
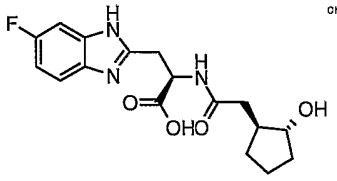
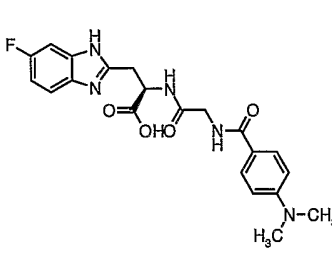
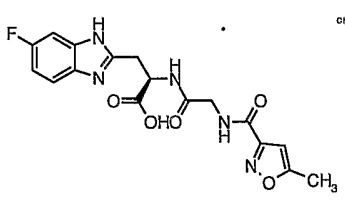
N-[4-(4-chloro-2-methylphenoxy)butanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		433.8649	434.865	8
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2E)-3-(1-naphthyl)prop-2-enoyl]-D-alanine		403.4112	404.411	92
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(tetrahydrofuran-3-ylcarbonyl)-D-alanine		321.3064	322.306	24
N-benzoylmethionyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		458.5117	459.512	33
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-fluorophenoxy)acetyl]-D-alanine		375.3295	376.33	18

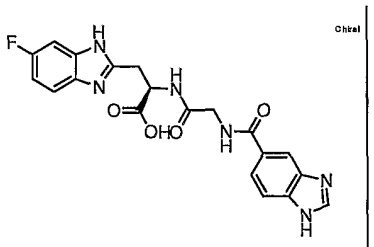
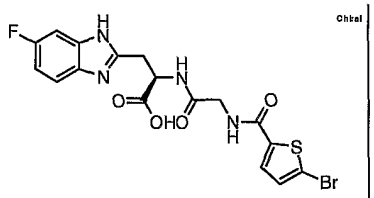
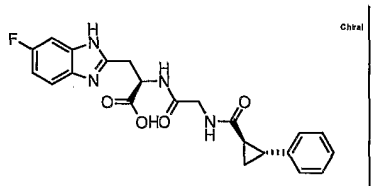
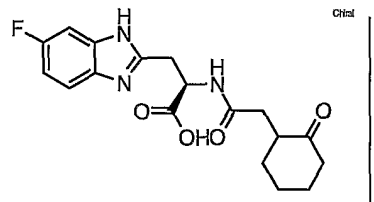
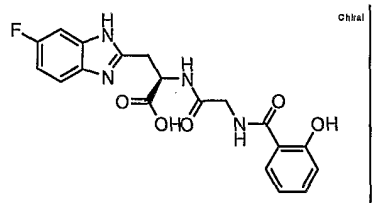
N-phenylglycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		356.3553	357.355	25
N-({[(dimethylamino)carbonothioyl]thio}acetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		384.4543	385.454	29
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(pyridin-3-ylacetyl)-D-alanine		342.3285	343.329	3
N-[(3-bromophenyl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		420.2365	421.236	27
N-[(benzyloxy)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		371.3662	372.366	0
N-({trans-4-[2-(3-cyanophenyl)-2-oxoethyl]cyclohexyl}carbonyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		476.5055	477.505	65

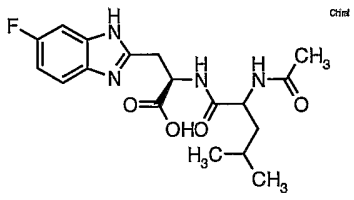
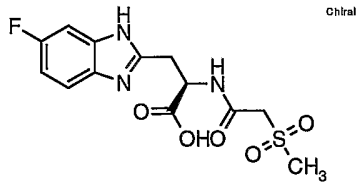
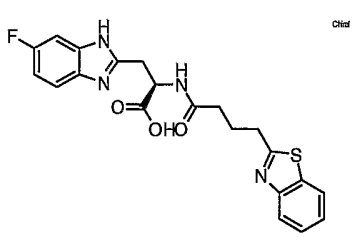
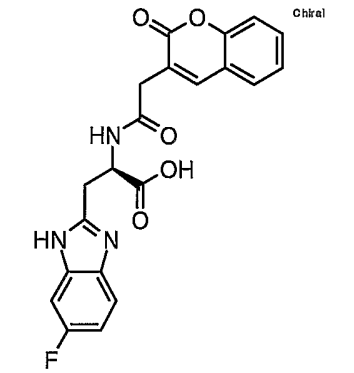
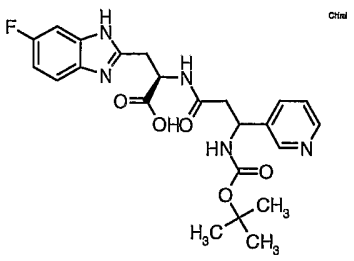
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(4-oxocyclohexyl)carbonyl]-D-alanine		347.3442	348.344	19
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[1-(3-methoxyphenyl)-5-oxopyrrolidin-3-yl]carbonyl}-D-alanine		440.4289	441.429	17
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{4-[methyl(phenyl)amino]-4-oxobutanoyl}-D-alanine		412.4189	413.419	25
N-(cyclopropylacetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		305.3074	306.307	31
N-2-furoylglycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		374.3265	375.327	7
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(methylthio)acetyl]-D-alanine		311.3356	312.336	22
3-(6-fluoro-1H-benzimidazol-2-yl)-N-(4,4,4-trifluorobutanoyl)-D-alanine		347.2667	348.267	3

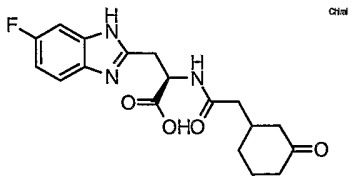
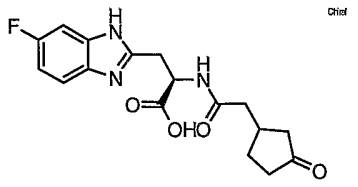
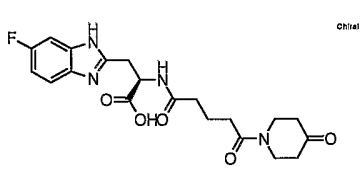
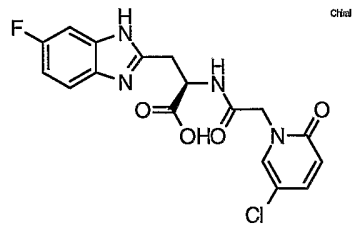
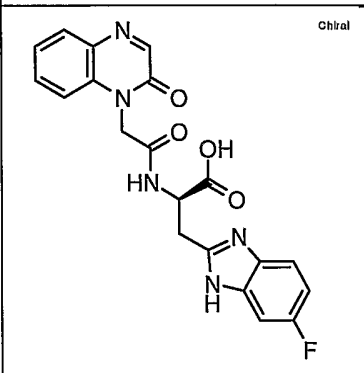
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(4R)-2-(4-fluorophenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		432.4492	433.449	19
N-{[(4R)-2-(4-cyanophenyl)-1,3-thiazolidin-4-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		439.4692	440.469	65
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(4R)-2-(3-furyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		404.4203	405.42	44
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(4S)-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		430.4581	431.458	41
N-{[(4R)-2-cyclohexyl-1,3-thiazolidin-4-yl]carbonyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		420.5065	421.507	35

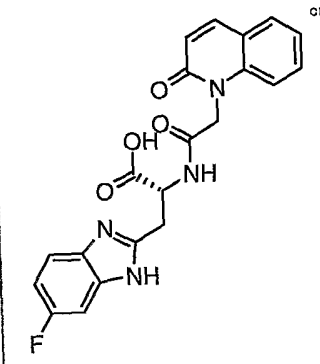
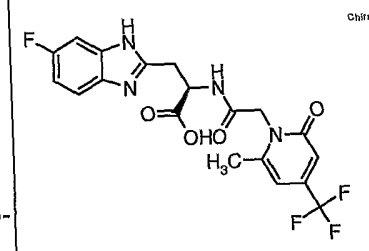
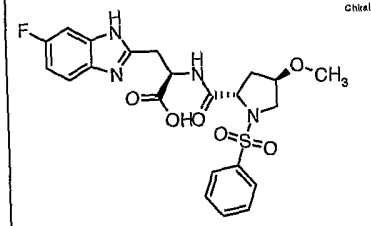
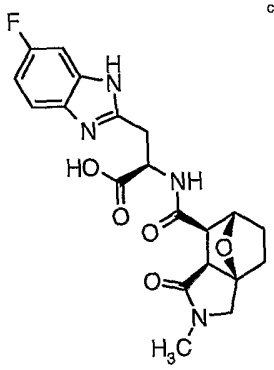
N-({cis-4-[(tert-butoxycarbonyl)amino]cyclohexyl}acetyl)-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		462.5189	463.519	33
N-[(2E)-3-(3,5-dimethyl-1H-pyrazol-4-yl)prop-2-enoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		371.3702	372.37	60
N-{3-[5-(aminocarbonyl)pyridin-3-yl]propanoyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		399.3802	400.38	3
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[3-(2-methylquinolin-6-yl)propanoyl]-D-alanine		420.4419	421.442	17
N-(phenylacetyl)glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		398.3921	399.392	1
N-(pyridin-3-ylcarbonyl)glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		385.3534	386.353	0

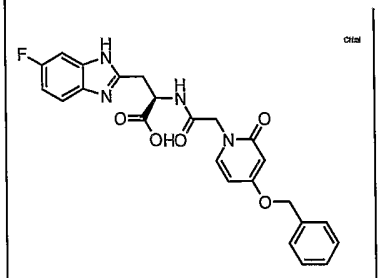
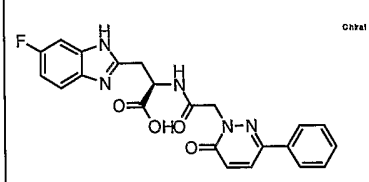
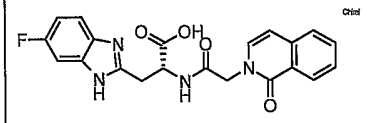
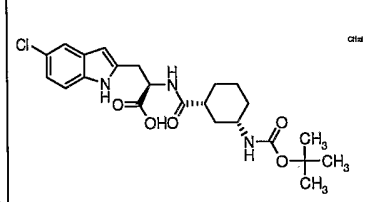
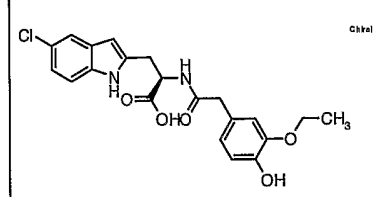
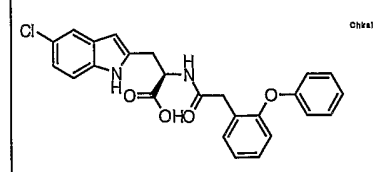
N-benzoyl-L-threonyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		428.4179	429.418	10
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(1S,2R)-2-hydroxycyclohexyl]acetyl}-D-alanine		363.3868	364.387	26
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(1S,2R)-2-hydroxycyclopentyl]acetyl}-D-alanine		349.36	350.36	30
N-[4-(dimethylamino)benzoyl]glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		427.4338	428.434	26
N-[(5-methylisoxazol-3-yl)carbonyl]glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		389.3414	390.341	9

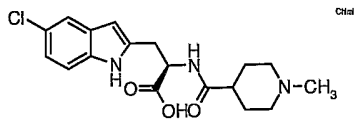
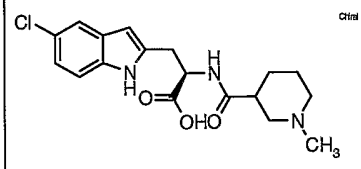
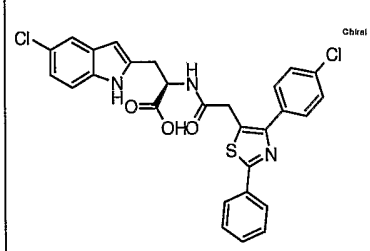
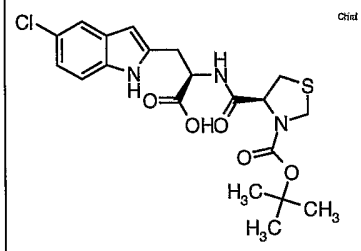
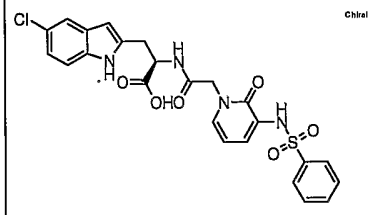
N-(1H-benzimidazol-5-ylcarbonyl)glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		424.3903	425.39	15
N-[(5-bromo-2-thienyl)carbonyl]glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		469.2896	470.29	42
N-{[(1R,2R)-2-phenylcyclopropyl]carbonyl}glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		424.4299	425.43	25
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-oxocyclohexyl)acetyl]-D-alanine		361.371	362.371	34
N-(2-hydroxybenzoyl)glycyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		400.3643	401.364	15

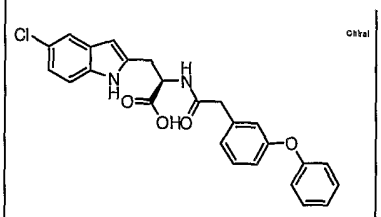
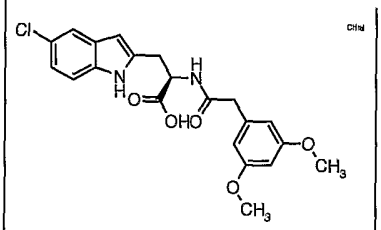
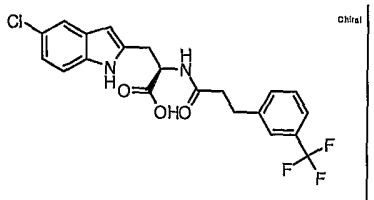
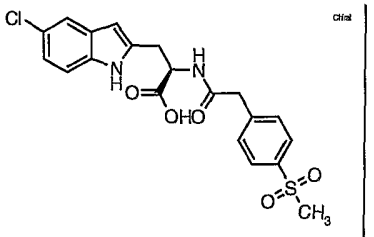
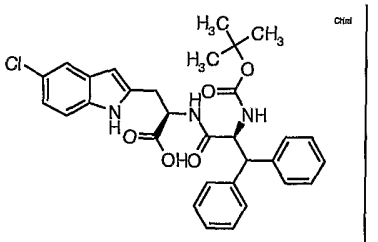
N-acetylleucyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		378.4017	379.402	22
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(methylsulfonyl)acetyl]-D-alanine		343.3336	344.334	16
N-[4-(1,3-benzothiazol-2-yl)butanoyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		426.4701	427.47	80
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-oxo-2H-chromen-3-yl)acetyl]-D-alanine		409.3714	410.371	16
N-{3-[(tert-butoxycarbonyl)amino]-3-pyridin-3-ylpropanoyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		471.4864	472.486	11

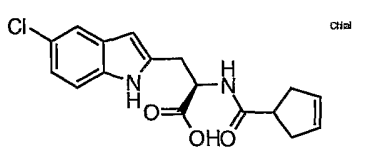
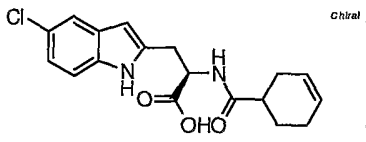
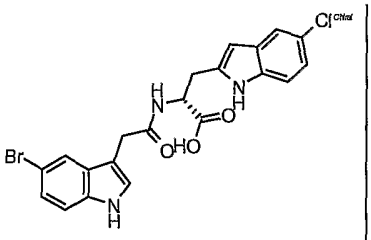
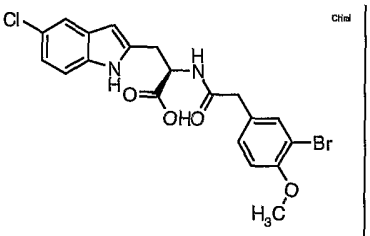
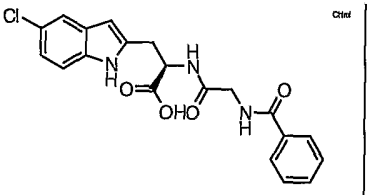
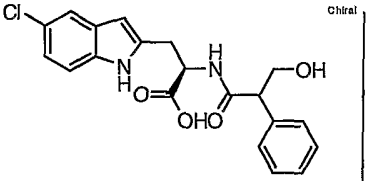
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-oxocyclohexyl)acetyl]-D-alanine		361.371	362.371	14
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(3-oxocyclopentyl)acetyl]-D-alanine		347.3442	348.344	12
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[5-oxo-5-(4-oxopiperidin-1-yl)pentanoyl]-D-alanine		418.4227	419.423	23
N-[(5-chloro-2-oxopyridin-1(2H)-yl)acetyl]-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		392.7726	393.773	11
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-oxoquinoxalin-1(2H)-yl)acetyl]-D-alanine		409.3754	410.375	18

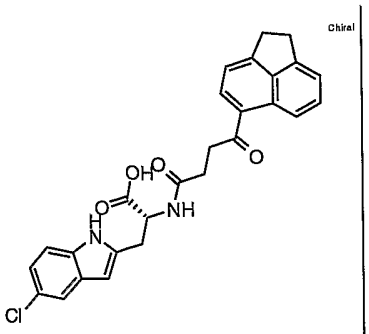
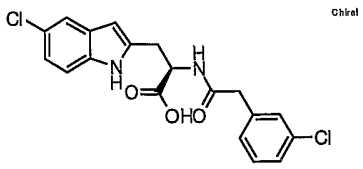
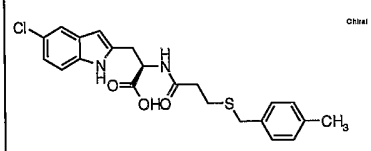
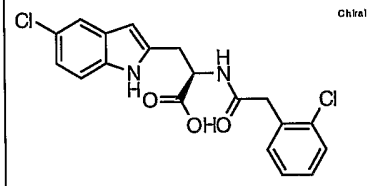
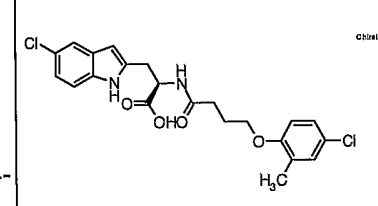
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(2-oxoquinolin-1(2H)-yl)acetyl]-D-alanine		408.3873	409.387	27
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[6-methyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl]acetyl}-D-alanine		440.3514	441.351	11
(4R)-4-methoxy-1-(phenylsulfonyl)-L-prolyl-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		490.5097	491.51	71
3-(6-fluoro-1H-benzimidazol-2-yl)-N-{[(3aR,6S,7R,7aS)-2-methyl-1-oxooctahydro-3a,6-epoxyisoindol-7-yl]carbonyl}-D-alanine		416.4069	417.407	29

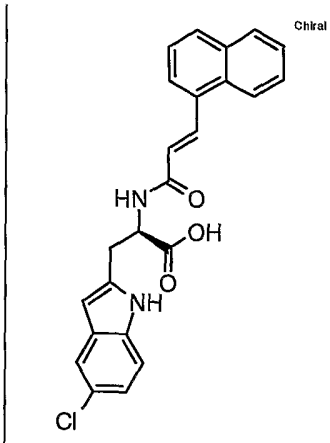
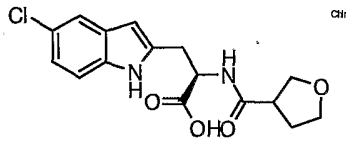
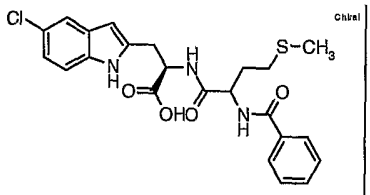
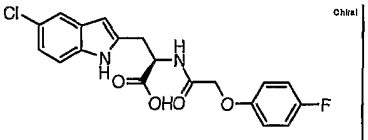
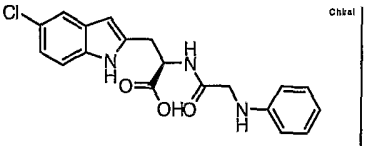
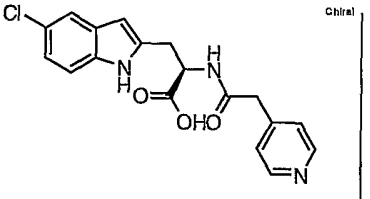
N-{[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]acetyl}-3-(6-fluoro-1H-benzimidazol-2-yl)-D-alanine		464.4509	465.451	11
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(6-oxo-3-phenylpyridazin-1(6H)-yl)acetyl]-D-alanine		435.4132	436.413	28
3-(6-fluoro-1H-benzimidazol-2-yl)-N-[(1-oxoisoquinolin-2(1H)-yl)acetyl]-D-alanine		408.3873	409.387	15
N-({(1R,3S)-3-[(tert-butoxycarbonyl)amino]cyclohexyl}carbonyl)-3-(5-chloro-1H-indol-2-yl)-D-alanine		463.959	464.959	18
3-(5-chloro-1H-indol-2-yl)-N-[(3-ethoxy-4-hydroxyphenyl)acetyl]-D-alanine		416.8589	417.859	11
3-(5-chloro-1H-indol-2-yl)-N-[(2-phenoxyphenyl)acetyl]-D-alanine		448.9039	449.904	36

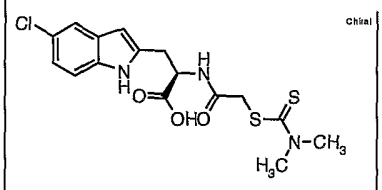
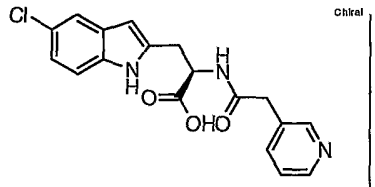
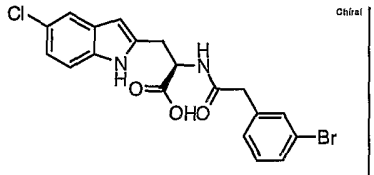
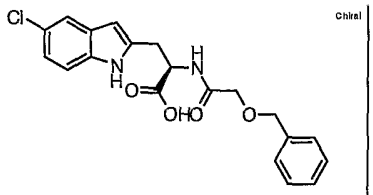
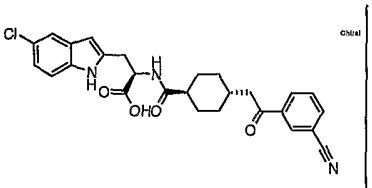
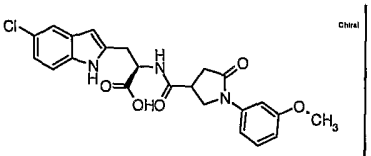
3-(5-chloro-1H-indol-2-yl)-N-[(1-methylpiperidin-4-yl)carbonyl]-D-alanine		363.8428	364.843	3
3-(5-chloro-1H-indol-2-yl)-N-[(1-methylpiperidin-3-yl)carbonyl]-D-alanine		363.8428	364.843	3
3-(5-chloro-1H-indol-2-yl)-N-{[4-(4-chlorophenyl)-2-phenyl-1,3-thiazol-5-yl]acetyl}-D-alanine		550.4639	551.464	64
N-{[(4S)-3-(tert-butoxycarbonyl)-1,3-thiazolidin-4-yl]carbonyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		453.9446	454.945	16
3-(5-chloro-1H-indol-2-yl)-N-{[2-oxo-3-[(phenylsulfonyl)amino]pyridin-1(2H)-yl]acetyl}-D-alanine		528.9709	529.971	15

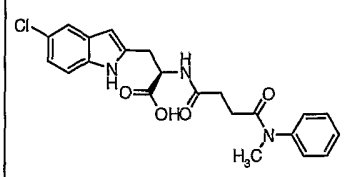
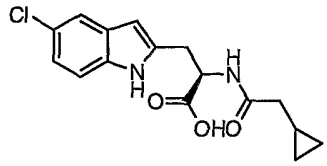
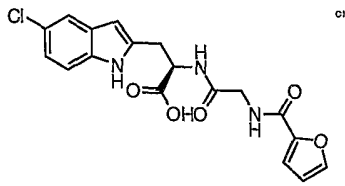
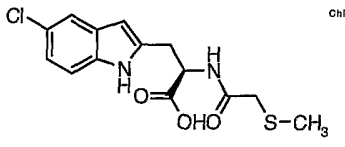
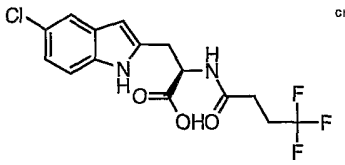
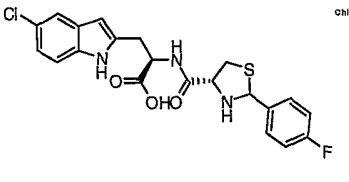
3-(5-chloro-1H-indol-2-yl)-N-[(3-phenoxyphenyl)acetyl]-D-alanine		448.9039	449.904	51
3-(5-chloro-1H-indol-2-yl)-N-[(3,5-dimethoxyphenyl)acetyl]-D-alanine		416.8589	417.859	19
3-(5-chloro-1H-indol-2-yl)-N-{3-[3-(trifluoromethyl)phenyl]propanoyl}-D-alanine		438.8312	439.831	41
3-(5-chloro-1H-indol-2-yl)-N-{[4-(methylsulfonyl)phenyl]acetyl}-D-alanine		434.8981	435.898	0
N-(tert-butoxycarbonyl)-beta-phenyl-L-phenylalanyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		562.0628	563.063	12

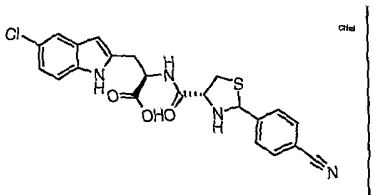
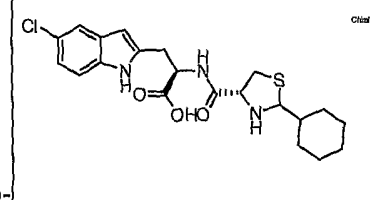
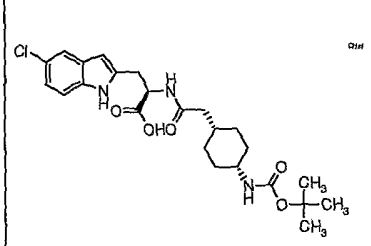
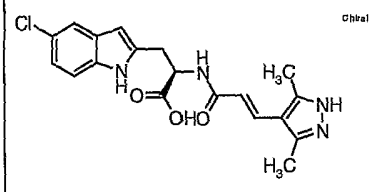
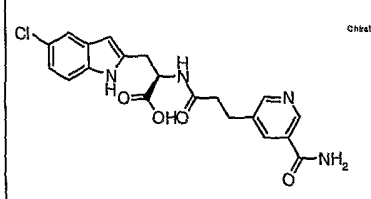
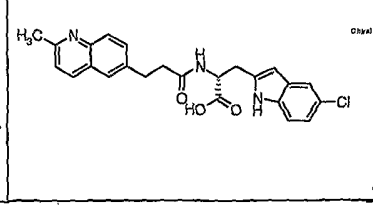
3-(5-chloro-1H-indol-2-yl)-N-(cyclopent-3-en-1-ylcarbonyl)-D-alanine		332.7853	333.785	31
3-(5-chloro-1H-indol-2-yl)-N-(cyclohex-3-en-1-ylcarbonyl)-D-alanine		346.8121	347.812	31
N-[(5-bromo-1H-indol-3-yl)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		474.7403	475.74	26
N-[(3-bromo-4-methoxyphenyl)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		465.7292	466.729	32
N-benzoylglycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		399.8322	400.832	2
3-(5-chloro-1H-indol-2-yl)-N-(3-hydroxy-2-phenylpropanoyl)-D-alanine		386.8331	387.833	9

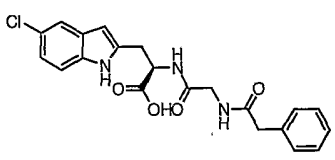
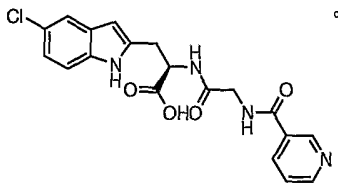
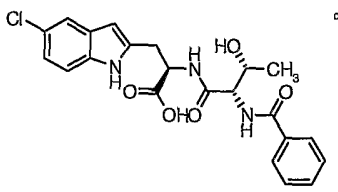
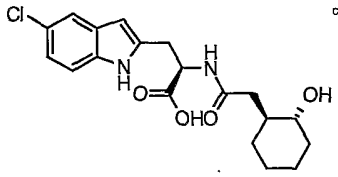
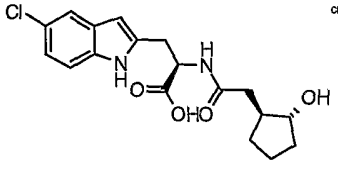
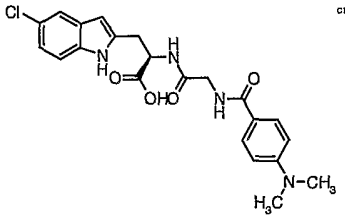
3-(5-chloro-1H-indol-2-yl)-N-[4-(1,2-dihydroacenaphthylen-5-yl)-4-oxobutanoyl]-D-alanine		474.9417	475.942	0
3-(5-chloro-1H-indol-2-yl)-N-[(3-chlorophenyl)acetyl]-D-alanine		391.2524	392.252	5
3-(5-chloro-1H-indol-2-yl)-N-{3-[(4-methylbenzyl)thio]propanoyl}-D-alanine		430.9537	431.954	2
3-(5-chloro-1H-indol-2-yl)-N-[(2-chlorophenyl)acetyl]-D-alanine		391.2524	392.252	37
3-(5-chloro-1H-indol-2-yl)-N-[4-(4-chloro-2-methylphenoxy)butanoyl]-D-alanine		449.3318	450.332	35

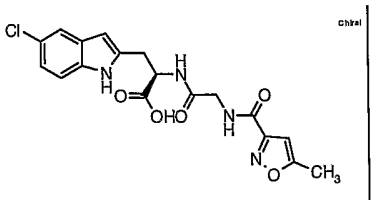
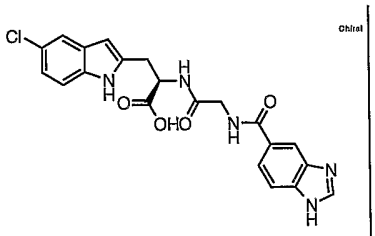
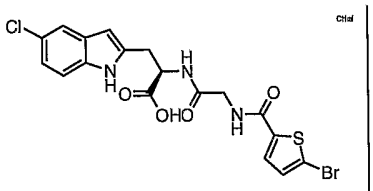
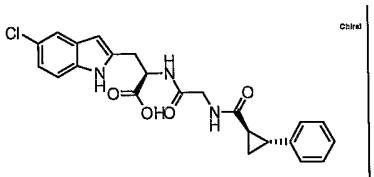
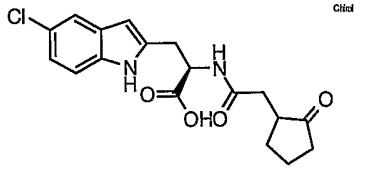
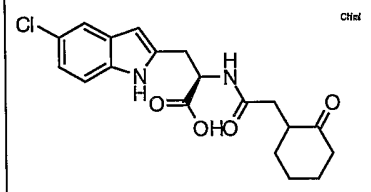
3-(5-chloro-1H-indol-2-yl)-N-[(2E)-3-(1-naphthyl)prop-2-enoyl]-D-alanine		418.8781	419.878	72
3-(5-chloro-1H-indol-2-yl)-N-(tetrahydrofuran-3-ylcarbonyl)-D-alanine		336.7733	337.773	23
N-benzoylmethionyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		473.9786	474.979	15
3-(5-chloro-1H-indol-2-yl)-N-[(4-fluorophenoxy)acetyl]-D-alanine		390.7964	391.796	41
N-phenylglycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		371.8222	372.822	13
3-(5-chloro-1H-indol-2-yl)-N-(pyridin-4-ylacetyl)-D-alanine		357.7954	358.795	15

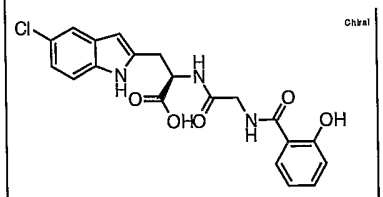
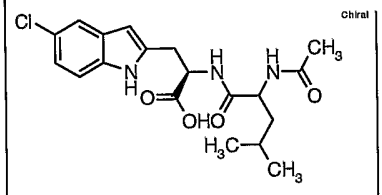
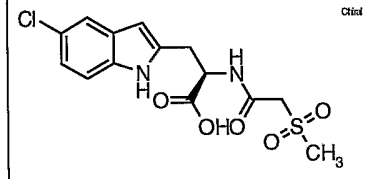
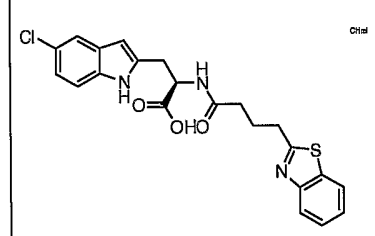
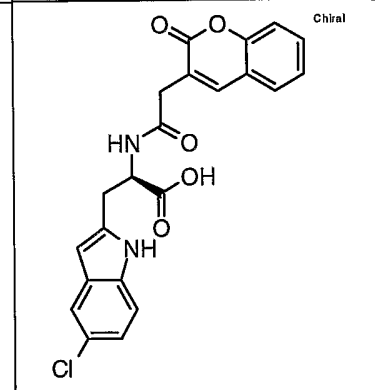
3-(5-chloro-1H-indol-2-yl)-N-({[(dimethylamino)carbonothioyl]thio}acetyl)-D-alanine		399.9212	400.921	20
3-(5-chloro-1H-indol-2-yl)-N-(pyridin-3-ylacetyl)-D-alanine		357.7954	358.795	5
N-[(3-bromophenyl)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		435.7034	436.703	26
N-[(benzyloxy)acetyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		386.8331	387.833	15
3-(5-chloro-1H-indol-2-yl)-N-({trans-4-[2-(3-cyanophenyl)-2-oxoethyl]cyclohexyl}carbonyl)-D-alanine		491.9724	492.972	61
3-(5-chloro-1H-indol-2-yl)-N-{[1-(3-methoxyphenyl)-5-oxopyrrolidin-3-yl]carbonyl}-D-alanine		455.8958	456.896	26

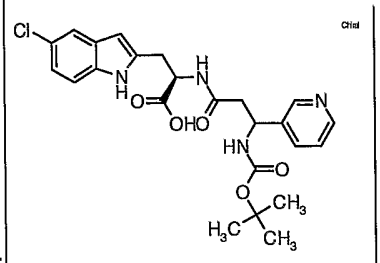
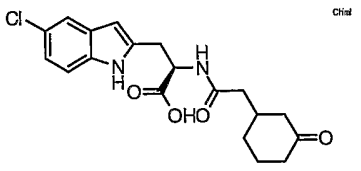
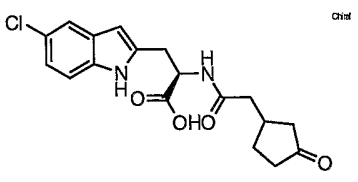
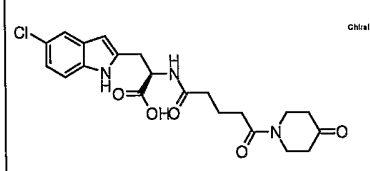
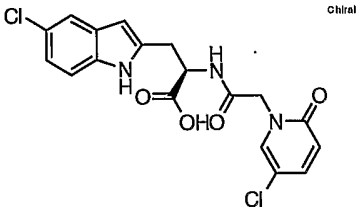
3-(5-chloro-1H-indol-2-yl)-N-{4-[methyl(phenyl)amino]-4-oxobutanoyl}-D-alanine		427.8858	428.886	33
3-(5-chloro-1H-indol-2-yl)-N-(cyclopropylacetyl)-D-alanine		320.7743	321.774	32
N-2-furoylglycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		389.7934	390.793	2
3-(5-chloro-1H-indol-2-yl)-N-[(methylthio)acetyl]-D-alanine		326.8025	327.803	6
3-(5-chloro-1H-indol-2-yl)-N-(4,4,4-trifluorobutanoyl)-D-alanine		362.7336	363.734	3
3-(5-chloro-1H-indol-2-yl)-N-{[(4R)-2-(4-fluorophenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		447.9161	448.916	24

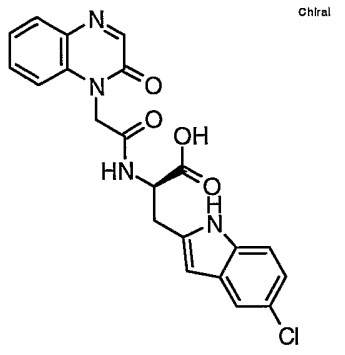
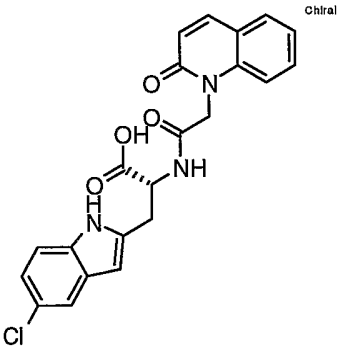
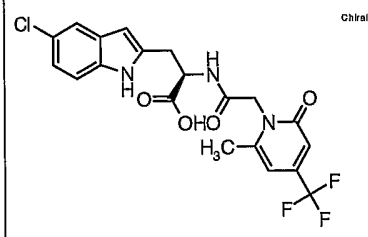
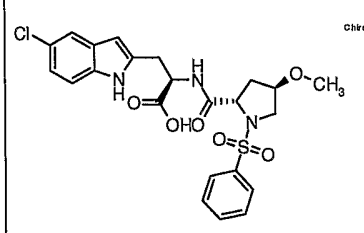
3-(5-chloro-1H-indol-2-yl)-N-{[(4R)-2-(4-cyanophenyl)-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		454.9361	455.936	13
3-(5-chloro-1H-indol-2-yl)-N-{[(4R)-2-cyclohexyl-1,3-thiazolidin-4-yl]carbonyl}-D-alanine		435.9734	436.973	18
N-({cis-4-[(tert-butoxycarbonyl)amino]cyclohexyl}acetyl)-3-(5-chloro-1H-indol-2-yl)-D-alanine		477.9858	478.986	30
3-(5-chloro-1H-indol-2-yl)-N-[(2E)-3-(3,5-dimethyl-1H-pyrazol-4-yl)prop-2-enoyl]-D-alanine		386.8371	387.837	35
N-{3-[5-(aminocarbonyl)pyridin-3-yl]propanoyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		414.8471	415.847	4
3-(5-chloro-1H-indol-2-yl)-N-[3-(2-methylquinolin-6-yl)propanoyl]-D-alanine		435.9088	436.909	36

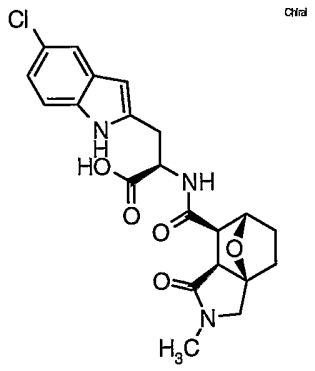
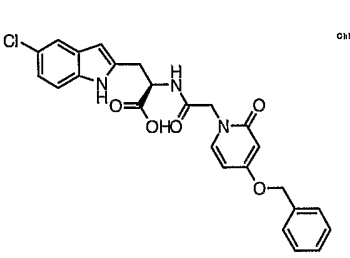
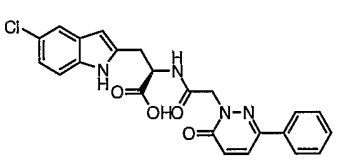
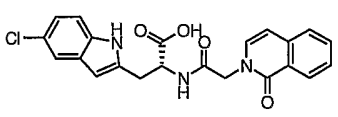
N-(phenylacetyl)glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		413.859	414.859	0
N-(pyridin-3-ylcarbonyl)glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		400.8203	401.82	0
N-benzoyl-L-threonyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		443.8848	444.885	11
3-(5-chloro-1H-indol-2-yl)-N-{[(1S,2R)-2-hydroxycyclohexyl]acetyl}-D-alanine		378.8537	379.854	37
3-(5-chloro-1H-indol-2-yl)-N-{[(1S,2R)-2-hydroxycyclopentyl]acetyl}-D-alanine		364.8269	365.827	38
N-[4-(dimethylamino)benzoyl]glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		442.9007	443.901	2

N-[(5-methylisoxazol-3-yl)carbonyl]glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		404.8083	405.808	6
N-(1H-benzimidazol-5-ylcarbonyl)glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		439.8572	440.857	5
N-[(5-bromo-2-thienyl)carbonyl]glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		484.7565	485.757	7
N-{[(1R,2R)-2-phenylcyclopropyl]carbonyl}glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		439.8968	440.897	0
3-(5-chloro-1H-indol-2-yl)-N-[(2-oxocyclopentyl)acetyl]-D-alanine		362.8111	363.811	47
3-(5-chloro-1H-indol-2-yl)-N-[(2-oxocyclohexyl)acetyl]-D-alanine		376.8379	377.838	18

N-(2-hydroxybenzoyl)glycyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		415.8312	416.831	0
N-acetylleucyl-3-(5-chloro-1H-indol-2-yl)-D-alanine		393.8686	394.869	0
3-(5-chloro-1H-indol-2-yl)-N-[(methylsulfonyl)acetyl]-D-alanine		358.8005	359.801	0
N-[4-(1,3-benzothiazol-2-yl)butanoyl]-3-(5-chloro-1H-indol-2-yl)-D-alanine		441.937	442.937	15
3-(5-chloro-1H-indol-2-yl)-N-[(2-oxo-2H-chromen-3-yl)acetyl]-D-alanine		424.8383	425.838	13

N-{3-[(tert-butoxycarbonyl)amino]-3-pyridin-3-ylpropanoyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		486.9533	487.953	33
3-(5-chloro-1H-indol-2-yl)-N-[(3-oxocyclohexyl)acetyl]-D-alanine		376.8379	377.838	0
3-(5-chloro-1H-indol-2-yl)-N-[(3-oxocyclopentyl)acetyl]-D-alanine		362.8111	363.811	0
3-(5-chloro-1H-indol-2-yl)-N-[5-oxo-5-(4-oxopiperidin-1-yl)pentanoyl]-D-alanine		433.8896	434.89	13
3-(5-chloro-1H-indol-2-yl)-N-[(5-chloro-2-oxopyridin-1(2H)-yl)acetyl]-D-alanine		408.2395	409.24	0

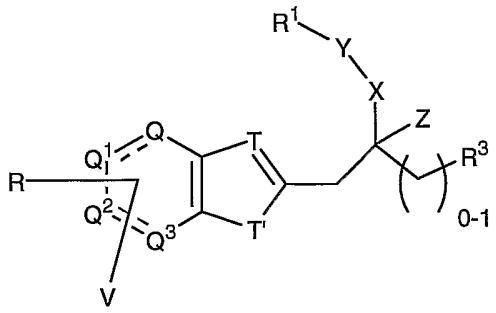
3-(5-chloro-1H-indol-2-yl)-N-[(2-oxoquinoxalin-1(2H)-yl)acetyl]-D-alanine	 Chiral	424.8423	425.842	13
3-(5-chloro-1H-indol-2-yl)-N-[(2-oxoquinolin-1(2H)-yl)acetyl]-D-alanine	 Chiral	423.8542	424.854	7
3-(5-chloro-1H-indol-2-yl)-N-{[6-methyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl]acetyl}-D-alanine	 Chiral	455.8183	456.818	2
(4R)-4-methoxy-1-(phenylsulfonyl)-L-prolyl-3-(5-chloro-1H-indol-2-yl)-D-alanine	 Chiral	505.9766	506.977	9

3-(5-chloro-1H-indol-2-yl)-N-{[(3aR,6S,7R,7aS)-2-methyl-1-oxooctahydro-3a,6-epoxyisoindol-7-yl]carbonyl}-D-alanine		431.8738	432.874	10
N-{[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]acetyl}-3-(5-chloro-1H-indol-2-yl)-D-alanine		479.9178	480.918	0
3-(5-chloro-1H-indol-2-yl)-N-[(6-oxo-3-phenylpyridazin-1(6H)-yl)acetyl]-D-alanine		450.8801	451.88	1
3-(5-chloro-1H-indol-2-yl)-N-[(1-oxoisoquinolin-2(1H)-yl)acetyl]-D-alanine		423.8542	424.854	11

The above specification, examples, and data provide a complete description of the manufacture and use of the invention. Unless otherwise specified, all patent and non-patent references cited are hereby incorporated by reference. Since many embodiments of the invention can be made without departing from the spirit and scope of the invention, the invention resides in the claims hereinafter appended.

We Claim:

1. Compounds comprising the structure of formula **1:**



1

and to pharmaceutically acceptable salts and solvates thereof, wherein:

Q, Q^1, Q^2, Q^3 are independently selected from N, CH_2 or CH and wherein not more than two Q are N;

T is CH, or N;

T' is O, NH, or NCH_3;

X is NH, O, -CH=, or NR' wherein R' can be alkyl or alkyl substituted with halogen, hydroxyl, amine, or carboxyl;

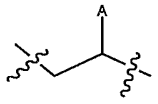
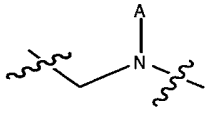
Y is -C(O)-, $-CH_2-$ or $-C(O)NR^2-$, or N wherein R^2 is H or C_1 to C_3 alkyl;

Z is H, alkyl, alkyl substituted with halogen, hydroxyl, amine, or carboxyl; or

X Y and Z can form a heterocyclic ring or

X and Y can form a heterocyclic ring;

R and V are independently H, halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile;

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, , , $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, -$CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

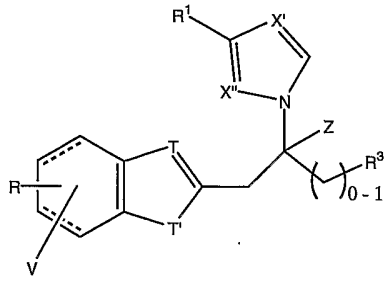
2. The compounds of claim 1 wherein,

X is NH, O or NR' wherein R' can be alkyl or alkyl substituted with halogen, hydroxyl, amine, or carboxyl;

Y is -C(O)-, $-CH_2-$ or $-C(O)NR^2-$ wherein R^2 is H or C_1 to C_3 alkyl;

Z is H, alkyl, or alkyl substituted with halogen, hydroxyl, amine, or carboxyl;

3. The compounds of claim 1 having the structure of formula **2**:

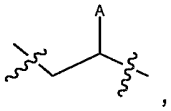
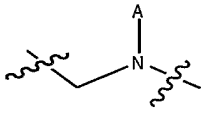


2

and to pharmaceutically acceptable salts and solvates thereof, wherein:

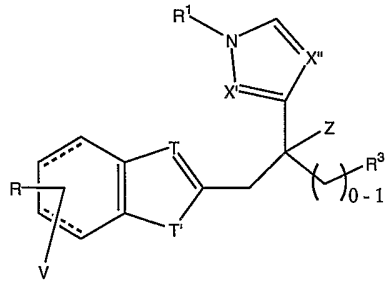
X' and X" are independently selected from CR^2, or N wherein R^2 is H or C_{1-3} alkyl;

R is halogen, alkyl, halogenated alkyl, alkoxy, hydroxyl, NH_2 and nitrile

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, , , $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

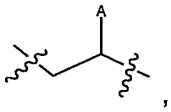
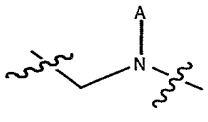
4. The compounds of claim 1 having the structure of formula **3**:



3

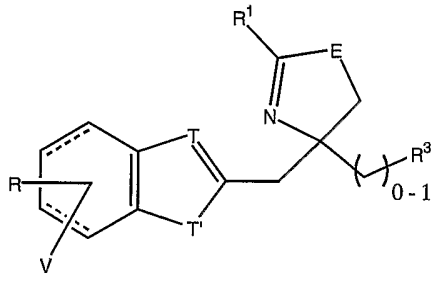
and to pharmaceutically acceptable salts and solvates thereof, wherein:

X' and X" are independently selected from CR^2, or N wherein R^2 is H or C_{1-3} alkyl;

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is O, S, vinyl, , , $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

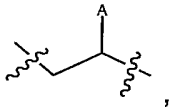
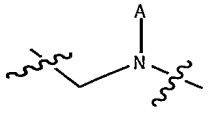
5. The compounds of claim 1 having the structure of formula 4:



4

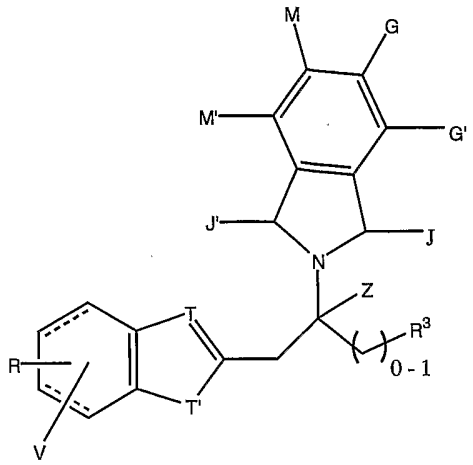
and the pharmaceutically active salts and solvates thereof wherein

E is independently selected from NR', O or S wherein R' can be H, alkyl or alkyl substituted with halogen, hydroxyl or nitrile;

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is vinyl, , , $-CH_2S-$, or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

6. The compounds of claim 1 having the structure of formula **5**:



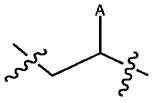
5

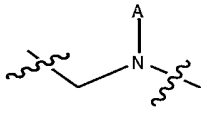
and the pharmaceutically active salts and solvates thereof wherein

Z is H, alkyl, substituted alkyl;

M, M', G and G" are independently H, halogen or M and G together form a cycloalkyl or an aromatic ring or M and M" and G and G' form a cycloalkyl or aromatic ring;

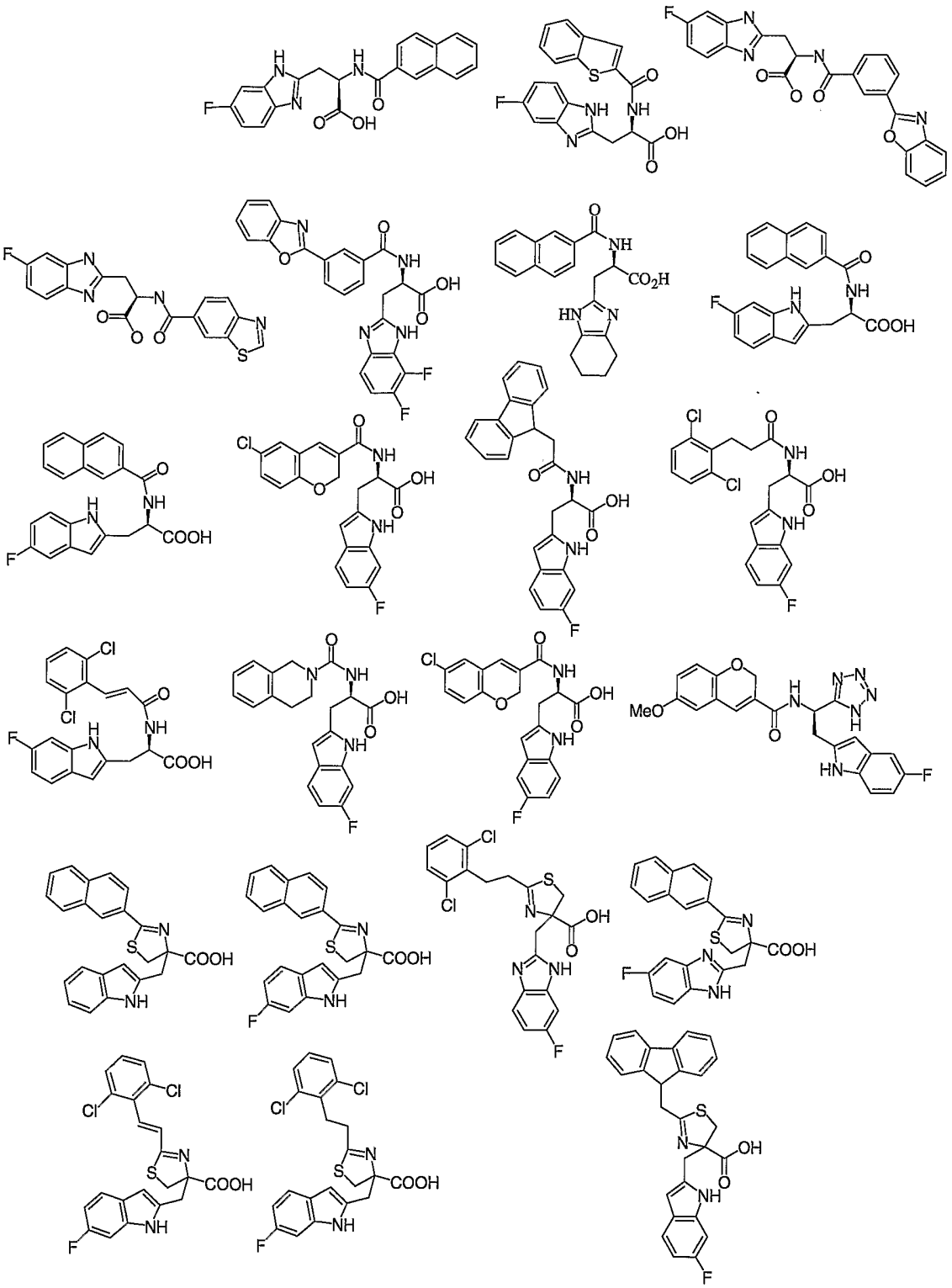
J and J' are independently H or =O;

R^1 is optionally substituted aryl, heteroaryl or –L-aryl wherein L is vinyl, ,

, $-CH_2S-$ or $-CH_2O-$ wherein A is H, aryl, substituted aryl or A and Ar can form a bicyclic or tricyclic ring or A and Ar can form a bicyclic or tricyclic heteroaryl ring; and

R^3 is –COOH, tetrazole, $CO_2CHR^4OCOR^4$, $-CONHR^5$, OH wherein R^4 is independently selected from H or alkyl and R^5 is H, alkoxy, OH, $-SO_2$-alkyl or $-SO_2H$.

7. A compound selected from the group consisting of:



8. The compounds of claim 2 wherein X is NH, Y is -C(O)- and R^1 is aryl or heteroaryl.

9. A method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth.

10. The method according to claim 9 wherein the abnormal cell growth is cancer.

11. The method according to claim 10 wherein said cancer is selected from lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.

12. The method according to claim 9 wherein said abnormal cell growth is a benign proliferative disease.

13. The method according to claim 9 wherein said abnormal cell growth is selected from psoriasis, benign prostatic hypertrophy and restinosis.

14. A method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

15. A pharmaceutical composition for the treatment of abnormal cell growth in a mammal comprising an amount of a compound of claim 1 that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003019

A. CLASSIFICATION OF SUBJECT MATTER

C07D401/12 C07D401/14 C07D235/16 C07D409/12 C07D417/14
C07D403/06 C07D413/12 C07D405/12 C07D403/14 C07D413/06
C07D417/06 A61K31/415 A61K31/40 A61K31/35 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/101993 A (NEOGENESIS PHARMACEUTICALS, INC) 11 December 2003 (2003-12-11) example 41; compounds 482, 494, 495, 506, 520, 523, 530, 599-604, 607	1,2,8
X	NANDI ET AL: "Studies on potential antibacterial & chelating agents: part I-Synthesis, physicochemical properties & antibacterial screening of some benzimidazoles" INDIAN JOURNAL OF CHEMISTRY, vol. 25B, 1986, pages 222-224, XP009060028 compounds IVA, IVB	1,2,8

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 January 2006	09/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bakboord, J

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003019

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HENNIG L ET AL: "Selective inactivation of parvulin-like peptidyl-prolyl cis/trans isomerases by juglone" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 37, 1998, pages 5953-5960, XP002253383 ISSN: 0006-2960 cited in the application the whole document	1-15
A	UCHIDA ET AL: "Pin1 and Par14 Peptidyl prolyl isomerase inhibitors block cell proliferation" CHEMISTRY & BIOLOGY, vol. 10, 2003, pages 15-24, XP002363138 figure 3	1-15
P,A	WO 2004/087720 A (PFIZER INC; GUO, CHUANGXING; DAGOSTINO, ELEANOR, FERRONYALKA; DONG, LI) 14 October 2004 (2004-10-14) claims 6,8	1-15
P,A	US 2004/214872 A1 (SUTO ET AL) 28 October 2004 (2004-10-28) claim 1	1-15

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/003019

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-14
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03101993 A	11-12-2003	AU 2003240488 A1	19-12-2003
		CA 2487211 A1	11-12-2003
		CN 1671710 A	21-09-2005
		EP 1511751 A1	09-03-2005
		JP 2005533040 T	04-11-2005
WO 2004087720 A	14-10-2004	CA 2517281 A1	14-10-2004
		EP 1603926 A1	14-12-2005
US 2004214872 A1	28-10-2004	AU 2003225669 A1	19-04-2004
		EP 1551396 A1	13-07-2005
		WO 2004028535 A1	08-04-2004